

Compounds and Compositions for Treating Conditions Associated with STING Activity

CROSS REFERENCE TO RELATED APPLICATIONS

5 This application claims the benefit of United States Provisional Application No. 63/231,672, filed on August 10, 2021, United States Provisional Application No. 63/298,889, filed on January 12, 2022, and United States Provisional Application No. 63/369,343, filed on July 25, 2022, each of these prior applications is incorporated by reference in its entirety.

TECHNICAL FIELD

10 This disclosure features chemical entities (e.g., a compound or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that inhibit (e.g., antagonize) Stimulator of Interferon Genes (STING). Said chemical entities are useful, e.g., for treating a condition, disease or disorder in which increased (e.g., excessive) STING activation (e.g., STING signaling) contributes to the
15 pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). This disclosure also features compositions containing the same as well as methods of using and making the same.

BACKGROUND

20 STING, also known as transmembrane protein 173 (TMEM173) and MPYS/MITA/ERIS, is a protein that in humans is encoded by the TMEM173 gene. STING has been shown to play a role in innate immunity. STING induces type I interferon production when cells are infected with intracellular pathogens, such as viruses, mycobacteria and intracellular parasites. Type I interferon, mediated by STING, protects infected cells and nearby cells from local infection in an autocrine and paracrine manner.

25 The STING pathway is pivotal in mediating the recognition of cytosolic DNA. In this context, STING, a transmembrane protein localized to the endoplasmic reticulum (ER), acts as a second messenger receptor for 2', 3' cyclic GMP-AMP (hereafter cGAMP), which is produced by cGAS after dsDNA binding. In addition, STING can also function

as a primary pattern recognition receptor for bacterial cyclic dinucleotides (CDNs) and small molecule agonists. The recognition of endogenous or prokaryotic CDNs proceeds through the carboxy-terminal domain of STING, which faces into the cytosol and creates a V-shaped binding pocket formed by a STING homodimer. Ligand-induced activation of STING triggers its re-localization to the Golgi, a process essential to promote the interaction of STING with TBK1. This protein complex, in turn, signals through the transcription factors IRF-3 to induce type I interferons (IFNs) and other co-regulated antiviral factors. In addition, STING was shown to trigger NF- κ B and MAP kinase activation. Following the initiation of signal transduction, STING is rapidly degraded, a step considered important in terminating the inflammatory response.

Excessive activation of STING is associated with a subset of monogenic autoinflammatory conditions, the so-called type I interferonopathies. Examples of these diseases include a clinical syndrome referred to as STING-associated vasculopathy with onset in infancy (SAVI), which is caused by gain-of-function mutations in TMEM173 (the gene name of STING). Moreover, STING is implicated in the pathogenesis of Aicardi-Goutières Syndrome (AGS) and genetic forms of lupus. As opposed to SAVI, it is the dysregulation of nucleic acid metabolism that underlies continuous innate immune activation in AGS. Apart from these genetic disorders, emerging evidence points to a more general pathogenic role for STING in a range of inflammation-associated disorders such as systemic lupus erythematosus, rheumatoid arthritis and cancer. Thus, small molecule-based pharmacological interventions into the STING signaling pathway hold significant potential for the treatment of a wide spectrum of diseases

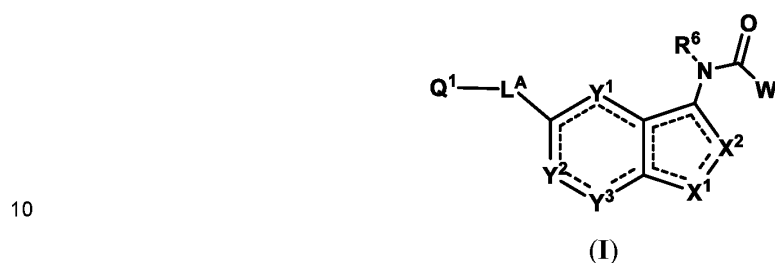
SUMMARY

This disclosure features chemical entities (e.g., a compound or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that inhibit (e.g., antagonize) Stimulator of Interferon Genes (STING). Said chemical entities are useful, e.g., for treating a condition, disease or disorder in which increased (e.g., excessive) STING activation (e.g., STING signaling) contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g.,

cancer) in a subject (e.g., a human). This disclosure also features compositions containing the same as well as methods of using and making the same.

5 An "antagonist" of STING includes compounds that, at the protein level, directly bind or modify STING such that an activity of STING is decreased, e.g., by inhibition, blocking or dampening agonist-mediated responses, altered distribution, or otherwise. STING antagonists include chemical entities, which interfere or inhibit STING signaling.

In one aspect, compounds of Formula (I), or a pharmaceutically acceptable salt thereof, are featured:



in which Q^1 , L^A , Y^1 , Y^2 , Y^3 , X^1 , X^2 , R^6 , and W can be as defined anywhere herein.

15 In one aspect, pharmaceutical compositions are featured that include a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same) and one or more pharmaceutically acceptable excipients.

20 In one aspect, methods for inhibiting (e.g., antagonizing) STING activity are featured that include contacting STING with a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same). Methods include *in vitro* methods, e.g., contacting a sample that includes one or more cells comprising STING (e.g., innate immune cells, e.g., mast cells, macrophages, dendritic cells (DCs), and natural killer cells) with the chemical entity. Methods can also include *in vivo* methods; e.g., administering
25 the chemical entity to a subject (e.g., a human) having a disease in which increased (e.g., excessive) STING signaling contributes to the pathology and/or symptoms and/or progression of the disease.

In one aspect, methods of treating a condition, disease or disorder ameliorated by antagonizing STING are featured, e.g., treating a condition, disease or disorder in which increased (e.g., excessive) STING activation (e.g., STING signaling) contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). The methods include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In another aspect, methods of treating cancer are featured that include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In a further aspect, methods of treating other STING-associated conditions are featured, e.g., type I interferonopathies (e.g., STING-associated vasculopathy with onset in infancy (SAVI)), Aicardi-Goutières Syndrome (AGS), genetic forms of lupus, and inflammation-associated disorders such as systemic lupus erythematosus, and rheumatoid arthritis. The methods include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In another aspect, methods of suppressing STING-dependent type I interferon production in a subject in need thereof are featured that include administering to the subject an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In a further aspect, methods of treating a disease in which increased (e.g., excessive) STING activation (e.g., STING signaling) contributes to the pathology and/or symptoms and/or progression of the disease are featured. The methods include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In another aspect, methods of treatment are featured that include administering an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same) to a subject; wherein the subject has (or is predisposed to have) a disease in which increased (e.g., excessive) STING activation (e.g., STING signaling) contributes to the pathology and/or symptoms and/or progression of the disease.

In a further aspect, methods of treatment that include administering to a subject a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same), wherein the chemical entity is administered in an amount effective to treat a disease in which increased (e.g., excessive) STING activation (e.g., STING signaling) contributes to the pathology and/or symptoms and/or progression of the disease, thereby treating the disease.

In another aspect, there is provided is a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein, for use in the treatment of a disease, condition or disorder modulated by STING inhibition.

In another aspect, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of a condition, disease or disorder associated with increased (e.g., excessive) STING activation.

In another aspect, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, described herein for use in the treatment of cancer.

In another aspect, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of cancer selected from the group consisting of melanoma, cervical cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, urothelial carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal carcinoma, colorectal cancer, pancreatic cancer, kidney cancer, hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia syndrome, multiple myeloma, transitional cell carcinoma, neuroblastoma, plasma cell neoplasms, Wilm's tumor, or hepatocellular carcinoma.

In another aspect, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of type I interferonopathies.

5 In another aspect, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of type I interferonopathies selected from STING-associated vasculopathy with onset in infancy (SAVI), Aicardi-Goutières Syndrome (AGS), genetic forms of lupus, and inflammation-associated disorders such as systemic lupus erythematosus, and rheumatoid arthritis.

10 In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of a condition, disease or disorder associated with increased (e.g., excessive) STING activation.

In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament
15 for the treatment of cancer.

In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of cancer selected from the group consisting of melanoma, cervical cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, urothelial
20 carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal carcinoma, colorectal cancer, pancreatic cancer, kidney cancer, hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia syndrome, multiple myeloma, transitional cell carcinoma, neuroblastoma, plasma cell neoplasms, Wilm's tumor, or
25 hepatocellular carcinoma.

In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of type I interferonopathies.

30 In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the manufacture of a medicament for the treatment of type I interferonopathies selected from STING-associated

vasculopathy with onset in infancy (SAVI)), Aicardi-Goutières Syndrome (AGS), genetic forms of lupus, and inflammation-associated disorders such as systemic lupus erythematosus, and rheumatoid arthritis.

5 In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein, for the treatment of a disease, condition or disorder modulated by STING inhibition.

In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for the treatment of a condition, disease or disorder associated with increased (e.g., excessive) STING activation.

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In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for the treatment of cancer.

15 In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for the treatment of cancer selected from the group consisting of melanoma, cervical cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, urothelial carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal carcinoma, colorectal cancer, pancreatic cancer, kidney cancer, hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia syndrome, multiple myeloma, transitional cell carcinoma, neuroblastoma, plasma cell neoplasms, Wilm's tumor, or hepatocellular carcinoma.

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In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for the treatment of type I interferonopathies.

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In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for the treatment of type I interferonopathies selected from STING-associated vasculopathy with onset in infancy (SAVI), Aicardi-Goutières Syndrome (AGS), genetic forms of lupus, and inflammation-associated disorders such as systemic lupus erythematosus, and rheumatoid arthritis.

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Embodiments can include one or more of the following features.

The chemical entity can be administered in combination with one or more additional therapeutic agents and/or regimens. For examples, methods can further include administering one or more (e.g., two, three, four, five, six, or more) additional agents.

5 The chemical entity can be administered in combination with one or more additional therapeutic agents and/or regimens that are useful for treating other STING-associated conditions, e.g., type I interferonopathies (e.g., STING-associated vasculopathy with onset in infancy (SAVI)), Aicardi-Goutières Syndrome (AGS), genetic forms of lupus, and inflammation-associated disorders such as systemic lupus erythematosus, and rheumatoid arthritis.

10 The chemical entity can be administered in combination with one or more additional cancer therapies (e.g., surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy, or a combination thereof; e.g., chemotherapy that includes administering one or more (e.g., two, three, four, five, six, or more) additional chemotherapeutic agents. Non-limiting examples of additional chemotherapeutic agents is
15 selected from an alkylating agent (e.g., cisplatin, carboplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide and/or oxaliplatin); an anti-metabolite (e.g., azathioprine and/or mercaptopurine); a terpenoid (e.g., a vinca alkaloid and/or a taxane; e.g., Vincristine, Vinblastine, Vinorelbine and/or Vindesine Taxol, Paclitaxel and/or Docetaxel); a topoisomerase (e.g., a type I topoisomerase and/or a type 2
20 topoisomerase; e.g., camptothecins, such as irinotecan and/or topotecan; amsacrine, etoposide, etoposide phosphate and/or teniposide); a cytotoxic antibiotic (e.g., actinomycin, anthracyclines, doxorubicin, daunorubicin, valrubicin, idarubicin, epirubicin, bleomycin, plicamycin and/or mitomycin); a hormone (e.g., a lutenizing hormone releasing hormone agonist; e.g., leuprolidine, goserelin, triptorelin, histrelin, bicalutamide,
25 flutamide and/or nilutamide); an antibody (e.g., Abciximab, Adalimumab, Alemtuzumab, Atlizumab, Basiliximab, Belimumab, Bevacizumab, Bretuximab vedotin, Canakinumab, Cetuximab, Ceertolizumab pegol, Daclizumab, Denosumab, Eculizumab, Efalizumab, Gemtuzumab, Golimumab, Golimumab, Ibritumomab tiuxetan, Infliximab, Ipilimumab, Muromonab-CD3, Natalizumab, Ofatumumab, Omalizumab, Palivizumab, Panitumab,
30 Ranibizumab, Rituximab, Tocilizumab, Tositumomab and/or Trastuzumab); an anti-angiogenic agent; a cytokine; a thrombotic agent; a growth inhibitory agent; an anti-

helminthic agent; and an immune checkpoint inhibitor that targets an immune checkpoint receptor selected from the group consisting of CTLA-4, PD-1, PD-L1, PD-1 – PD-L1, PD-1 – PD-L2, interleukin-2 (IL-2), indoleamine 2,3-dioxygenase (IDO), IL-10, transforming growth factor- β (TGF β), T cell immunoglobulin and mucin 3 (TIM3 or HAVCR2),
 5 Galectin 9 – TIM3, Phosphatidylserine – TIM3, lymphocyte activation gene 3 protein (LAG3), MHC class II – LAG3, 4-1BB–4-1BB ligand, OX40–OX40 ligand, GITR, GITR ligand – GITR, CD27, CD70–CD27, TNFRSF25, TNFRSF25–TL1A, CD40L, CD40–CD40 ligand, HVEM–LIGHT–LTA, HVEM, HVEM – BTLA, HVEM – CD160, HVEM – LIGHT, HVEM–BTLA–CD160, CD80, CD80 – PDL-1, PDL2 – CD80, CD244, CD48
 10 – CD244, CD244, ICOS, ICOS–ICOS ligand, B7-H3, B7-H4, VISTA, TMIGD2, HHLA2–TMIGD2, Butyrophilins, including BTNL2, Siglec family, TIGIT and PVR family members, KIRs, ILTs and LIRs, NKG2D and NKG2A, MICA and MICB, CD244, CD28, CD86 – CD28, CD86 – CTLA, CD80 – CD28, CD39, CD73 Adenosine–CD39–CD73, CXCR4–CXCL12, Phosphatidylserine, TIM3, Phosphatidylserine – TIM3,
 15 SIRPA–CD47, VEGF, Neuropilin, CD160, CD30, and CD155 (e.g., CTLA-4 or PD1 or PD-L1).

The subject can have cancer; e.g., the subject has undergone and/or is undergoing and/or will undergo one or more cancer therapies.

Non-limiting examples of cancer include melanoma, cervical cancer, breast cancer,
 20 ovarian cancer, prostate cancer, testicular cancer, urothelial carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal carcinoma, colorectal cancer, pancreatic cancer, kidney cancer, hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia syndrome, multiple myeloma, transitional cell carcinoma,
 25 neuroblastoma, plasma cell neoplasms, Wilm's tumor, or hepatocellular carcinoma. In certain embodiments, the cancer can be a refractory cancer.

The chemical entity can be administered intratumorally.

The methods can further include identifying the subject.

Other embodiments include those described in the Detailed Description and/or in the claims.

Additional Definitions

5 To facilitate understanding of the disclosure set forth herein, a number of additional terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly
10 understood by one of ordinary skill in the art to which this disclosure belongs. Each of the patents, applications, published applications, and other publications that are mentioned throughout the specification and the attached appendices are incorporated herein by reference in their entireties.

As used herein, the term “STING” is meant to include, without limitation, nucleic
15 acids, polynucleotides, oligonucleotides, sense and antisense polynucleotide strands, complementary sequences, peptides, polypeptides, proteins, homologous and/or orthologous STING molecules, isoforms, precursors, mutants, variants, derivatives, splice variants, alleles, different species, and active fragments thereof.

The term “acceptable” with respect to a formulation, composition or ingredient, as
20 used herein, means having no persistent detrimental effect on the general health of the subject being treated.

“API” refers to an active pharmaceutical ingredient.

The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of a chemical entity being administered which will relieve to
25 some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An
30 appropriate “effective” amount in any individual case is determined using any suitable technique, such as a dose escalation study.

The term “excipient” or “pharmaceutically acceptable excipient” means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, carrier, solvent, or encapsulating material. In one embodiment, each component is “pharmaceutically acceptable” in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. See, e.g., *Remington: The Science and Practice of Pharmacy*, 21st ed.; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients*, 6th ed.; Rowe et al., Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives*, 3rd ed.; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation*, 2nd ed.; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

The term “pharmaceutically acceptable salt” refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined. The pharmacologically acceptable salt is not specifically limited as far as it can be used in medicaments. Examples of a salt that the compounds described herein form with a base include the following: salts thereof with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; salts thereof with organic bases such as methylamine, ethylamine and ethanolamine; salts thereof with basic amino acids

such as lysine and ornithine; and ammonium salt. The salts may be acid addition salts, which are specifically exemplified by acid addition salts with the following: mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid; organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, and ethanesulfonic acid; acidic amino acids such as aspartic acid and glutamic acid.

The term “pharmaceutical composition” refers to a mixture of a compound described herein with other chemical components (referred to collectively herein as “excipients”), such as carriers, stabilizers, diluents, dispersing agents, suspending agents, and/or thickening agents. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: rectal, oral, intravenous, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

The term “subject” refers to an animal, including, but not limited to, a primate (*e.g.*, human), monkey, cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms “subject” and “patient” are used interchangeably herein in reference, for example, to a mammalian subject, such as a human.

The terms “treat,” “treating,” and “treatment,” in the context of treating a disease or disorder, are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or to slowing the progression, spread or worsening of a disease, disorder or condition or of one or more symptoms thereof. The “treatment of cancer”, refers to one or more of the following effects: (1) inhibition, to some extent, of tumor growth, including, (i) slowing down and (ii) complete growth arrest; (2) reduction in the number of tumor cells; (3) maintaining tumor size; (4) reduction in tumor size; (5) inhibition, including (i) reduction, (ii) slowing down or (iii) complete prevention, of tumor cell infiltration into peripheral organs; (6) inhibition, including (i) reduction, (ii) slowing down or (iii) complete prevention, of metastasis; (7) enhancement of anti-tumor immune response, which may result in (i) maintaining tumor size, (ii) reducing tumor size, (iii) slowing the growth of a

tumor, (iv) reducing, slowing or preventing invasion and/or (8) relief, to some extent, of the severity or number of one or more symptoms associated with the disorder.

The term "halo" refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

5 The term "alkyl" refers to a saturated acyclic hydrocarbon radical that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C₁₋₁₀ indicates that the group may have from 1 to 10 (inclusive) carbon atoms in it. Alkyl groups can either be unsubstituted or substituted with one or more substituents. Non-limiting examples include methyl, ethyl, *iso*-propyl, *tert*-butyl, *n*-hexyl. The term "saturated" as used in this context means only single bonds present between constituent
10 carbon atoms and other available valences occupied by hydrogen and/or other substituents as defined herein.

The term "haloalkyl" refers to an alkyl, in which one or more hydrogen atoms is/are replaced with an independently selected halo.

The term "alkoxy" refers to an -O-alkyl radical (e.g., -OCH₃).

15 The term "alkylene" refers to a divalent alkyl (e.g., -CH₂-).

The term "alkenyl" refers to an acyclic hydrocarbon chain that may be a straight chain or branched chain having one or more carbon-carbon double bonds. The alkenyl moiety contains the indicated number of carbon atoms. For example, C₂₋₆ indicates that the group may have from 2 to 6 (inclusive) carbon atoms in it. Alkenyl groups can either be
20 unsubstituted or substituted with one or more substituents.

The term "alkynyl" refers to an acyclic hydrocarbon chain that may be a straight chain or branched chain having one or more carbon-carbon triple bonds. The alkynyl moiety contains the indicated number of carbon atoms. For example, C₂₋₆ indicates that the group may have from 2 to 6 (inclusive) carbon atoms in it. Alkynyl groups can either be
25 unsubstituted or substituted with one or more substituents.

The term "aryl" refers to a 6-20 carbon mono-, bi-, tri- or polycyclic group wherein at least one ring in the system is aromatic (e.g., 6-carbon monocyclic, 10-carbon bicyclic, or 14-carbon tricyclic aromatic ring system); and wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent. Examples of aryl groups include phenyl, naphthyl,
30 tetrahydronaphthyl, dihydro-1H-indenyl and the like.

The term "cycloalkyl" as used herein refers to cyclic saturated hydrocarbon groups having, e.g., 3 to 20 ring carbons, preferably 3 to 16 ring carbons, and more preferably 3 to 12 ring carbons or 3-10 ring carbons or 3-6 ring carbons, wherein the cycloalkyl group may be optionally substituted. Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Cycloalkyl may include multiple fused and/or bridged rings. Non-limiting examples of fused/bridged cycloalkyl includes: bicyclo[1.1.0]butanyl, bicyclo[2.1.0]pentanyl, bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexanyl, bicyclo[2.1.1]hexanyl, bicyclo[3.2.0]heptanyl, bicyclo[4.1.0]heptanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, bicyclo[4.2.0]octanyl, bicyclo[3.2.1]octanyl, bicyclo[2.2.2]octanyl, and the like. Cycloalkyl also includes spirocyclic rings (e.g., spirocyclic bicycle wherein two rings are connected through just one atom). Non-limiting examples of spirocyclic cycloalkyls include spiro[2.2]pentanyl, spiro[2.5]octanyl, spiro[3.5]nonanyl, spiro[3.5]nonanyl, spiro[3.5]nonanyl, spiro[4.4]nonanyl, spiro[2.6]nonanyl, spiro[4.5]decanyl, spiro[3.6]decanyl, spiro[5.5]undecanyl, and the like. The term "saturated" as used in this context means only single bonds present between constituent carbon atoms.

The term "cycloalkenyl" as used herein means partially unsaturated cyclic hydrocarbon groups having 3 to 20 ring carbons, preferably 3 to 16 ring carbons, and more preferably 3 to 12 ring carbons or 3-10 ring carbons or 3-6 ring carbons, wherein the cycloalkenyl group may be optionally substituted. Examples of cycloalkenyl groups include, without limitation, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. As partially unsaturated cyclic hydrocarbon groups, cycloalkenyl groups may have any degree of unsaturation provided that one or more double bonds is present in the ring, none of the rings in the ring system are aromatic, and the cycloalkenyl group is not fully saturated overall. Cycloalkenyl may include multiple fused and/or bridged and/or spirocyclic rings.

The term "heteroaryl", as used herein, means a mono-, bi-, tri- or polycyclic group having 5 to 20 ring atoms, alternatively 5, 6, 9, 10, or 14 ring atoms; and having 6, 10, or 14 pi electrons shared in a cyclic array; wherein at least one ring in the system is aromatic, and at least one ring in the system contains one or more heteroatoms independently selected from the group consisting of N, O, and S (but does not have to be a ring which contains a heteroatom, e.g. tetrahydroisoquinoliny, e.g., tetrahydroquinoliny). Heteroaryl groups

can either be unsubstituted or substituted with one or more substituents. Examples of heteroaryl include thienyl, pyridinyl, furyl, oxazolyl, oxadiazolyl, pyrrolyl, imidazolyl, triazolyl, thiodiazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiazolyl benzothienyl, benzoxadiazolyl, benzofuranyl, benzimidazolyl, benzotriazolyl, cinnolinyl, indazolyl, indolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, purinyl, thienopyridinyl, pyrido[2,3-*d*]pyrimidinyl, pyrrolo[2,3-*b*]pyridinyl, quinazolinyl, quinolinyl, thieno[2,3-*c*]pyridinyl, pyrazolo[3,4-*b*]pyridinyl, pyrazolo[3,4-*c*]pyridinyl, pyrazolo[4,3-*c*]pyridinyl, pyrazolo[4,3-*b*]pyridinyl, tetrazolyl, chromanyl, 2,3-dihydrobenzo[*b*][1,4]dioxinyl, benzo[*d*][1,3]dioxolyl, 2,3-dihydrobenzofuranyl, tetrahydroquinolinyl, 2,3-dihydrobenzo[*b*][1,4]oxathiinyl, isoindolinyl, and others. In some embodiments, the heteroaryl is selected from thienyl, pyridinyl, furyl, pyrazolyl, imidazolyl, isoindolinyl, pyranyl, pyrazinyl, and pyrimidinyl.

The term "heterocyclyl" refers to a mon-, bi-, tri-, or polycyclic saturated ring system with 3-16 ring atoms (e.g., 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system) having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic or polycyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent. Examples of heterocyclyl groups include piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl, and the like. Heterocyclyl may include multiple fused and bridged rings. Non-limiting examples of fused/bridged heterocyclyl includes: 2-azabicyclo[1.1.0]butanyl, 2-azabicyclo[2.1.0]pentanyl, 2-azabicyclo[1.1.1]pentanyl, 3-azabicyclo[3.1.0]hexanyl, 5-azabicyclo[2.1.1]hexanyl, 3-azabicyclo[3.2.0]heptanyl, octahydrocyclopenta[*c*]pyrrolyl, 3-azabicyclo[4.1.0]heptanyl, 7-azabicyclo[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 7-azabicyclo[4.2.0]octanyl, 2-azabicyclo[2.2.2]octanyl, 3-azabicyclo[3.2.1]octanyl, 2-oxabicyclo[1.1.0]butanyl, 2-oxabicyclo[2.1.0]pentanyl, 2-oxabicyclo[1.1.1]pentanyl, 3-oxabicyclo[3.1.0]hexanyl, 5-oxabicyclo[2.1.1]hexanyl, 3-oxabicyclo[3.2.0]heptanyl, 3-oxabicyclo[4.1.0]heptanyl, 7-oxabicyclo[2.2.1]heptanyl, 6-oxabicyclo[3.1.1]heptanyl, 7-oxabicyclo[4.2.0]octanyl, 2-oxabicyclo[2.2.2]octanyl, 3-oxabicyclo[3.2.1]octanyl, and the like. Heterocyclyl also

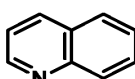
includes spirocyclic rings (e.g., spirocyclic bicycle wherein two rings are connected through just one atom). Non-limiting examples of spirocyclic heterocyclyls include 2-azaspiro[2.2]pentanyl, 4-azaspiro[2.5]octanyl, 1-azaspiro[3.5]nonanyl, 2-azaspiro[3.5]nonanyl, 7-azaspiro[3.5]nonanyl, 2-azaspiro[4.4]nonanyl, 6-azaspiro[2.6]nonanyl, 1,7-diazaspiro[4.5]decanyl, 7-azaspiro[4.5]decanyl, 2,5-diazaspiro[3.6]decanyl, 3-azaspiro[5.5]undecanyl, 2-oxaspiro[2.2]pentanyl, 4-oxaspiro[2.5]octanyl, 1-oxaspiro[3.5]nonanyl, 2-oxaspiro[3.5]nonanyl, 7-oxaspiro[3.5]nonanyl, 2-oxaspiro[4.4]nonanyl, 6-oxaspiro[2.6]nonane, 1,7-dioxaspiro[4.5]decanyl, 2,5-dioxaspiro[3.6]decanyl, 1-oxaspiro[5.5]undecanyl, 3-oxaspiro[5.5]undecanyl, 3-oxa-9-azaspiro[5.5]undecanyl and the like. The term “saturated” as used in this context means only single bonds present between constituent ring atoms and other available valences occupied by hydrogen and/or other substituents as defined herein.

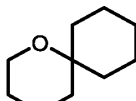
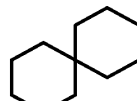
The term “heterocycloalkenyl” as used herein means partially unsaturated cyclic ring system with 3-16 ring atoms (e.g., 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system) having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic or polycyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent. Examples of heterocycloalkenyl groups include, without limitation, tetrahydropyridyl, dihydropyrazinyl, dihydropyridyl, dihydropyrrolyl, dihydrofuranyl, dihydrothiophenyl. As partially unsaturated cyclic groups, heterocycloalkenyl groups may have any degree of unsaturation provided that one or more double bonds is present in the ring, none of the rings in the ring system are aromatic, and the heterocycloalkenyl group is not fully saturated overall. Heterocycloalkenyl may include multiple fused and/or bridged and/or spirocyclic rings.

As used herein, when a ring is described as being “aromatic”, it means said ring has a continuous, delocalized π -electron system. Typically, the number of out of plane π -electrons corresponds to the Hückel rule ($4n+2$). Examples of such rings include: benzene, pyridine, pyrimidine, pyrazine, pyridazine, pyridone, pyrrole, pyrazole, oxazole, thiazole, isoxazole, isothiazole, and the like.

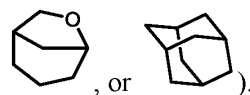
As used herein, when a ring is described as being “partially unsaturated”, it means said ring has one or more additional degrees of unsaturation (in addition to the degree of unsaturation attributed to the ring itself; e.g., one or more double or triple bonds between constituent ring atoms), provided that the ring is not aromatic. Examples of such rings include: cyclopentene, cyclohexene, cycloheptene, dihydropyridine, tetrahydropyridine, dihydropyrrole, dihydrofuran, dihydrothiophene, and the like.

For the avoidance of doubt, and unless otherwise specified, for rings and cyclic groups (e.g., aryl, heteroaryl, heterocyclyl, heterocycloalkenyl, cycloalkenyl, cycloalkyl, and the like described herein) containing a sufficient number of ring atoms to form bicyclic or higher order ring systems (e.g., tricyclic, polycyclic ring systems), it is understood that such rings and cyclic groups encompass those having fused rings, including those in which the points of fusion are located (i) on adjacent ring atoms (e.g., [x.x.0] ring systems, in

which 0 represents a zero atom bridge (e.g., )); (ii) a single ring atom (spiro-

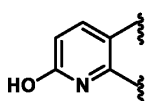
fused ring systems) (e.g., , , or ), or (iii) a contiguous

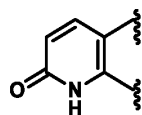
array of ring atoms (bridged ring systems having all bridge lengths > 0) (e.g., ,



In addition, atoms making up the compounds of the present embodiments are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C .

In addition, the compounds generically or specifically disclosed herein are intended to include all tautomeric forms. Thus, by way of example, a compound containing the

moiety:  encompasses the tautomeric form containing the moiety:



. Similarly, a pyridinyl or pyrimidinyl moiety that is described to be optionally substituted with hydroxyl encompasses pyridone or pyrimidone tautomeric forms.

5 As used herein, the phrase “optionally substituted” when used in conjunction with a structural moiety (e.g., alkyl) is intended to encompass both the unsubstituted structural moiety (i.e., none of the substitutable hydrogen atoms are replaced with one or more non-hydrogen substituents) and substituted structural moieties substituted with the indicated range of non-hydrogen substituents. For example, “C₁-C₄ alkyl optionally substituted with
10 1-4 **R^a**” is intended to encompass both unsubstituted C₁-C₄ alkyl and C₁-C₄ alkyl substituted with 1-4 **R^a**.

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

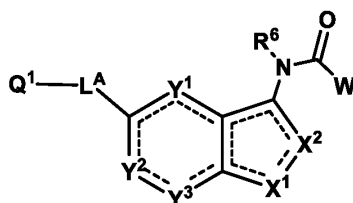
DETAILED DESCRIPTION

This disclosure features chemical entities (e.g., a compound or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that inhibit (e.g., antagonize) Stimulator of Interferon Genes (STING). Said
20 chemical entities are useful, e.g., for treating a condition, disease or disorder in which increased (e.g., excessive) STING activation (e.g., STING signaling) contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). This disclosure also features compositions containing the same as well as methods of using and making the same.

25

Formula I Compounds

In one aspect, the disclosure features a compound of Formula (**I**):



Formula I

or a pharmaceutically acceptable salt thereof or a tautomer thereof, wherein:

L^A is $-(L^1)_{a1}-(L^2)_{a2}-(L^3)_{a3}-(L^4)_{a4}-(L^5)_{a5}-*$, wherein * represents the point of attachment to Q^1 ;

$a1$, $a2$, $a3$, $a4$, and $a5$ are each independently 0 or 1,

provided that $a1 + a2 + a3 + a4 + a5 \geq 1$, and

each of L^1 , L^3 , and L^5 is independently selected from the group consisting of: -O-, -N(H)-, -N(R^d)-, S(O)₀₋₂, and -C(=O)-;

provided that when one or both of $a2$ and $a4$ is 0, then the combinations of L^1 , L^3 , and L^5 cannot form O-O, N-O, N-N, O-S, S-S, or N-S(O)₀ bonds, and

each of L^2 and L^4 is independently selected from the group consisting of:

- straight-chain C₁₋₆ alkylene, straight-chain C₂₋₆ alkenylene, or straight-chain C₂₋₆ alkynylene, each of which is optionally substituted with 1-6 R^b ;
- C₃₋₁₀ cycloalkylene or C₃₋₁₀ cycloalkenylene, each of which is optionally substituted with 1-3 R^c , provided the C₃₋₁₀ cycloalkylene or C₃₋₁₀ cycloalkenylene is not directly connected to the 6-membered ring containing Y¹, Y², and Y³; and
- heterocyclylene or heterocycloalkenylene, each having 4-10 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), N(R^d), O, and S(O)₀₋₂, wherein the heterocyclylene or heterocycloalkenylene is optionally substituted with 1-3 R^c , provided the heterocyclylene or heterocycloalkenylene is not directly connected to the 6-membered ring containing Y¹, Y², and Y³;

Q^1 is $-R^g$;

Y^1 , Y^2 , and Y^3 are each independently selected from the group consisting of CR^1 ,
 5 $C(=O)$, N, and NR^2 ;

X^1 is selected from the group consisting of O, S, N, NR^2 , and CR^1 ;

X^2 is selected from the group consisting of O, S, N, NR^4 , and CR^5 ;

each $\equiv$ is independently a single bond or a double bond, provided that the five-
 membered ring comprising X^1 and X^2 is heteroaryl, and that the six-membered ring
 10 comprising Y^1 , Y^2 , and Y^3 is aryl or heteroaryl;

each occurrence of R^1 and R^5 is independently selected from the group consisting
 of: H; R^c ; R^g ; and $-(L^g)_{hg}-R^g$;

each occurrence of R^2 and R^4 is independently selected from the group consisting
 15 of: H; R^d ; R^g ; and $-(L^g)_{hg}-R^g$;

R^6 is selected from the group consisting of: H; R^d ; and R^g ;

W is selected from the group consisting of:

- 20
- H;
 - C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl, each of which is optionally substituted with 1-6 R^{a2} ;
 - monocyclic C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo
 25 and R^c ; and
 - monocyclic heterocyclyl or heterocycloalkenyl of 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group
 30 consisting of oxo and R^c ;

provided that when **W** is heterocyclyl or heterocycloalkenyl, it is attached to the C(=O)NR⁶ group via a ring carbon atom;

each occurrence of **R^a** and **R^{a2}** is independently selected from the group consisting of: -OH; -halo; -NR^eR^f; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -C(=O)O(C₁₋₄ alkyl); -C(=O)(C₁₋₄ alkyl); -C(=O)OH; -CONR^{'R''}; -S(O)₁₋₂NR^{'R''}; -S(O)₁₋₂(C₁₋₄ alkyl); and cyano;

each occurrence of **R^b** and **R^c** is independently selected from the group consisting of: halo; cyano; C₁₋₁₀ alkyl which is optionally substituted with 1-6 independently selected **R^a**; C₂₋₆ alkenyl; C₂₋₆ alkynyl; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -S(O)₁₋₂(C₁₋₄ alkyl); -S(O)(=NH)(C₁₋₄ alkyl); -NR^eR^f; -OH; -S(O)₁₋₂NR^{'R''}; -C₁₋₄ thioalkoxy; -NO₂; -C(=O)(C₁₋₁₀ alkyl); -C(=O)O(C₁₋₄ alkyl); -C(=O)OH; -C(=O)NR^{'R''}; and -SF₅;

each occurrence of **R^d** is independently selected from the group consisting of: C₁₋₆ alkyl optionally substituted with 1-3 independently selected **R^a**; -C(O)(C₁₋₄ alkyl); -C(O)O(C₁₋₄ alkyl); -CONR^{'R''}; -S(O)₁₋₂NR^{'R''}; -S(O)₁₋₂(C₁₋₄ alkyl); -OH; and C₁₋₄ alkoxy;

each occurrence of **R^e** and **R^f** is independently selected from the group consisting of: H; C₁₋₆ alkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of NR^{'R''}, -OH, halo, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy; -C(O)(C₁₋₄ alkyl); -C(O)O(C₁₋₄ alkyl); -CONR^{'R''}; -S(O)₁₋₂NR^{'R''}; -S(O)₁₋₂(C₁₋₄ alkyl); -OH; and C₁₋₄ alkoxy;

each occurrence of **R^g** is independently selected from the group consisting of:

- C₃₋₁₂ cycloalkyl or C₃₋₁₂ cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**;
- heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally

substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c ;

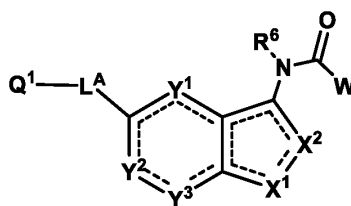
- heteroaryl of 5-12 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), $N(R^d)$, O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 R^c ; and
- C_{6-10} aryl optionally substituted with 1-4 R^c ;

each occurrence of L^g is independently selected from the group consisting of: -O-, -NH-, $-NR^d$, $-S(O)_{0-2}$, C(O), and C_{1-3} alkylene optionally substituted with 1-3 R^a ;

each occurrence of bg is independently 1, 2, or 3; and

each occurrence of R' and R'' is independently selected from the group consisting of: H; -OH; and C_{1-4} alkyl.

In another aspect, this disclosure features a compound of Formula (I):



Formula I

or a pharmaceutically acceptable salt thereof or a tautomer thereof, wherein:

L^A is $-(L^1)_{a1}-(L^2)_{a2}-(L^3)_{a3}-(L^4)_{a4}-(L^5)_{a5}-*$, wherein * represents the point of attachment to Q^1 ;

$a1$, $a2$, $a3$, $a4$, and $a5$ are each independently 0 or 1, provided that $a1 + a2 + a3 + a4 + a5 \geq 1$, and

each of L^1 , L^3 , and L^5 is independently selected from the group consisting of: -O-, -N(H)-, $-N(R^d)$ -, $S(O)_{0-2}$, and $-C(=O)-$;

provided that when one or both of $a2$ and $a4$ is 0, then the combinations of L^1 , L^3 , and L^5 cannot form O-O, N-O, N-N, O-S, S-S, or N-S(O)₀ bonds, and

each of L^2 and L^4 is independently selected from the group consisting of:

- straight-chain C_{1-6} alkylene, straight-chain C_{2-6} alkenylene, or straight-chain C_{2-6} alkynylene, each of which is optionally substituted with 1-6 R^b ;
- 5 • C_{3-10} cycloalkylene or C_{3-10} cycloalkenylene, each of which is optionally substituted with 1-3 R^c provided the C_{3-10} cycloalkylene or C_{3-10} cycloalkenylene is not directly connected to the 6-membered ring containing Y^1 , Y^2 , and Y^3 ; and
- heterocyclylene or heterocycloalkenylene, each having 4-10 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), N(R^d), O, and S(O)₀₋₂, wherein the heterocyclylene or heterocycloalkenylene is optionally substituted with 1-3 R^c , provided the heterocyclylene or heterocycloalkenylene is not directly connected to the 6-membered ring containing Y^1 , Y^2 , and Y^3 ;

15 Q^1 is $-R^g$;

Y^1 , Y^2 , and Y^3 are each independently selected from the group consisting of CR^1 , C(=O), N, and NR^2 ;

X^1 is selected from the group consisting of O, S, N, NR^2 , and CR^1 ;

20 X^2 is selected from the group consisting of O, S, N, NR^4 , and CR^5 ;

each $\equiv$ is independently a single bond or a double bond, provided that the five-membered ring comprising X^1 and X^2 is heteroaryl, and that the six-membered ring comprising Y^1 , Y^2 , and Y^3 is aryl or heteroaryl;

further provided that L^A cannot include a cyclic group directly attached to the 6-membered ring containing Y^1 , Y^2 , and Y^3 ;

each occurrence of R^1 and R^5 is independently selected from the group consisting of: H; R^c ; R^g ; and $-(L^g)_{bg}-R^g$;

each occurrence of R^2 and R^4 is independently selected from the group consisting of: H; R^d ; R^g ; and $-(L^g)_{bg}-R^g$;

R⁶ is selected from the group consisting of: H; **R**^d; and **R**^g;

W is selected from the group consisting of:

- H;
- 5 • C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl, each of which is optionally substituted with 1-6 **R**^{a2}, wherein one or more of the internal optionally substituted methylene group can be replaced by one or more heteroatom selected from O or S, wherein when **W** is alkenyl or alkynyl, the heteroatom is not directed connected to the *sp*² or *sp* carbon;
- 10 • monocyclic C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R**^c; and
- monocyclic heterocyclyl or heterocycloalkenyl of 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of
- 15 N, N(H), N(**R**^d), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R**^c,

provided that when **W** is heterocyclyl or heterocycloalkenyl, it is attached to the C(=O)NR⁶ group via a ring carbon atom;

20

each occurrence of **R**^a and **R**^{a2} is independently selected from the group consisting of: -OH; -halo; -NR^eR^f; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -C(=O)O(C₁₋₄ alkyl); -C(=O)(C₁₋₄ alkyl); -C(=O)OH; -CONR^eR^{e'}; -S(O)₁₋₂NR^eR^{e'}; -S(O)₁₋₂(C₁₋₄ alkyl); and cyano;

- 25 each occurrence of **R**^b and **R**^c is independently selected from the group consisting of: halo; cyano; C₁₋₁₀ alkyl which is optionally substituted with 1-6 independently selected **R**^a; C₂₋₆ alkenyl; C₂₋₆ alkynyl; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -S(O)₁₋₂(C₁₋₄ alkyl); -S(O)(=NH)(C₁₋₄ alkyl); -NR^eR^f; -OH; -S(O)₁₋₂NR^eR^{e'}; -C₁₋₄ thioalkoxy; -NO₂; -C(=O)(C₁₋₁₀ alkyl); -C(=O)O(C₁₋₄ alkyl); -C(=O)OH; -C(=O)NR^eR^{e'}; and -SF₅;

30

each occurrence of $\mathbf{R}^d$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with 1-3 independently selected $\mathbf{R}^a$; $-\text{C}(\text{O})(\text{C}_{1-4} \text{ alkyl})$; $-\text{C}(\text{O})\text{O}(\text{C}_{1-4} \text{ alkyl})$; $-\text{CONR}^{\mathbf{R}''}$; $-\text{S}(\text{O})_{1-2}\text{NR}^{\mathbf{R}''}$; $-\text{S}(\text{O})_{1-2}(\text{C}_{1-4} \text{ alkyl})$; $-\text{OH}$; and C_{1-4} alkoxy;

5

each occurrence of $\mathbf{R}^e$ and $\mathbf{R}^f$ is independently selected from the group consisting of: H; C_{1-6} alkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of $\text{NR}^{\mathbf{R}''}$, $-\text{OH}$, halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; $-\text{C}(\text{O})(\text{C}_{1-4} \text{ alkyl})$; $-\text{C}(\text{O})\text{O}(\text{C}_{1-4} \text{ alkyl})$; $-\text{CONR}^{\mathbf{R}''}$; $-\text{S}(\text{O})_{1-2}\text{NR}^{\mathbf{R}''}$; $-\text{S}(\text{O})_{1-2}(\text{C}_{1-4} \text{ alkyl})$; $-\text{OH}$; and C_{1-4} alkoxy;

10

each occurrence of $\mathbf{R}^g$ is independently selected from the group consisting of:

- C_{3-12} cycloalkyl or C_{3-12} cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R}^e$;

15

- heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^d$), O, and $\text{S}(\text{O})_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R}^e$;

20

- heteroaryl of 5-12 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^d$), O, and $\text{S}(\text{O})_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 $\mathbf{R}^e$; and

- C_{6-10} aryl optionally substituted with 1-4 $\mathbf{R}^e$;

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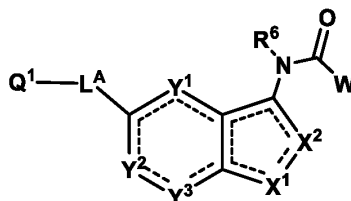
each occurrence of $\mathbf{L}^g$ is independently selected from the group consisting of: $-\text{O}-$, $-\text{NH}-$, $-\text{NR}^d$, $-\text{S}(\text{O})_{0-2}$, $\text{C}(\text{O})$, and C_{1-3} alkylene optionally substituted with 1-3 $\mathbf{R}^a$;

each occurrence of $\mathbf{bg}$ is independently 1, 2, or 3; and

each occurrence of $\mathbf{R}'$ and $\mathbf{R}''$ is independently selected from the group consisting of: H; $-\text{OH}$; and C_{1-4} alkyl.

30

In another aspect, this disclosure features a compound of Formula (I):



Formula I

5 or a pharmaceutically acceptable salt thereof or a tautomer thereof, wherein:

L^A is $-(L^1)_{a1}-(L^2)_{a2}-(L^3)_{a3}-(L^4)_{a4}-(L^5)_{a5}-*$, wherein * represents the point of attachment to Q^1 ;

$a1$, $a2$, $a3$, $a4$, and $a5$ are each independently 0 or 1,

provided that $a1 + a2 + a3 + a4 + a5 \geq 1$, and

10

each of L^1 , L^3 , and L^5 is independently selected from the group consisting of: -O-, -N(H)-, -N(R^d)-, S(O)₀₋₂, and -C(=O)-;

provided that when one or both of $a2$ and $a4$ is 0, then the combinations of L^1 , L^3 , and L^5 cannot form O-O, N-O, N-N, O-S, S-S, or N-S(O)₀ bonds, and

15

each of L^2 and L^4 is independently selected from the group consisting of:

- straight-chain C₁₋₆ alkylene, straight-chain C₂₋₆ alkenylene, or straight-chain C₂₋₆ alkynylene, each of which is optionally substituted with 1-6 R^b ;

20

- C₃₋₁₀ cycloalkylene or C₃₋₁₀ cycloalkenylene, each of which is optionally substituted with 1-3 R^c provided the C₃₋₁₀ cycloalkylene or C₃₋₁₀ cycloalkenylene is not directly connected to the 6-membered ring containing Y¹, Y², and Y³; and

25

- heterocyclylene or heterocycloalkenylene, each having 4-10 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), N(R^d), O, and S(O)₀₋₂, wherein the heterocyclylene or heterocycloalkenylene is optionally substituted with 1-3 R^c , provided the heterocyclylene or heterocycloalkenylene is not directly connected to the 6-membered ring containing Y¹, Y², and Y³;

Q^1 is $-R^g$;

Y^1 , Y^2 , and Y^3 are each independently selected from the group consisting of CR^1 ,
 5 C(=O), N, and NR^2 ;

X^1 is selected from the group consisting of O, S, N, NR^2 , and CR^1 ;

X^2 is selected from the group consisting of O, S, N, NR^4 , and CR^5 ;

each $\equiv$ is independently a single bond or a double bond, provided that the five-membered ring comprising X^1 and X^2 is heteroaryl, and that the six-membered ring
 10 comprising Y^1 , Y^2 , and Y^3 is aryl or heteroaryl;

further provided that L^A cannot include a cyclic group directly attached to the 6-membered ring containing Y^1 , Y^2 , and Y^3 ;

each occurrence of R^1 and R^5 is independently selected from the group consisting
 15 of: H; R^c ; R^g ; and $-(L^g)_{hg}-R^g$;

each occurrence of R^2 and R^4 is independently selected from the group consisting
 of: H; R^d ; R^g ; and $-(L^g)_{hg}-R^g$;

R^6 is selected from the group consisting of: H; R^d ; and R^g ;

20

W is selected from the group consisting of:

- H;
- C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl, each of which is optionally substituted with 1-6 R^{a2} , wherein one or more of the internal optionally substituted
 25 methylene group can be replaced by one or more heteroatom selected from O or S, wherein when W is alkenyl or alkynyl, the heteroatom is not directed connected to the sp^2 or sp carbon;
- monocyclic C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo
 30 and R^c ; and

- monocyclic heterocyclyl or heterocycloalkenyl of 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**,

provided that when **W** is heterocyclyl or heterocycloalkenyl, it is attached to the C(=O)NR⁶ group via a ring carbon atom;

- each occurrence of **R^a** and **R^{a2}** is independently selected from the group consisting of: -OH; -halo; -NR^eR^f; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -C(=O)O(C₁₋₄ alkyl); -C(=O)(C₁₋₄ alkyl); -C(=O)OH; -CONR'R''; -S(O)₁₋₂NR'R''; -S(O)₁₋₂(C₁₋₄ alkyl); and cyano;

- each occurrence of **R^b** and **R^c** is independently selected from the group consisting of: halo; cyano; C₁₋₁₀ alkyl which is optionally substituted with 1-6 independently selected **R^a**; C₂₋₆ alkenyl; C₂₋₆ alkynyl; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -S(O)₁₋₂(C₁₋₄ alkyl); -S(O)(=NH)(C₁₋₄ alkyl); -NR^eR^f; -OH; -S(O)₁₋₂NR'R''; -C₁₋₄ thioalkoxy; -NO₂; -C(=O)(C₁₋₁₀ alkyl); -C(=O)O(C₁₋₄ alkyl); -C(=O)OH; -C(=O)NR'R''; and -SF₅;

- each occurrence of **R^d** is independently selected from the group consisting of: C₁₋₆ alkyl optionally substituted with 1-3 independently selected **R^a**; -C(O)(C₁₋₄ alkyl); -C(O)O(C₁₋₄ alkyl); -CONR'R''; -S(O)₁₋₂NR'R''; -S(O)₁₋₂(C₁₋₄ alkyl); -OH; and C₁₋₄ alkoxy;

- each occurrence of **R^e** and **R^f** is independently selected from the group consisting of: H; C₁₋₆ alkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of NR'R'', -OH, halo, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy; -C(O)(C₁₋₄ alkyl); -C(O)O(C₁₋₄ alkyl); -CONR'R''; -S(O)₁₋₂NR'R''; -S(O)₁₋₂(C₁₋₄ alkyl); -OH; and C₁₋₄ alkoxy;

- each occurrence of **R^g** is independently selected from the group consisting of:

- C₃₋₁₂ cycloalkyl or C₃₋₁₂ cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, **R^c**, and **R^h**;
 - heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, **R^c**, and **R^h**;
 - heteroaryl of 5-12 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, **R^c**, and **R^h**; and
 - C₆₋₁₀ aryl optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, **R^c**, and **R^h**;
- each occurrence of **R^h** is independently selected from the group consisting of:
- C₃₋₁₂ cycloalkyl or C₃₋₁₂ cycloalkenyl, each of which is optionally substituted with 1-4 **Rⁱ**;
 - heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 **Rⁱ**;
 - heteroaryl of 5-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heteroaryl is optionally substituted with 1-4 **Rⁱ**; and
 - C₆₋₁₀ aryl optionally substituted with 1-4 **Rⁱ**;

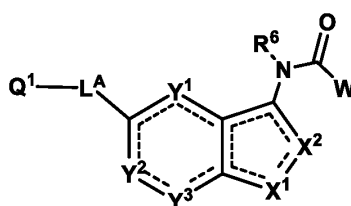
each occurrence of **Rⁱ** is independently selected from the group consisting of: C₁₋₆ alkyl; C₁₋₄ haloalkyl; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; and halo;

each occurrence of L^g is independently selected from the group consisting of: -O-, -NH-, -NR^d, -S(O)₀₋₂, C(O), and C₁₋₃ alkylene optionally substituted with 1-3 R^a;

each occurrence of **bg** is independently 1, 2, or 3; and

- 5 each occurrence of R' and R'' is independently selected from the group consisting of: H; -OH; and C₁₋₄ alkyl.

In still another aspect, this disclosure features A compound of Formula (I):



10 **Formula I**

or a pharmaceutically acceptable salt thereof or a tautomer thereof, wherein:

L^A is $-(L^1)_{a1}-(L^2)_{a2}-(L^3)_{a3}-(L^4)_{a4}-(L^5)_{a5}-*$, wherein * represents the point of attachment to Q¹;

a1, a2, a3, a4, and a5 are each independently 0 or 1,

- 15 provided that $a1 + a2 + a3 + a4 + a5 \geq 1$, and

each of L^1 , L^3 , and L^5 is independently selected from the group consisting of: -O-, -N(H)-, -N(R^d)-, S(O)₀₋₂, and -C(=O)-;

- 20 provided that when one or both of a2 and a4 is 0, then the combinations of L^1 , L^3 , and L^5 cannot form O-O, N-O, N-N, O-S, S-S, or N-S(O)₀ bonds, and

each of L^2 and L^4 is independently selected from the group consisting of:

- straight-chain C₁₋₆ alkylene, straight-chain C₂₋₆ alkenylene, or straight-chain C₂₋₆ alkynylene, each of which is optionally substituted with 1-6 R^b;
- 25 • C₃₋₁₀ cycloalkylene or C₃₋₁₀ cycloalkenylene, each of which is optionally substituted with 1-3 R^c provided the C₃₋₁₀ cycloalkylene or C₃₋₁₀ cycloalkenylene is not directly connected to the 6-membered ring containing Y¹, Y², and Y³; and

- heterocyclylene or heterocycloalkenylene, each having 4-10 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), N(R^d), O, and S(O)₀₋₂, wherein the heterocyclylene or heterocycloalkenylene is optionally substituted with 1-3 R^c, provided the heterocyclylene or heterocycloalkenylene is not directly connected to the 6-membered ring containing Y¹, Y², and Y³;

Q¹ is -R^g;

- Y¹, Y², and Y³ are each independently selected from the group consisting of CR¹, C(=O), N, and NR²;

X¹ is selected from the group consisting of O, S, N, NR², and CR¹;

X² is selected from the group consisting of O, S, N, NR⁴, and CR⁵;

- each $\equiv$ is independently a single bond or a double bond, provided that the five-membered ring comprising X¹ and X² is heteroaryl, and that the six-membered ring comprising Y¹, Y², and Y³ is aryl or heteroaryl;

further provided that L^A cannot include a cyclic group directly attached to the 6-membered ring containing Y¹, Y², and Y³;

- each occurrence of R¹ and R⁵ is independently selected from the group consisting of: H; R^c; R^g; and -(L^g)_{bg}-R^g;

each occurrence of R² and R⁴ is independently selected from the group consisting of: H; R^d; R^g; and -(L^g)_{bg}-R^g;

- R⁶ is selected from the group consisting of: H; R^d; and R^g;

W is selected from the group consisting of:

- H;
- C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl, each of which is optionally substituted with 1-6 R^{a2}, wherein one or more of the internal optionally substituted methylene group can be replaced by one or more heteroatom selected from O or S, wherein

when **W** is alkenyl or alkynyl, the heteroatom is not directed connected to the sp^2 or sp carbon;

- monocyclic C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**; and
- monocyclic heterocyclyl or heterocycloalkenyl of 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**,

provided that when **W** is heterocyclyl or heterocycloalkenyl, it is attached to the C(=O)NR⁶ group via a ring carbon atom;

- each occurrence of **R^a** and **R^{a2}** is independently selected from the group consisting of: -OH; -halo; -NR^eR^f; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -C(=O)O(C₁₋₄ alkyl); -C(=O)(C₁₋₄ alkyl); -C(=O)OH; -CONR'R''; -S(O)₁₋₂NR'R''; -S(O)₁₋₂(C₁₋₄ alkyl); and cyano;

- each occurrence of **R^b** and **R^c** is independently selected from the group consisting of: halo; cyano; C₁₋₁₀ alkyl which is optionally substituted with 1-6 independently selected **R^a**; C₂₋₆ alkenyl; C₂₋₆ alkynyl; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -S(O)₁₋₂(C₁₋₄ alkyl); -S(O)(=NH)(C₁₋₄ alkyl); -NR^eR^f; -OH; -S(O)₁₋₂NR'R''; -C₁₋₄ thioalkoxy; -NO₂; -C(=O)(C₁₋₁₀ alkyl); -C(=O)O(C₁₋₄ alkyl); -C(=O)OH; -C(=O)NR'R''; -NR'C(=O)(C₁₋₄ alkyl) and -SF₅;

- each occurrence of **R^d** is independently selected from the group consisting of: C₁₋₆ alkyl optionally substituted with 1-3 independently selected **R^a**; -C(O)(C₁₋₄ alkyl); -C(O)O(C₁₋₄ alkyl); -CONR'R''; -S(O)₁₋₂NR'R''; -S(O)₁₋₂(C₁₋₄ alkyl); -OH; and C₁₋₄ alkoxy;

- each occurrence of **R^e** and **R^f** is independently selected from the group consisting of: H; C₁₋₆ alkyl optionally substituted with 1-3 substituents each independently selected

from the group consisting of $\text{NR}'\text{R}''$, $-\text{OH}$, halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; $-\text{C}(\text{O})(\text{C}_{1-4} \text{ alkyl})$; $-\text{C}(\text{O})\text{O}(\text{C}_{1-4} \text{ alkyl})$; $-\text{CONR}'\text{R}''$; $-\text{S}(\text{O})_{1-2}\text{NR}'\text{R}''$; $-\text{S}(\text{O})_{1-2}(\text{C}_{1-4} \text{ alkyl})$; $-\text{OH}$; and C_{1-4} alkoxy;

- 5 each occurrence of $\text{R}^{\#}$ is independently selected from the group consisting of:
- C_{3-12} cycloalkyl or C_{3-12} cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, R^{c} , and R^{h} ;
 - heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring
10 atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^{d}), O, and $\text{S}(\text{O})_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, R^{c} , and R^{h} ;
 - heteroaryl of 5-12 ring atoms, wherein 1-4 ring atoms are heteroatoms,
15 each independently selected from the group consisting of N, N(H), N(R^{d}), O, and $\text{S}(\text{O})_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, R^{c} , and R^{h} ; and
 - C_{6-10} aryl optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, R^{c} , and R^{h} ;

20

each occurrence of R^{h} is independently selected from the group consisting of:

- C_{3-12} cycloalkyl or C_{3-12} cycloalkenyl, each of which is optionally substituted with 1-4 R^{i} ;
- heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring
25 atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^{d}), O, and $\text{S}(\text{O})_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 R^{i} ;
- heteroaryl of 5-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^{d}), O, and $\text{S}(\text{O})_{0-2}$,
30 and wherein the heteroaryl is optionally substituted with 1-4 R^{i} ; and
- C_{6-10} aryl optionally substituted with 1-4 R^{i} ;

each occurrence of R^i is independently selected from the group consisting of: C₁₋₆ alkyl; C₁₋₄ haloalkyl; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; and halo;

5 each occurrence of L^g is independently selected from the group consisting of: -O-, -NH-, -NR^d, -S(O)₀₋₂, C(O), and C₁₋₃ alkylene optionally substituted with 1-3 R^a ;

each occurrence of bg is independently 1, 2, or 3; and

10 each occurrence of R' and R'' is independently selected from the group consisting of: H; -OH; and C₁₋₄ alkyl.

15 **Variable L^A $-(L^1)_{a1}-(L^2)_{a2}-(L^3)_{a3}-(L^4)_{a4}-(L^5)_{a5}^*$, wherein * represents the point of attachment to Q^1**

In some embodiments, L^A is a divalent moiety having a 1-6 (e.g., 2-6 (e.g., 2, 3, or 4)) linear array of substituted or unsubstituted carbon and/or heteroatoms. In some embodiments, L^A is a divalent moiety having a combination of a cyclic moiety and a 1-6 (e.g., 2-6 (e.g., 2, 3, or 4)) linear array of substituted or unsubstituted carbon and/or heteroatoms. For example, one cyclic moiety (e.g., C₃₋₆, e.g., C₄ cycloalkylene), and an acyclic moiety (e.g., O).

In some embodiments, provided that when $a3$ is 0; and $a4$ is 1, then L^4 is other than straight-chain C₁₋₆ alkylene, straight-chain C₂₋₆ alkenylene, or straight-chain C₂₋₆ alkynylene, each of which is optionally substituted with 1-6 R^b ;

25 In some embodiments, $a2$ is 1. In some embodiments, $a2$ is 0.

In certain embodiments (when $a2$ is 1), L^2 is straight-chain C₁₋₆ alkylene, straight-chain C₂₋₆ alkenylene, or straight-chain C₂₋₆ alkynylene, each of which is optionally substituted with 1-6 R^b .

30 In certain of the foregoing embodiments, L^2 is straight-chain C₁₋₆ alkylene, which is optionally substituted with 1-6 R^b .

In certain of the foregoing embodiments, L^2 is straight-chain C_{1-3} alkylene, which is optionally substituted with 1-3 R^b .

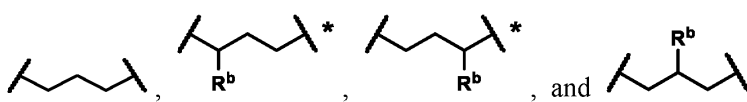
In certain embodiments, L^2 is selected from the group consisting of: $-CH_2-$, $-CHR^b-$, and $-C(R^b)_2-$. For example, L^2 can be $-CH_2-$.

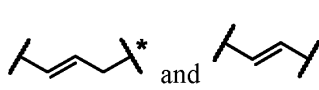
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In certain embodiments (when L^2 is straight-chain C_{1-6} alkylene, which is optionally substituted with 1-6 R^b), L^2 is straight-chain C_{2-3} alkylene which is optionally substituted with 1-3 R^b .

10 In certain of these embodiments, L^2 is straight-chain C_2 alkylene which is optionally substituted with 1-3 R^b . In certain of the foregoing embodiments, L^2 is selected from the group consisting of: $-CH_2CH_2-$, $-CH_2CH(R^b)-*$, and $-CH_2C(R^b)_2-*$, wherein the asterisk represents point of attachment to $-(L^3)_{a3}-$. For example, L^2 can be $-CH_2CH_2-$.

In certain embodiments, L^2 is straight-chain C_3 alkylene which is optionally substituted with 1-3 R^b . For example, L^2 can be selected from the group consisting of:

15 , wherein the asterisk represents point of attachment to $-(L^3)_{a3}-$.

In certain embodiments (when a_2 is 1), L^2 is straight-chain C_{2-6} alkenylene, which is optionally substituted with 1-6 R^b . In certain of these embodiments, L^2 is straight-chain
20 C_{2-4} alkenylene, which is optionally substituted with 1-3 R^b . For example, L^2 can be selected from the group consisting of: , wherein the asterisk represents the point of attachment to $-(L^3)_{a3}-$.

25 In certain embodiments (when a_2 is 1), L^2 is selected from the group consisting of:

- C_{3-10} cycloalkylene or C_{3-10} cycloalkenylene, each of which is optionally substituted with 1-3 R^c ; and

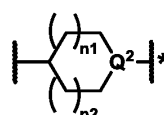
- heterocyclylene or heterocycloalkenylene, each having 4-10 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group

consisting of: N, N(H), N(R^d), O, and S(O)₀₋₂, wherein the heterocyclene or heterocycloalkenylene is optionally substituted with 1-3 R^c.

In certain of these embodiments, L² is selected from the group consisting of:

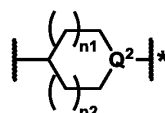
- 5 • C₃₋₈ cycloalkylene, which is optionally substituted with 1-3 R^c; and
- heterocyclene having 4-8 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), N(R^d), O, and S(O)₀₋₂, wherein the heterocyclene is optionally substituted with 1-3 R^c.

10

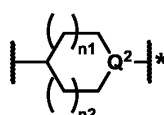


In certain of the foregoing embodiments, L² is: which is optionally substituted with 1-2 R^c, wherein n₁ and n₂ are independently 0, 1, or 2; Q² is CH, CR^c, or N; and the asterisk represents the point of attachment to -(L³)_{a3}.

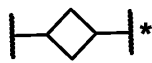
In certain of these embodiments, Q² is CH.



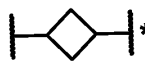
- 15 In certain embodiments (when L² is: as defined *supra*), n₁ and n₂ are each 0.



As a non-limiting example (when L² is: as defined *supra*), L² can be



, wherein the asterisk represents the point of attachment to -(L³)_{a3} or -(L¹)_{a1},

e.g., -(L¹)_{a1}, in which a₁ is 1. For example, L² can be , wherein the asterisk represents the point of attachment to -(L¹)_{a1}. In certain of these embodiments, -(L¹)_{a1} is O.

20

In certain of the foregoing embodiments, each of a₃, a₄, and a₅ is 0.

In some embodiments, **a1** is 1. In some embodiments, **a1** is 0.

In certain embodiments (when **a1** is 1), **L¹** is selected from the group consisting of: -O-, -N(H)-, -N(**R^d**)-, and -S-. In certain of these embodiments, **L¹** is -O-.

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In some embodiments, **a3** is 1. In some embodiments, **a3** is 0.

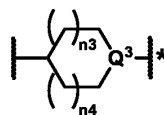
In certain embodiments (when **a3** is 1), **L³** is selected from the group consisting of: -O-, -N(H)-, -N(**R^d**)-, and -S-. In certain of these embodiments, **L³** is -O-. In certain other
10 embodiments, **L³** is -N(H)- or -N(**R^d**)- (e.g., -N(H)-).

In some embodiments, **a4** is 1. In some embodiments, **a4** is 0.

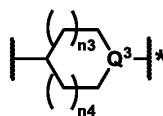
In certain embodiments (when **a4** is 1), **L⁴** is straight-chain C₁₋₃ alkylene, which is
15 optionally substituted with 1-3 **R^b**. In certain of these embodiments, **L⁴** is -CH₂-.

In certain embodiments (when **a4** is 1), **L⁴** is selected from the group consisting of:

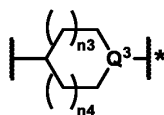
- C₃₋₈ cycloalkylene, which is optionally substituted with 1-3 **R^c**; and
- heterocyclylene having 4-8 ring atoms wherein 1-3 ring atoms are ring
20 heteroatoms each independently selected from the group consisting of: N, N(H), N(**R^d**), O, and S(O)₀₋₂, wherein the heterocyclylene is optionally substituted with 1-3 **R^c**.



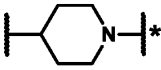
In certain of these embodiments, **L⁴** is: which is optionally
substituted with 1-2 **R^c**, wherein **n3** and **n4** are independently 0, 1, or 2; **Q³** is CH, **CR^c**, or
25 N; and the asterisk represents the point of attachment to -(**L⁵**)_{a5}-.



In certain embodiments (when **L⁴** is:), **n3** and **n4** are each 1. In



certain embodiments (when **L⁴** is:), **Q³** is N.

As a non-limiting example of the foregoing embodiments, L^4 can be , wherein the asterisk represents the point of attachment to $-(L^5)_{a5}-$.

In some embodiments, $a5$ is 0.

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Non-Limiting Combinations of $-(L^1)_{a1}-(L^2)_{a2}-(L^3)_{a3}-(L^4)_{a4}-(L^5)_{a5}-^*$

In some embodiments, $-(L^1)_{a1}-(L^2)_{a2}-(L^3)_{a3}-(L^4)_{a4}-(L^5)_{a5}-^*$ has a length of from 1 atom to 8 atoms (as used here and for counting purposes only, moieties such as CH_2 , $C(O)$, CF_2 and the like, whether present in acyclic or cyclic moieties, count as 1 atom); e.g., from 1 atom to 6 atoms, or from 1 atom to 5 atoms, or from 1 atom to 4 atoms; or from from 1 atom to 3 atoms; or from 2 atoms to 6 atoms; or from 2 atoms to 4 atoms.

10

In certain embodiments, one of $a1$, $a3$, and $a5$ is 1, and the other two of $a1$, $a3$, and $a5$ are 0. In certain embodiments, $a1$ is 1, e.g., when L^2 is a cyclic group (e.g., cycloalkylene).

15

In certain embodiments, one of $a2$ and $a4$ is 1, and the other of $a2$ and $a4$ is 0 or 1.

In certain of the foregoing embodiments,

one of $a1$, $a3$, and $a5$ is 1, and the other two of $a1$, $a3$, and $a5$ are 0; and

20

one of $a2$ and $a4$ is 1, and the other of $a2$ and $a4$ is 0 or 1.

In certain embodiments, $1 \leq a1+a2+a3+a4+a5 \leq 4$. In certain of these embodiments, $1 \leq a1+a2+a3+a4+a5 \leq 3$.

25

In certain embodiments, $a1$ and $a2$ are each 1.

[AA1] In certain embodiments,

$a1$ and $a2$ are each 1;

L^1 is $-O-$, $-N(H)-$, or $-N(R^d)-$;

L^2 is selected from the group consisting of:

- straight-chain C_{1-3} alkylene, which is optionally substituted with 1-3 R^b ;
 - C_{3-8} cycloalkylene, which is optionally substituted with 1-3 R^c ; and
 - heterocyclylene having 4-8 ring atoms wherein 1-3 ring atoms are ring
- 5 heteroatoms each independently selected from the group consisting of: N, N(H), N(R^d), O, and S(O)₀₋₂, wherein the heterocyclylene is optionally substituted with 1-3 R^c .

[AA2] In certain embodiments,

$a1$ and $a2$ are each 1;

10 L^1 is $-O-$; and

L^2 is straight-chain C_{1-3} alkylene, which is optionally substituted with 1-3 R^b .

[AA3] In certain embodiments,

$a1$ and $a2$ are each 1;

15 L^1 is $-O-$; and

L^2 is selected from the group consisting of: $-CH_2-$, $-CHR^b-$, and $-C(R^b)_2-$.

[AA4] In certain embodiments,

$a1$ and $a2$ are each 1;

20 L^1 is $-O-$; and

L^2 is straight-chain C_{2-3} alkylene which is optionally substituted with 1-3 R^b .

In certain embodiments of [AA4], L^2 is straight-chain C_2 alkylene which is optionally substituted with 1-3 R^b . As non-limiting examples of the foregoing

25 embodiments, L^2 can be selected from the group consisting of: $-CH_2CH_2-$, $-CH_2CH(R^b)-$, $-CH_2CH(R^b)-^*$, and $-CH_2C(R^b)_2-^*$, wherein the asterisk represents point of attachment to $-(L^3)_{a3}-$. For example, L^2 can be $-CH_2CH_2-$.

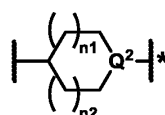
[AA5] In certain embodiments,

30 $a1$ and $a2$ are each 1;

L^1 is $-O-$;

L^2 is selected from the group consisting of:

- C_{3-8} cycloalkylene, which is optionally substituted with 1-3 R^c ; and
- heterocyclylene having 4-8 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), N(R^d), O, and S(O)₀₋₂, wherein the heterocyclylene is optionally substituted with 1-3 R^c .



In certain embodiments of [AA5], L^2 is: which is optionally substituted with 1-2 R^c , wherein $n1$ and $n2$ are independently 0, 1, or 2; Q^2 is CH, CR^c , or N; and the asterisk represents the point of attachment to $-(L^3)_{a3}-$.

In certain of these embodiments, $n1$ and $n2$ are independently 0 or 1, optionally 0; and Q^2 is CH. For example, $n1$ and $n2$ can both be 0; and Q^2 can be CH, e.g., L^2 can be optionally substituted cyclobutane-diyl, e.g., optionally substituted cyclobutane-1,3-diyl.

In certain embodiments when $a1$ and $a2$ are each 1, $a3$, $a4$, and $a5$ are each 0.

In certain embodiments of [AA1], $a3$, $a4$, and $a5$ are each 0. In certain embodiments of [AA2], $a3$, $a4$, and $a5$ are each 0. In certain embodiments of [AA3], $a3$, $a4$, and $a5$ are each 0. In certain embodiments of [AA4], $a3$, $a4$, and $a5$ are each 0. In certain embodiments of [AA5], $a3$, $a4$, and $a5$ are each 0.

In certain embodiments when $a1$ and $a2$ are each 1, $a3$ and $a5$ are 0; and $a4$ is 1.

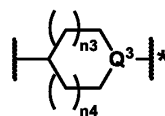
In certain embodiments of [AA1], $a3$ and $a5$ are 0; and $a4$ is 1. In certain embodiments of [AA2], $a3$ and $a5$ are 0; and $a4$ is 1. In certain embodiments of [AA3], $a3$ and $a5$ are 0; and $a4$ is 1. In certain embodiments of [AA4], $a3$ and $a5$ are 0; and $a4$ is 1. In certain embodiments of [AA5], $a3$ and $a5$ are 0; and $a4$ is 1.

In certain embodiments (when $a1$ and $a2$ are each 1, $a3$ and $a5$ are 0; and $a4$ is 1), L^4 is selected from the group consisting of:

- C_{3-8} cycloalkylene, which is optionally substituted with 1-3 R^c ; and

• heterocyclylene having 4-8 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), N(R^d), O, and S(O)₀₋₂, wherein the heterocyclylene is optionally substituted with 1-3 R^c.

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In certain of these embodiments, L⁴ is: which is optionally substituted with 1-2 R^c, wherein n₃ and n₄ are independently 0, 1, or 2; Q³ is CH, CR^c, or N; and the asterisk represents the point of attachment to -(L⁵)_{a5}-. In certain of the foregoing embodiments, n₃ and n₄ are independently 0 or 1; and Q³ is N.

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In certain embodiments, a₁ is 0; and a₂ is 1.

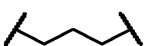
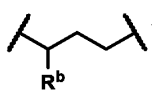
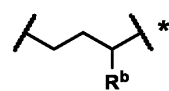
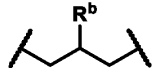
[BB1] In certain embodiments, a₁ is 0; a₂ is 1; and L² is straight-chain C₁₋₆ alkylene, which is optionally substituted with 1-6 R^b.

In certain embodiments of [BB1], L² is straight-chain C₁₋₃ alkylene, which is optionally substituted with 1-3 R^b. In certain of the foregoing embodiments, L² is selected from the group consisting of: -CH₂-, -CHR^b-, and -C(R^b)₂-. For example, L² can be -CH₂-.

In certain embodiments of [BB1], L² is straight-chain C₂₋₃ alkylene which is optionally substituted with 1-3 R^b. In certain of the foregoing embodiments, L² is straight-chain C₂ alkylene, which is optionally substituted with 1-3 R^b. As non-limiting examples, L² can be selected from the group consisting of: -CH₂CH₂-, -CH₂CH(R^b)-*, and -CH₂C(R^b)₂-, wherein the asterisk represents point of attachment to -(L³)_{a3}-. For example, L² can be -CH₂CH₂-.

In certain embodiments of [BB1], L² is straight-chain C₃ alkylene, which is optionally substituted with 1-3 R^b. In certain of these embodiments, L² is selected from the

25

group consisting of: , , , and , wherein the asterisk represents point of attachment to -(L³)_{a3}-.

In certain embodiments (when **a1** is 0; and **a2** is 1), **a3** is 0; and **a4** is 0.

In certain embodiments of [BB1], **a3** is 0; and **a4** is 0.

5 In certain embodiments (when **a1** is 0; and **a2** is 1), **a3** is 1. In certain embodiments of [BB1], **a3** is 1.

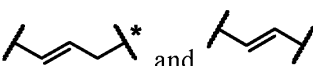
In certain embodiments (when **a1** is 0; and **a2** is 1) or in certain embodiments of [BB1], **a3** is 1; and **L³** is selected from the group consisting of: is -O-, -N(H)-, and -N(**R^d**)-. In certain of these embodiments, **a3** is 1; and **L³** is -O-. In certain other embodiments,
10 **a3** is 1; and **L³** is -N(H)- or -N(**R^d**)-, optionally -N(H)-.

In certain embodiments (when **a1** is 0; and **a2** is 1) or in certain embodiments of [BB1], **a4** is 1; and **L⁴** is straight-chain C₁₋₃ alkylene, which is optionally substituted with 1-3 **R^b**. In certain of these embodiments, **a4** is 1; and **L⁴** is -CH₂-.

In certain embodiments (when **a1** is 0; and **a2** is 1) or in certain embodiments of
15 [BB1], **a4** is 0.

[CC1] In certain embodiments, **a1** is 0; **a2** is 1; **L²** is straight-chain C₂₋₄ alkenylene, which is optionally substituted with 1-3 **R^b**.

In certain embodiments of [CC1], **L²** is selected from the group consisting of:

20 , wherein the asterisk represents the point of attachment to -
(**L³**)_{a3}-.

In certain embodiments of [CC1], **a3** is 0; and **a4** is 0.

For the avoidance of doubt when any one or more of **a1**, **a2**, **a3**, **a4**, and **a5** are 0,
25 this means that the corresponding variable (**L¹-L⁵**) is absent from **L^A**. For example, when each of **a3**, **a4**, and **a5** are 0, this means that **L^A** has the formula -**L¹-L²**-.

In certain embodiments, **L^A** is -**L¹-L²**-.

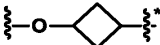
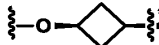
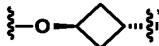
In certain embodiments, **L^A** is -**L²-L³**-.

30 In certain embodiments, **L^A** is -**L²-L³-L⁴**-.

In certain embodiments, L^A can be $-\text{CH}_2\text{CH}_2-\text{O}-*$, wherein $*$ represents the point of attachment to Q^1 .

In certain embodiments, L^A can be $-\text{O}-\text{CH}_2\text{CH}_2-$, wherein $*$ represents the point of attachment to Q^1 .

In certain embodiments, L^A can be $-\text{CH}_2-\text{O}-\text{CH}_2-$.

In certain embodiments, L^A can be  (such as  or ) , wherein $*$ represents the point of attachment to Q^1 .

Variable Q^1

In some embodiments, Q^1 is selected from the group consisting of:

- heteroaryl of 5-12 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heteroaryl is optionally substituted with 1-4 R^c ; and
- C₆₋₁₀ aryl optionally substituted with 1-4 R^c .

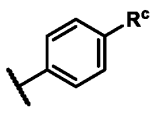
In certain of these embodiments, Q^1 is selected from the group consisting of:

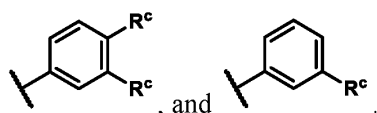
- heteroaryl of 5-6 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heteroaryl is optionally substituted with 1-3 R^c ; and
- phenyl optionally substituted with 1-3 R^c .

In certain of the foregoing embodiments, Q^1 is selected from the group consisting of:

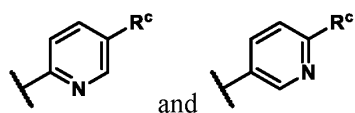
- heteroaryl of 6 ring atoms, wherein 1-2 ring atoms are ring nitrogen atoms, and wherein the heteroaryl is optionally substituted with 1-3 R^c ; and
- phenyl optionally substituted with 1-3 R^c .

In certain embodiments, Q^1 is phenyl optionally substituted with 1-3 R^c . In certain

of these embodiments, Q^1 is selected from the group consisting of: ,



5 In certain embodiments, Q^1 is heteroaryl of 6 ring atoms, wherein 1-2 ring atoms are ring nitrogen atoms, and wherein the heteroaryl is optionally substituted with 1-3 R^c . In certain of these embodiments, Q^1 is pyridyl, which is optionally substituted with 1-3 R^c . In certain of the foregoing embodiments, Q^1 is selected from the group consisting of:



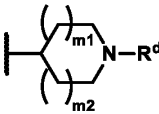
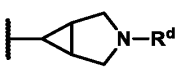
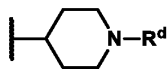
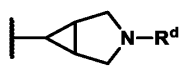
10

In certain embodiments, Q^1 is heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c .

15 In certain of these embodiments, Q^1 is heterocyclyl of 4-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heterocyclyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c .

20 In certain of the foregoing embodiments, Q^1 is heterocyclyl of 4-8 ring atoms, wherein 1-2 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, provided that one ring atom is N(R^d),

25 and wherein the heterocyclyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c .

As non-limiting examples of the foregoing embodiments, Q^1 can be  or , wherein $m1$ and $m2$ are each independently 0, 1, or 2; and wherein Q^1 is optionally substituted with 1-2 R^c . For example, Q^1 can be . As another non-limiting example, Q^1 can be .

5

In certain embodiments, each R^d present in Q^1 is independently selected from the group consisting of: $-C(O)O(C_{1-4} \text{ alkyl})$; and C_{1-6} alkyl optionally substituted with 1-3 independently selected R^a .

10 In certain of the foregoing embodiments, each R^d present in Q^1 is C_{1-6} alkyl optionally substituted with 1-3 independently selected halo.

In certain of the foregoing embodiments, each R^d present in Q^1 is C_{1-4} alkyl substituted with 1-3 $-F$. In certain embodiments, each R^d present in Q^1 is C_{2-3} alkyl substituted with 1-3 $-F$. For example, each R^d present in Q^1 can be $-CH_2CF_3$.

15 In certain embodiments, each R^c present in Q^1 is independently selected from the group consisting of: halo; cyano; C_{1-4} alkoxy; C_{1-4} haloalkoxy; and C_{1-10} alkyl which is optionally substituted with 1-6 independently selected R^a .

In certain embodiments, each R^c present in Q^1 is independently selected from the group consisting of: halo; cyano; C_{1-4} alkoxy; C_{1-4} haloalkoxy; and C_{1-6} alkyl which is optionally substituted with 1-6 independently selected halo.

20 In certain of the foregoing embodiments, each R^c present in Q^1 is independently selected from the group consisting of: halo and C_{1-3} alkyl which is optionally substituted with 1-6 independently selected halo.

In certain embodiments, each R^c present in Q^1 is C_{1-3} alkyl which is optionally substituted with 1-6 $-F$. For example, each R^c present in Q^1 can be CF_3 .

25 In certain embodiments, each R^c present in Q^1 is an independently selected halo (e.g., $-F$ or $-Cl$).

Variables Y^1 , Y^2 , Y^3 , X^1 , and X^2

In some embodiments, Y^1 is CR^1 .

In some embodiments, Y^2 is CR^1 .

5 In some embodiments, Y^3 is CR^1 .

In certain embodiments, each occurrence of R^1 is independently H or R^c . In certain of these embodiments, each occurrence of R^1 is H.

10 In certain other embodiments, 1-2 occurrence of R^1 is R^c ; and each remaining occurrence of R^1 is H. For example, one occurrence of R^1 can be halo (e.g., -F or -Cl); and each remaining occurrence of R^1 can be H.

In certain embodiments, Y^1 , Y^2 , and Y^3 are each independently selected CR^1 .

15 In certain embodiments, Y^1 , Y^2 , and Y^3 are each CH.

In certain embodiments, one of Y^1 , Y^2 , and Y^3 is CR^c , optionally C-halo; and each of the remaining two Y^1 , Y^2 , and Y^3 is CH.

In some embodiments, X^1 is NR^2 . In certain of these embodiments, X^1 is NH.

20 In some embodiments, X^2 is CR^5 . In certain of these embodiments, X^2 is CH.

In certain embodiments, X^1 is NR^2 ; and X^2 is CR^5 . In certain of the foregoing embodiments, X^1 is NH; and X^2 is CH.

25 In certain embodiments, Y^1 , Y^2 , and Y^3 are each an independently selected CR^1 ; X^1 is NR^2 ; and X^2 is CR^5 . In certain of the foregoing embodiments, Y^1 , Y^2 , and Y^3 are each CH; X^1 is NH; and X^2 is CH.

Variables R^6 and W

30 In some embodiments, R^6 is H.

In some embodiments, **W** is C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkenyl, each of which is optionally substituted with 1-6 **R**^{a2}.

In certain of these embodiments, **W** is C₁₋₁₀ alkyl, which is optionally substituted with 1-6 **R**^{a2}. In certain of the foregoing embodiments, **W** is C₁₋₆ alkyl, which is optionally substituted with 1-6 **R**^{a2}.

In certain embodiments, **W** is C₁₋₄ alkyl, which is optionally substituted with 1-6 **R**^{a2}.

In certain of the foregoing embodiments, **W** is unsubstituted C₁₋₄ alkyl. As non-limiting examples of the foregoing embodiments, **W** can be selected from the group consisting of: methyl, ethyl, n-propyl, isopropyl, and isobutyl. For example, **W** can be methyl or ethyl.

In some embodiments, **W** is C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkenyl, each of which is optionally substituted with 1-6 **R**^{a2}, wherein one or more of the internal optionally substituted methylene group is replaced by one or more heteroatom selected from O or S, wherein when **W** is alkenyl or alkynyl, the heteroatom is not directed connected to the *sp*² or *sp* carbon;

In certain embodiments, **W** is C₁₋₄ alkyl, which is optionally substituted with 1-6 **R**^{a2}, wherein one or more of the internal optionally substituted methylene group is replaced by one or more heteroatom selected from O or S, wherein when **W** is alkenyl or alkynyl, the heteroatom is not directed connected to the *sp*² or *sp* carbon;

In certain embodiments, **W** is C₁₋₄ alkyl, which is optionally substituted with one **R**^{a2}, wherein one or more of the internal methylene group is replaced by O.

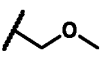
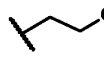
In certain embodiments, **W** is -CH₂-O-(CH₂)₂-OCH₃.

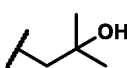
In certain embodiments, **W** is C₁₋₄ alkyl, which is substituted with 1-6 **R**^{a2}.

In certain of these embodiments, each **R**^{a2} is independently selected from the group consisting of: -OH; -halo; -NR^cR^f; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -C(=O)O(C₁₋₄ alkyl); -

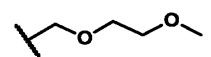
C(=O)(C₁₋₄ alkyl); and cyano. For example, each **R^{a2}** can be independently selected from the group consisting of halo; -OH; C₁₋₄ alkoxy; and C₁₋₄ haloalkoxy.

In certain embodiments, **W** is C₁₋₄ alkyl which is substituted with 1-3 substituents
 5 each independently selected from the group consisting of: halo; -OH; C₁₋₄ alkoxy; and C₁₋

4 haloalkoxy. As non-limiting examples, **W** can be , , 

, and .

As another non-limiting example of the foregoing embodiments, **W** can be



10

In some embodiments, **W** is selected from the group consisting of:

- monocyclic C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**; and
- monocyclic heterocyclyl or heterocycloalkenyl of from 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected
 20 from the group consisting of oxo and **R^c**.

In certain of the foregoing embodiments, **W** is monocyclic C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**.

25 In certain of these embodiments, **W** is monocyclic C₃₋₈ cycloalkyl, which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**.

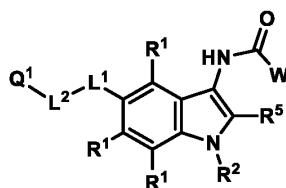
In certain embodiments, **W** is unsubstituted C₃₋₈ cycloalkyl. As non-limiting examples of the foregoing embodiments, **W** can be cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. For example, **W** can be cyclobutyl.

30

In some embodiments, **W** is H.

5 Non-Limiting Combinations

In certain embodiments, the compound is a compound of Formula **(I-a)**:



Formula **(I-a)**

or a pharmaceutically acceptable salt thereof, wherein:

10 **L¹** is selected from the group consisting of: -O-, -N(H)-, and -N(**Rᵈ**)-;

L² is selected from the group consisting of:

- straight-chain C₁₋₃ alkylene, which is optionally substituted with 1-3 **Rᵇ**;
- C₃₋₈ cycloalkylene, which is optionally substituted with 1-3 **Rᶜ**; and
- heterocyclylene having 4-8 ring atoms wherein 1-3 ring atoms are ring

15 heteroatoms each independently selected from the group consisting of: N, N(H), N(**Rᵈ**), O, and S(O)₀₋₂, wherein the heterocyclylene is optionally substituted with 1-3 **Rᶜ**.

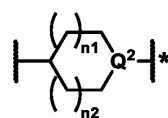
In certain embodiments of Formula **(I-a)**, **L¹** is -O-.

20 In certain embodiments of Formula **(I-a)**, **L²** is straight-chain C₁₋₃ alkylene, which is optionally substituted with 1-3 **Rᵇ**.

In certain embodiments of Formula **(I-a)**, **L²** is selected from the group consisting of: -CH₂-, -CH**Rᵇ**-, and -C(**Rᵇ**)₂-, optionally wherein **L²** is -CH₂-.

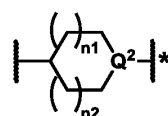
In certain embodiments of Formula **(I-a)**, **L²** is straight-chain C₂ alkylene which is optionally substituted with 1-3 **Rᵇ**. In certain of these embodiments, **L²** is selected from the group consisting of: -CH₂CH₂-, -CH₂CH(**Rᵇ**)-*, and -CH₂C(**Rᵇ**)₂-, wherein the asterisk
25 represents point of attachment to -**Q¹**. For example, **L²** can be -CH₂CH₂-.

In certain embodiments of Formula (I-a), L^2 is straight-chain C_3 alkylene which is optionally substituted with 1-3 R^b .



In certain embodiments of Formula (I-a), L^2 is: which is optionally substituted with 1-2 R^c , wherein n_1 and n_2 are independently 0, 1, or 2; Q^2 is CH, CR^c , or N; and the asterisk represents the point of attachment to Q^1 .

In certain of these embodiments, n_1 and n_2 are independently 0 or 1, optionally 0; and Q^2 is CH. For example, n_1 and n_2 can both be 0; and Q^2 can be CH, e.g., L^2 can be optionally substituted cyclobutane-diyl, e.g., optionally substituted cyclobutane-1,3-diyl.



In certain embodiments of Formula (I-a), L^1 is $-O-$; and L^2 is: which is optionally substituted with 1-2 R^c , wherein n_1 and n_2 are independently 0 or 1, optionally 0; and Q^2 is CH. For example, n_1 and n_2 can both be 0; and Q^2 can be CH, e.g., L^2 can be optionally substituted cyclobutane-diyl, e.g., optionally substituted 1,3-cyclobutane-1,3-diyl, e.g., unsubstituted cyclobutane-diyl, e.g., unsubstituted cyclobutane-1,3-diyl.

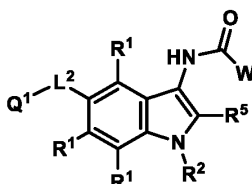
In certain embodiments of Formula (I-a), L^1 is $-O-$; and L^2 is straight-chain C_{2-3} alkylene which is optionally substituted with 1-3 R^b .

In certain of the foregoing embodiments of Formula (I-a), L^2 is straight-chain C_2 alkylene which is optionally substituted with 1-3 R^b .

In certain of the foregoing embodiments, L^2 is selected from the group consisting of: $-CH_2CH_2-$, $-CH_2CH(R^b)-*$, and $-CH_2C(R^b)_2-*$, wherein the asterisk represents point of attachment to Q^1 . For example, L^2 can be $-CH_2CH_2-$.

In certain embodiments of Formula (I-a), L^1 is $-O-$; and L^2 is selected from the group consisting of: $-CH_2-$, $-CHR^b-$, and $-C(R^b)_2$. For example, L^2 can be $-CH_2-$.

5 In certain embodiments, the compound is a compound of Formula (I-b):



Formula (I-b)

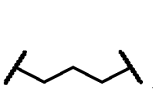
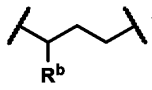
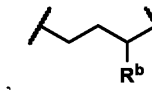
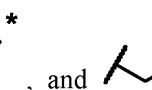
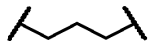
or a pharmaceutically acceptable salt thereof, wherein:

L^2 is straight-chain C_{1-6} alkylene or straight-chain C_{2-6} alkenylene, each of which
10 is optionally substituted with 1-6 R^b .

In certain embodiments of Formula (I-b), L^2 is straight-chain C_{2-3} alkylene which is optionally substituted with 1-3 R^b .

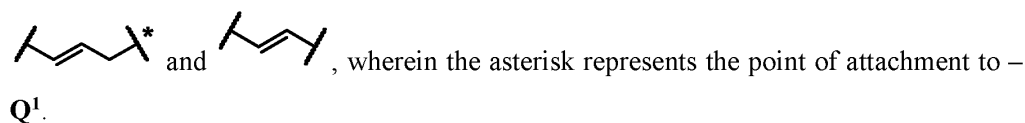
In certain embodiments of Formula (I-b), L^2 is straight-chain C_2 alkylene which is
15 optionally substituted with 1-3 R^b . In certain of these embodiments, L^2 is selected from the group consisting of: $-CH_2CH_2-$, $-CH_2CH(R^b)-^*$, and $-CH_2C(R^b)_2-^*$, wherein the asterisk represents point of attachment to $-Q^1$. For example, L^2 can be $-CH_2CH_2-$.

In certain embodiments of Formula (I-b), L^2 is straight-chain C_3 alkylene which is optionally substituted with 1-3 R^b . In certain of these embodiments, L^2 is selected from the

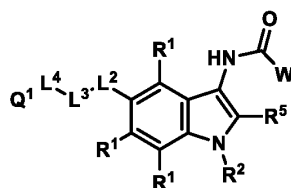
20 group consisting of: , , , and , wherein the asterisk represents point of attachment to $-Q^1$. For example, L^2 can be .

In certain embodiments of Formula (I-b), L^2 is straight-chain C_{2-4} alkenylene,
25 which is optionally substituted with 1-3 R^b .

In certain of these embodiments, L^2 is selected from the group consisting of:



5 In certain embodiments, the compound is a compound of Formula (I-c):



Formula (I-c)

or a pharmaceutically acceptable salt thereof, wherein:

L^2 and L^4 are independently selected straight-chain C_{1-3} alkylene which is
10 optionally substituted with 1-6 R^b ; and

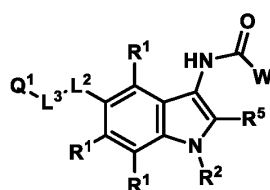
L^3 is selected from the group consisting of: -O-, -N(H)-, and -N(R^d)-.

In certain embodiments of Formula (I-c), L^2 and L^4 are independently selected from
the group consisting of: -CH₂-, -CHR^b-, and -C(R^b)₂-. In certain of these embodiments, L^2
15 and L^4 are each -CH₂-.

In certain embodiments of Formula (I-c), L^3 is -O-.

In certain embodiments of Formula (I-c), L^3 is -N(H)- or -N(R^d)-. For example,
 L^3 can be -N(H)-.

20 In certain embodiments, the compound is a compound of Formula (I-d):



Formula (I-d)

or a pharmaceutically acceptable salt thereof, wherein:

L^2 is straight-chain C_{1-3} alkylene which is optionally substituted with 1-6 R^b ; and

L^3 is selected from the group consisting of: -O-, -N(H)-, and -N(R^d)-.

In certain embodiments of Formula (I-d), L^2 is selected from the group consisting of: -CH₂-, -CHR^b-, and -C(R^b)₂.

5 In certain embodiments of Formula (I-d), L^2 is straight-chain C₂ alkylene which is optionally substituted with 1-3 R^b . In certain of these embodiments, L^2 is selected from the group consisting of: -CH₂CH₂-, -CH₂CH(R^b)-*, and -CH₂C(R^b)₂-, wherein the asterisk represents point of attachment to - L^3 . For example, L^2 can be -CH₂CH₂-.

In certain embodiments of Formula (I-d), L^3 is -O-.

10 In certain embodiments of Formula (I-d), L^3 is -N(H)- or -N(R^d)-. For example, L^3 can be -N(H)-.

In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), Q^1 is selected from the group consisting of:

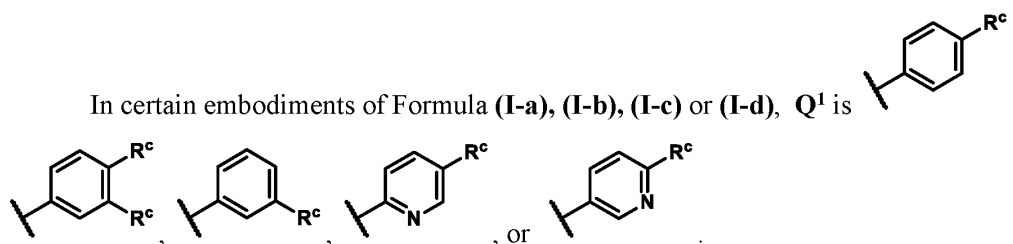
- 15
- heteroaryl of 5-6 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heteroaryl is optionally substituted with 1-3 R^c ; and
 - phenyl optionally substituted with 1-3 R^c .

20 In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), Q^1 is selected from the group consisting of:

- heteroaryl of 6 ring atoms, wherein 1-2 ring atoms are ring nitrogen atoms, and wherein the heteroaryl is optionally substituted with 1-3 R^c ; and
- phenyl optionally substituted with 1-3 R^c .

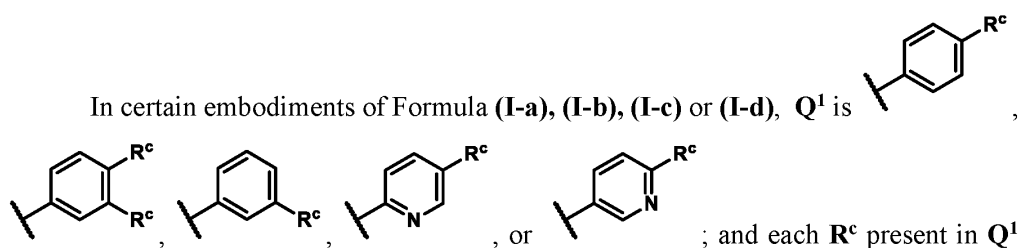
25

In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), Q^1 is phenyl or pyridyl, each optionally substituted with 1-3 R^c .



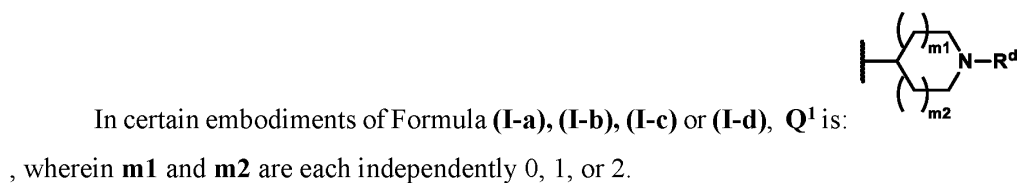
In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), Q^1 is phenyl or pyridyl, each optionally substituted with 1-3 R^c ,

5 wherein each R^c present in Q^1 is independently selected from the group consisting of: halo and C_{1-3} alkyl which is optionally substituted with 1-6 independently selected halo.



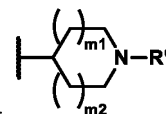
10 is independently selected from the group consisting of: -F, -Cl, and $-CF_3$.

In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), Q^1 is heterocyclyl of 4-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heterocyclyl
15 is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c .



20 In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), Q^1 is





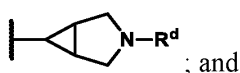
In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), Q^1 is:

; and

the R^d present in Q^1 is selected from the group consisting of: $-C(O)O(C_{1-4} \text{ alkyl})$; and C_{1-6} alkyl optionally substituted with 1-3 independently selected R^a ; or

5 wherein the R^d present in Q^1 is C_{2-3} alkyl substituted with 1-3 $-F$.

In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), Q^1 is:



; and

the R^d present in Q^1 is selected from the group consisting of: $-C(O)O(C_{1-4} \text{ alkyl})$; and C_{1-6} alkyl optionally substituted with 1-3 independently selected R^a ; or

10 wherein the R^d present in Q^1 is C_{2-3} alkyl substituted with 1-3 $-F$.

In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), each R^1 is H.

In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), one occurrence of
15 R^1 is R^c ; and each remaining R^1 is H.

In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), R^2 is H; and R^5 is H.

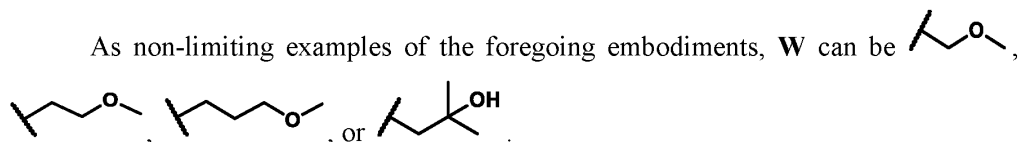
20 In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), W is C_{1-6} alkyl, which is optionally substituted with 1-6 R^{a2} .

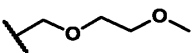
In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), W is C_{1-6} alkyl, which is optionally substituted with 1-6 R^{a2} , wherein one or more of the internal optionally substituted methylene group is replaced by one or more heteroatom selected from O or S,
25 wherein when W is alkenyl or alkynyl, the heteroatom is not directed connected to the sp^2 or sp carbon;

In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), W is unsubstituted C_{1-4} alkyl. For example, W can be methyl or ethyl.

In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), **W** is C₁₋₄ alkyl, which is substituted with 1-6 **R^{a2}**.

In certain of these embodiments, **W** is: C₁₋₄ alkyl which is substituted with 1-3
 5 substituents each independently selected from the group consisting of: halo; -OH; C₁₋₄ alkoxy; and C₁₋₄ haloalkoxy.



As another non-limiting example of the foregoing embodiments, **W** can be
 10 .

In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), **W** is selected from the group consisting of:

- monocyclic C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl, each of which is optionally
 15 substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**; and
- monocyclic heterocyclyl or heterocycloalkenyl of from 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heterocyclyl or
 20 heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**.

In certain embodiments of Formula (I-a), (I-b), (I-c) or (I-d), **W** is monocyclic C₃₋₈ cycloalkyl, which is optionally substituted with 1-4 substituents independently selected
 25 from the group consisting of oxo and **R^c**. In certain of these embodiments, **W** is unsubstituted C₃₋₈ cycloalkyl. For example, **W** can be cyclobutyl.

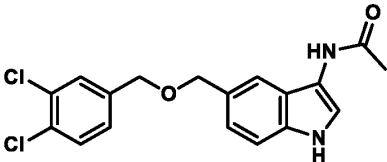
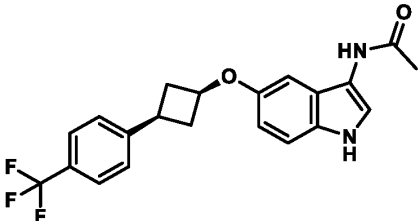
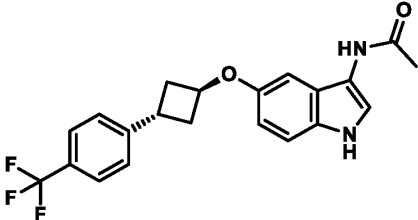
Non-Limiting Exemplary Compounds

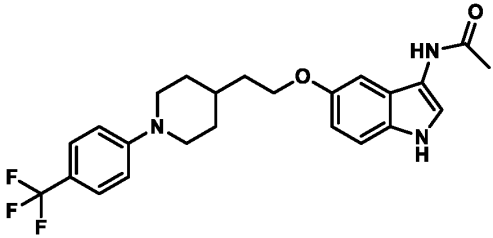
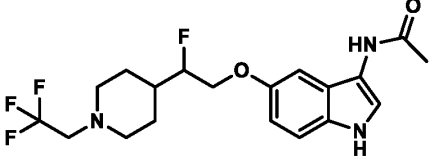
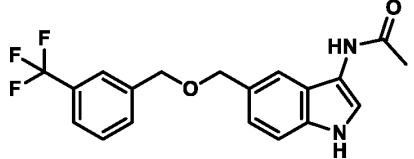
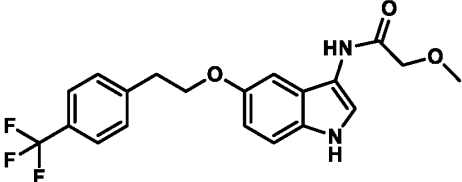
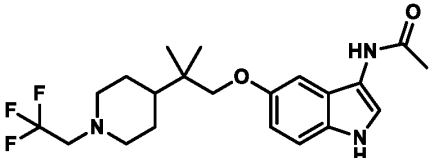
In some embodiments, the compound is selected from the group consisting of the compounds delineated in **Table C1** or a pharmaceutically acceptable salt thereof.

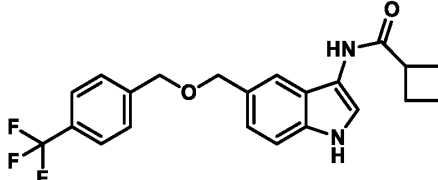
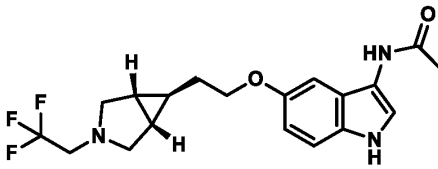
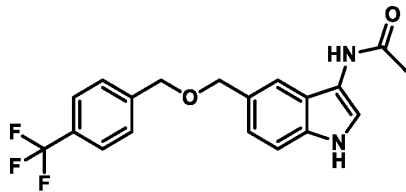
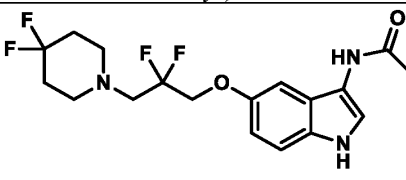
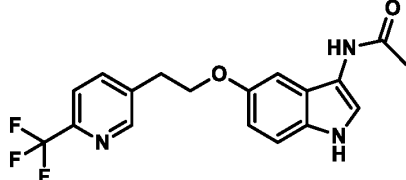
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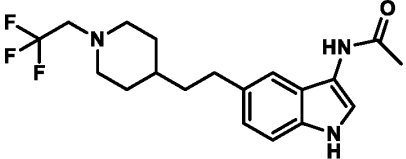
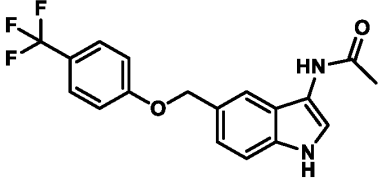
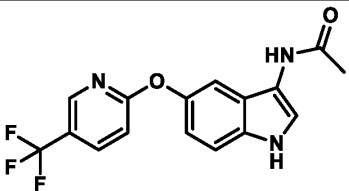
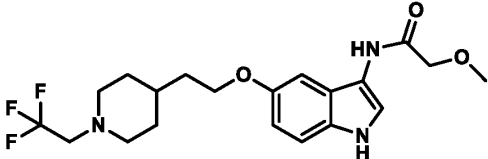
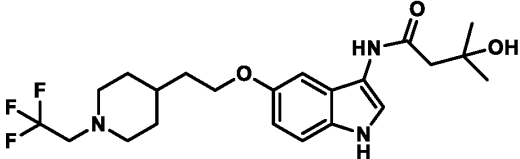
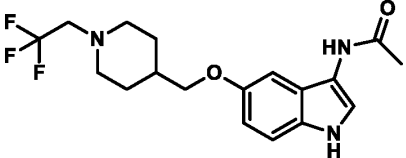
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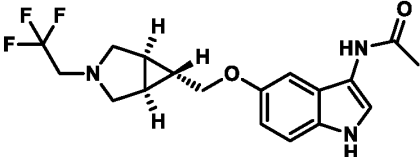
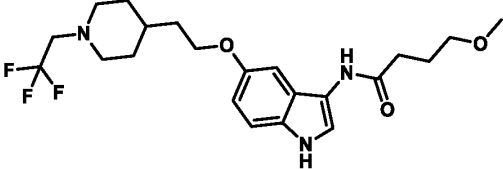
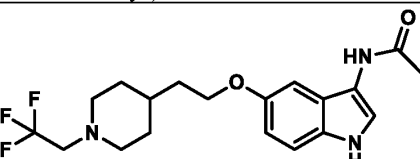
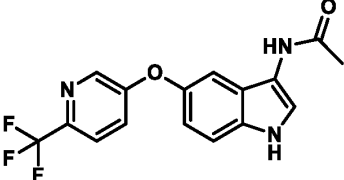
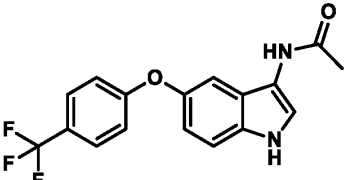
Table C1

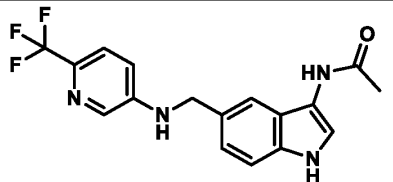
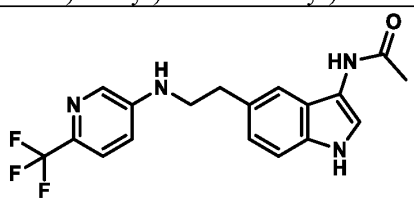
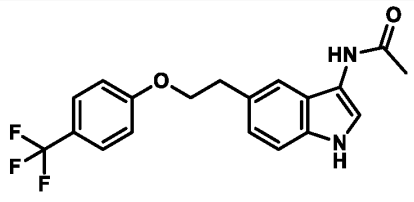
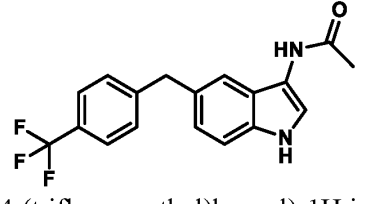
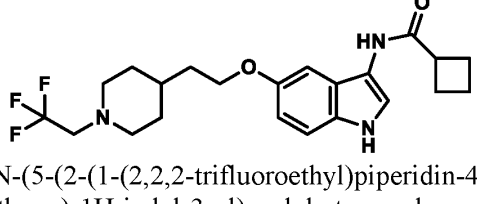
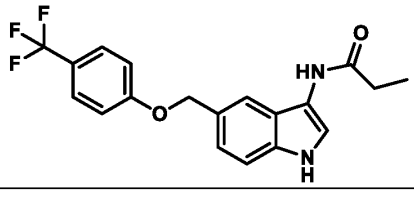
Compound No.	Structure	LC-MS
101	 <chem>CC(=O)Nc1c[nH]c2ccc(OCC3=CC=C(Cl)C(Cl)=C3)cc12</chem> N-(5-(((3,4-dichlorobenzyl)oxy)methyl)-1H-indol-3-yl)acetamide	361.0
102	 <chem>CC(=O)Nc1c[nH]c2ccc(O[C@H]3CC[C@H]3Cc4ccc(C(F)(F)F)cc4)cc12</chem> N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)acetamide	387.2
103	 <chem>CC(=O)Nc1c[nH]c2ccc(O[C@H]3CC[C@@H]3Cc4ccc(C(F)(F)F)cc4)cc12</chem>	389.3

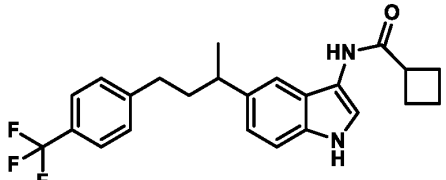
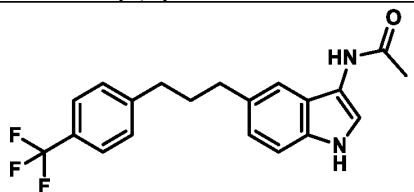
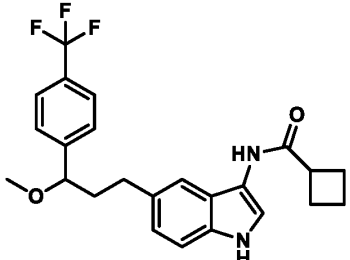
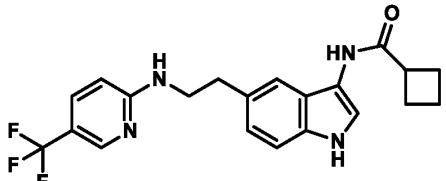
	N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)acetamide	
104	 N-(5-(2-(1-(4-(trifluoromethyl)phenyl)piperidin-4-yl)ethoxy)-1H-indol-3-yl)acetamide	446.2
105	 N-(5-(2-fluoro-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethoxy)-1H-indol-3-yl)acetamide	402.2
106	 N-(5-(((3-(trifluoromethyl)benzyl)oxy)methyl)-1H-indol-3-yl)acetamide	361.2
107	 2-methoxy-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)acetamide	393.3
108		412.4

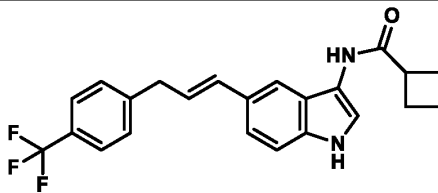
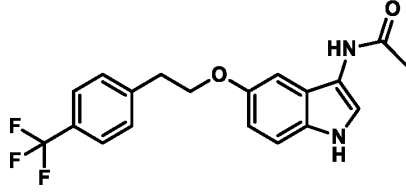
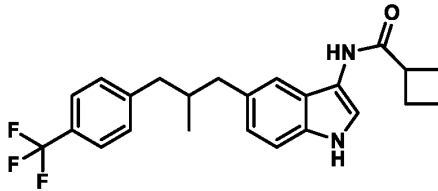
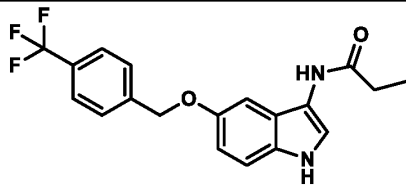
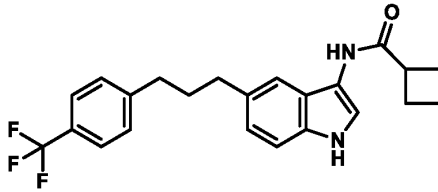
	N-(5-(2-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)propoxy)-1H-indol-3-yl)acetamide	
109	 N-(5-(((4-(trifluoromethyl)benzyl)oxy)methyl)-1H-indol-3-yl)cyclobutanecarboxamide	401.2
110	 N-(5-(2-(((1R,5S,6s)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethoxy)-1H-indol-3-yl)acetamide	382.2
111	 N-(5-(((4-(trifluoromethyl)benzyl)oxy)methyl)-1H-indol-3-yl)acetamide	363.1
112	 N-(5-(3-(4,4-difluoropiperidin-1-yl)-2,2-difluoropropoxy)-1H-indol-3-yl)acetamide	388.3
113	 N-(5-(2-(6-(trifluoromethyl)pyridin-3-yl)ethoxy)-1H-indol-3-yl)acetamide	364.1

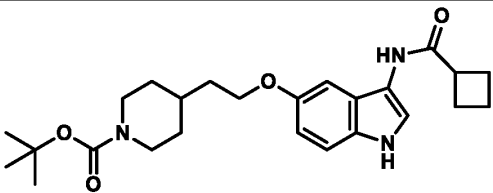
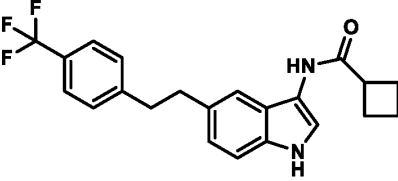
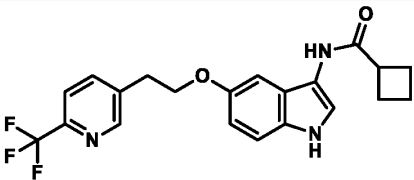
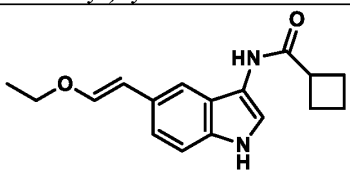
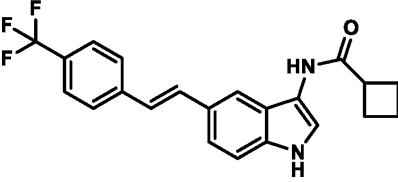
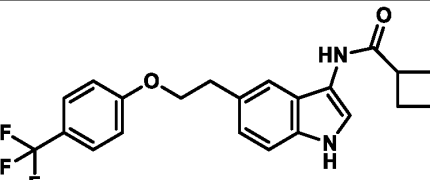
114	 N-(5-(2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indol-3-yl)acetamide	368.1
115	 N-(5-((4-(trifluoromethyl)phenoxy)methyl)-1H-indol-3-yl)acetamide	347.15
116	 N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-indol-3-yl)acetamide	336.05
117	 2-methoxy-N-(5-(2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethoxy)-1H-indol-3-yl)acetamide	414.1
118	 3-hydroxy-3-methyl-N-(5-(2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethoxy)-1H-indol-3-yl)butanamide	442.3
119	 N-(5-(2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethoxy)-1H-indol-3-yl)acetamide	370.3

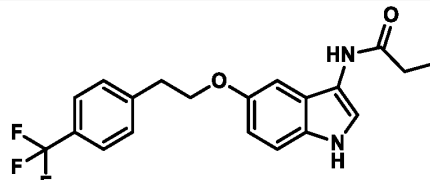
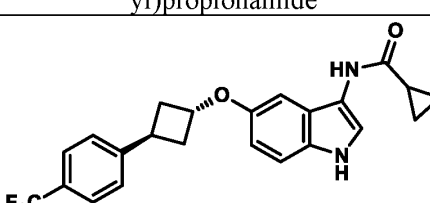
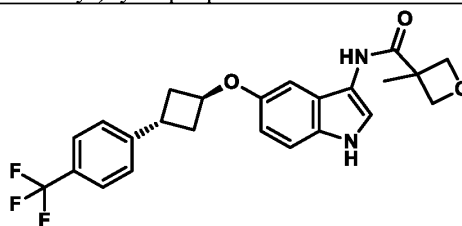
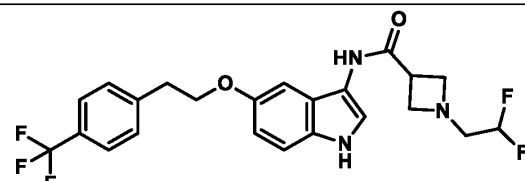
	N-(5-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)methoxy)-1H-indol-3-yl)acetamide	
120	 N-(5-(((1R,5S,6r)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexan-6-yl)methoxy)-1H-indol-3-yl)acetamide	368.3
121	 4-methoxy-N-(5-(2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethoxy)-1H-indol-3-yl)butanamide	442.2
122	 N-(5-(2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethoxy)-1H-indol-3-yl)acetamide	384.1
123	 N-(5-((6-(trifluoromethyl)pyridin-3-yl)oxy)-1H-indol-3-yl)acetamide	336.0
124	 N-(5-(4-(trifluoromethyl)phenoxy)-1H-indol-3-yl)acetamide	335.2

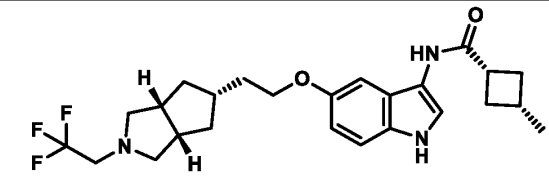
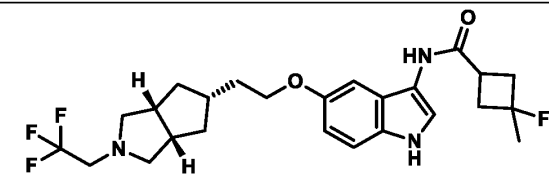
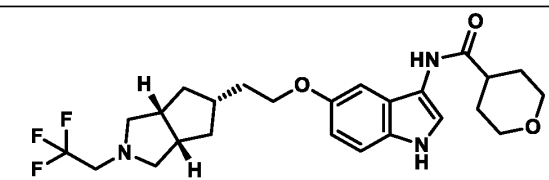
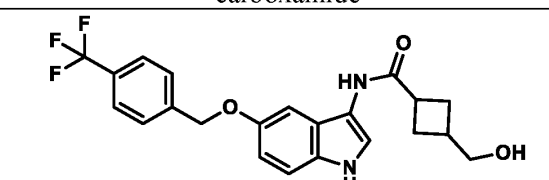
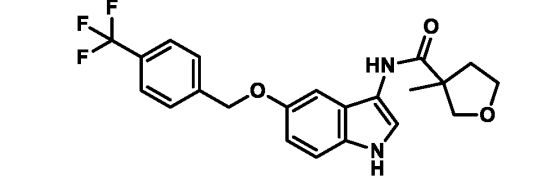
125	 N-(5-(((6-(trifluoromethyl)pyridin-3-yl)amino)methyl)-1H-indol-3-yl)acetamide	349.0
126	 N-(5-(2-((6-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-1H-indol-3-yl)acetamide	363.1
127	 N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	363.1
128	 N-(5-(4-(trifluoromethyl)benzyl)-1H-indol-3-yl)acetamide	333.1
129	 N-(5-(2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethoxy)-1H-indol-3-yl)cyclobutanecarboxamide	424.1
130	 N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	361.1

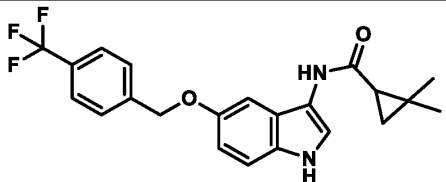
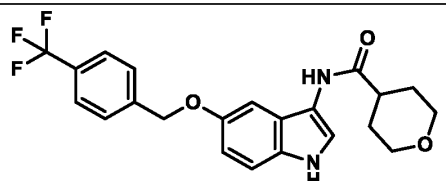
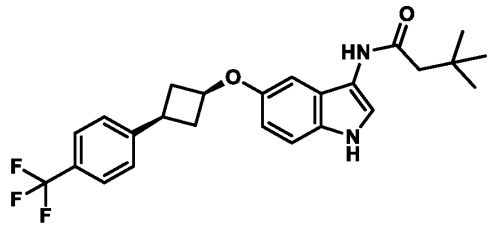
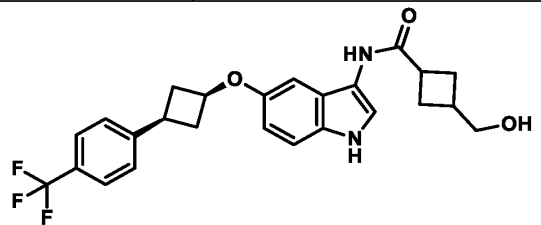
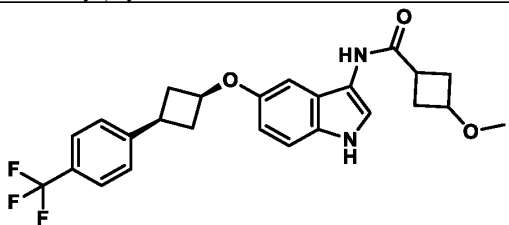
	N-(5-((4-(trifluoromethyl)phenoxy)methyl)-1H-indol-3-yl)propionamide	
131	 N-(5-(4-(4-(trifluoromethyl)phenyl)butan-2-yl)-1H-indol-3-yl)cyclobutanecarboxamide	415.2
132	 N-(5-(3-(4-(trifluoromethyl)phenyl)propyl)-1H-indol-3-yl)acetamide	359.1
133	 N-(5-(3-methoxy-3-(4-(trifluoromethyl)phenyl)propyl)-1H-indol-3-yl)cyclobutanecarboxamide	431.2
134	 N-(5-(2-((5-(trifluoromethyl)pyridin-2-yl)amino)ethyl)-1H-indol-3-yl)cyclobutanecarboxamide	403.2

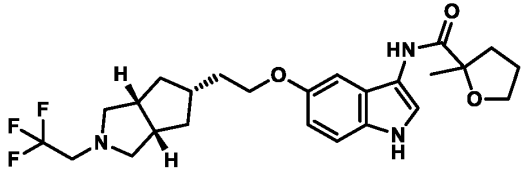
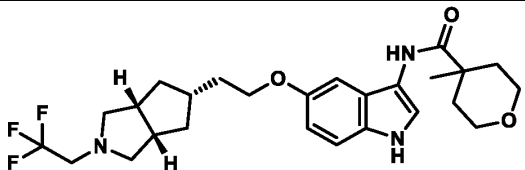
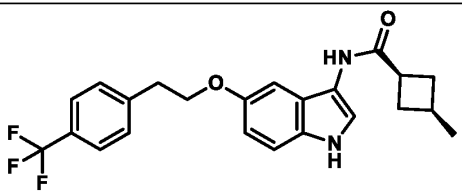
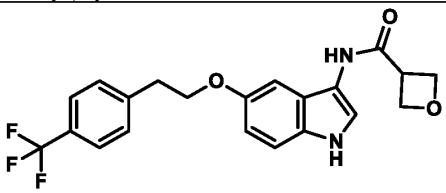
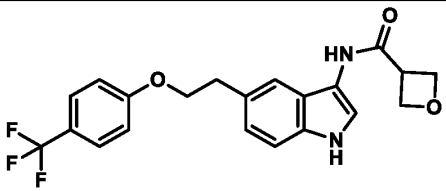
135	 (E)-N-(5-(3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-1H-indol-3-yl)cyclobutanecarboxamide	399.2
136	 N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)acetamide	363.1
137	 N-(5-(2-methyl-3-(4-(trifluoromethyl)phenyl)propyl)-1H-indol-3-yl)cyclobutanecarboxamide	415.1
138	 N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)propionamide	363.1
139	 N-(5-(3-(4-(trifluoromethyl)phenyl)propyl)-1H-indol-3-yl)cyclobutanecarboxamide	401.2

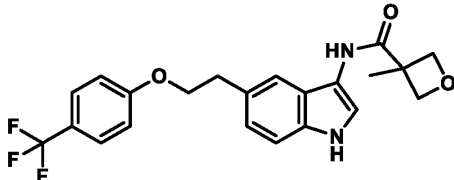
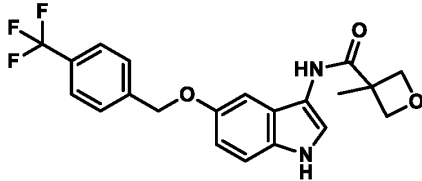
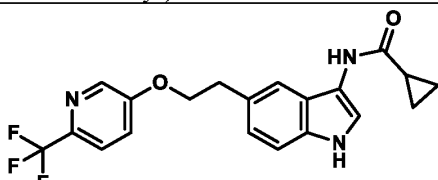
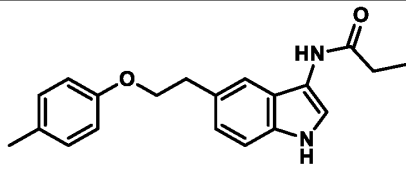
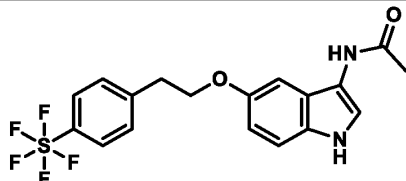
140	 tert-butyl 4-(2-((3-(cyclobutanecarboxamido)-1H-indol-5-yl)oxy)ethyl)piperidine-1-carboxylate	440.2
141	 N-(5-(4-(trifluoromethyl)phenethyl)-1H-indol-3-yl)cyclobutanecarboxamide	385.2
142	 N-(5-(2-(6-(trifluoromethyl)pyridin-3-yl)ethoxy)-1H-indol-3-yl)cyclobutanecarboxamide	404.1
143	 (E)-N-(5-(2-ethoxyvinyl)-1H-indol-3-yl)cyclobutanecarboxamide	285.2
144	 (E)-N-(5-(4-(trifluoromethyl)styryl)-1H-indol-3-yl)cyclobutanecarboxamide	385.2
145	 N-(5-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutanecarboxamide	403.1

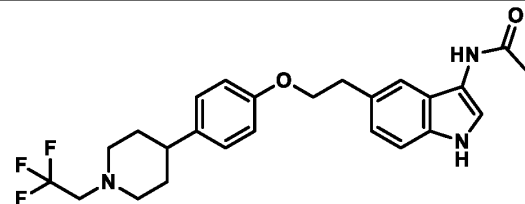
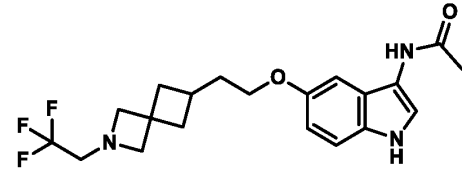
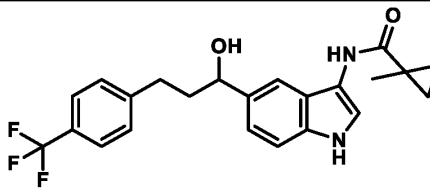
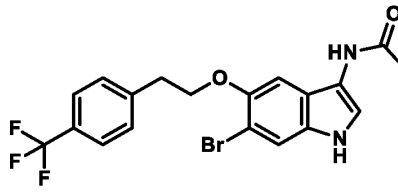
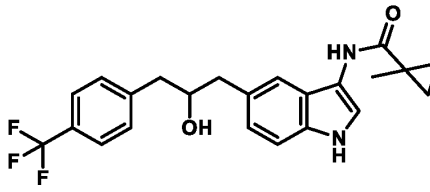
	N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutanecarboxamide	
146	 N-(5-(4-(trifluoromethyl)phenoxy)-1H-indol-3-yl)propionamide	377.1
147	 <i>trans</i>-N-(5-(3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropanecarboxamide	415.1
148	 3-methyl-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)oxetane-3-carboxamide	445.3
149	 1-(2,2-difluoroethyl)-N-(5-(4-(trifluoromethyl)phenoxy)-1H-indol-3-yl)azetidine-3-carboxamide	466.1

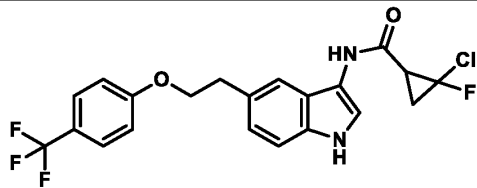
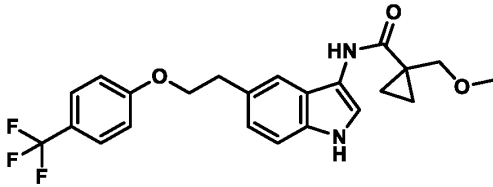
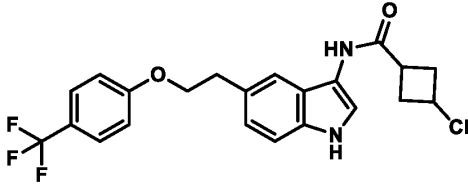
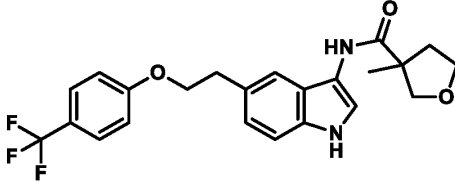
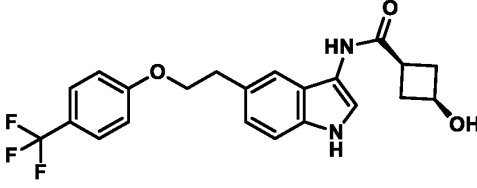
150	 (1s,3S)-3-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	464.4
151	 3-fluoro-3-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	482.1
152	 N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)tetrahydro-2H-pyran-4-carboxamide	480.1
153	 3-(hydroxymethyl)-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	419.3
154	 3-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)tetrahydrofuran-3-carboxamide	419.3

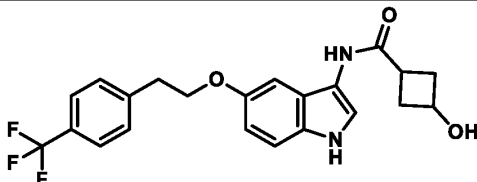
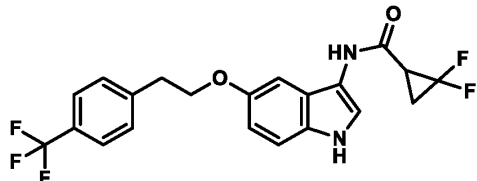
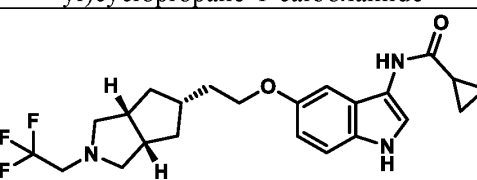
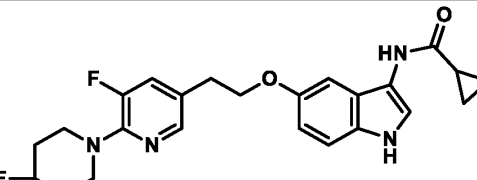
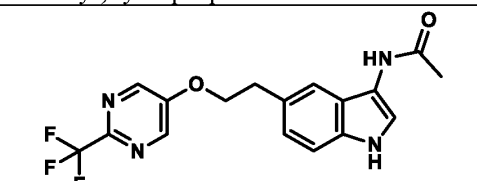
155	 2,2-dimethyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	403.3
156	 N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)tetrahydro-2H-pyran-4-carboxamide	419.3
157	 3,3-dimethyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)butanamide	445.4
158	 3-(hydroxymethyl)-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	459.3
159		459.3

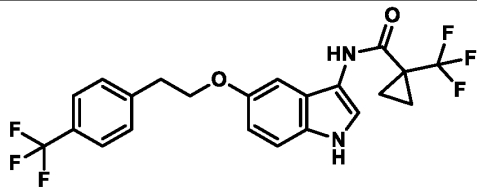
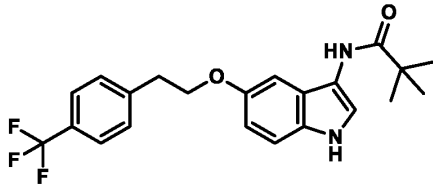
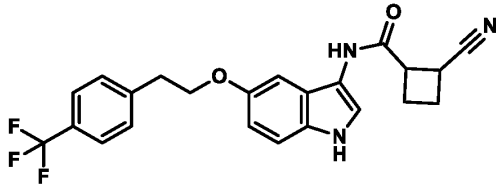
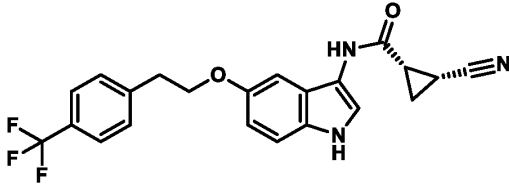
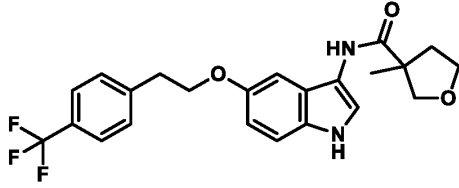
	3-methoxy-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	
160	 2-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)tetrahydrofuran-2-carboxamide	480.3
161	 4-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)tetrahydro-2H-pyran-4-carboxamide	494.4
162	 cis-3-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	417.3
163	 N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)oxetane-3-carboxamide	405.2
164		403.05

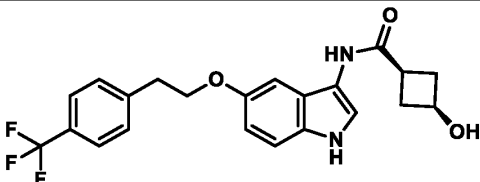
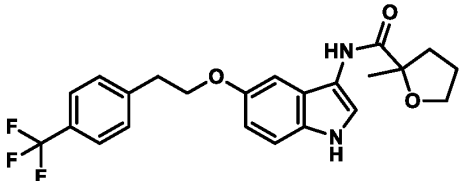
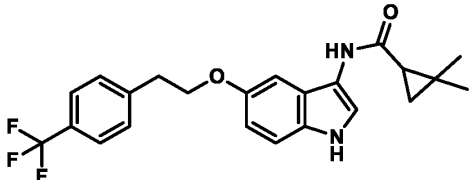
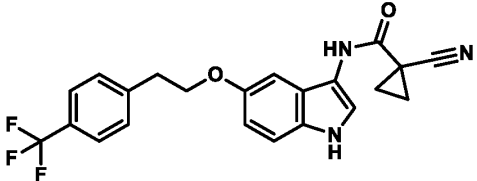
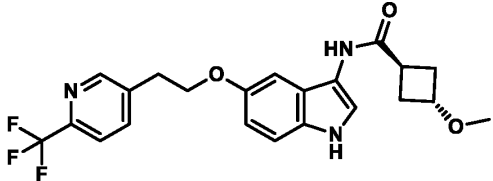
	N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)oxetane-3-carboxamide	
165	 3-methyl-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)oxetane-3-carboxamide	417.1
166	 3-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)oxetane-3-carboxamide	405.1
167	 N-(5-(2-((6-(trifluoromethyl)pyridin-3-yl)oxy)ethyl)-1H-indol-3-yl)cyclopropanecarboxamide	390.1
168	 N-(5-(2-(p-tolyloxy)ethyl)-1H-indol-3-yl)propionamide	323.15
169	 N-(5-(4-(pentafluoro-16-sulfaneyl)phenethoxy)-1H-indol-3-yl)acetamide	419.05

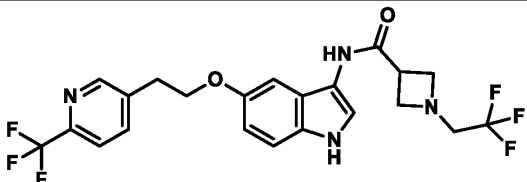
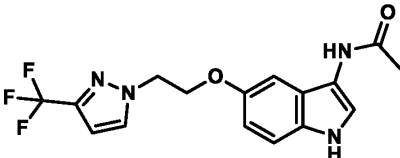
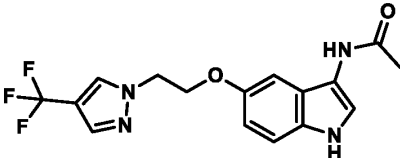
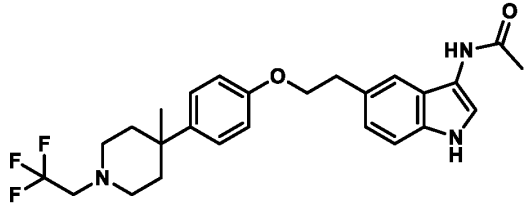
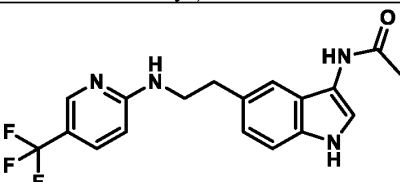
170	 N-(5-(2-(4-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	460.25
171	 N-(5-(2-(2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl)ethoxy)-1H-indol-3-yl)acetamide	396.3
172	 N-(5-(1-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1H-indol-3-yl)-1-methylcyclopropane-1-carboxamide	417.1
173	 N-(6-bromo-5-(4-(trifluoromethyl)phenoxy)-1H-indol-3-yl)acetamide	440.95
174	 N-(5-(2-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1H-indol-3-yl)-1-methylcyclopropane-1-carboxamide	417.05

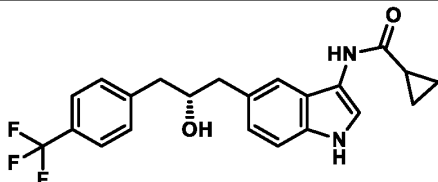
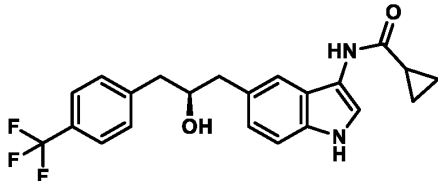
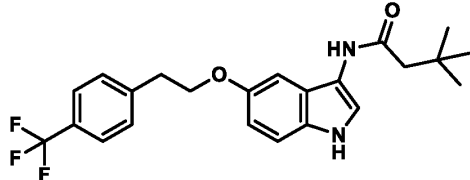
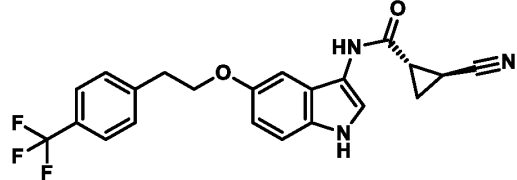
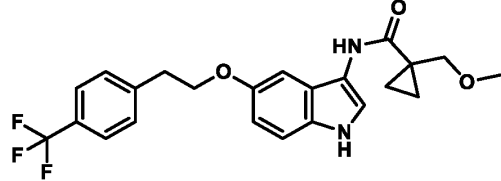
175	 2-chloro-2-fluoro-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclopropane-1-carboxamide	441.1
176	 1-(methoxymethyl)-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclopropane-1-carboxamide	433.2
177	 3-chloro-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	437.2
178	 3-methyl-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)tetrahydrofuran-3-carboxamide	433.3
179	 cis-3-hydroxy-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	419.2

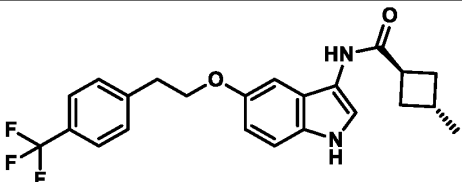
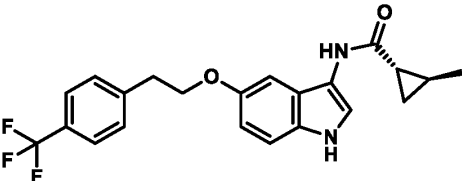
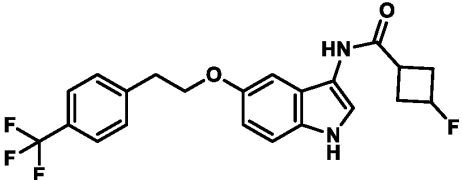
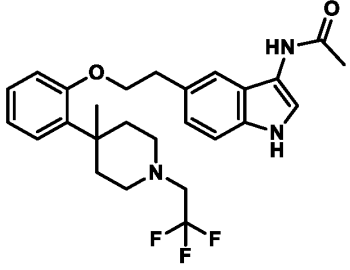
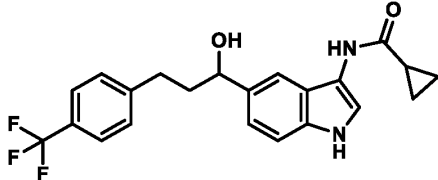
180	 3-hydroxy-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	419.2
181	 2,2-difluoro-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	425.2
182	 N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclopropanecarboxamide	436.15
183	 N-(5-(2-(6-(4,4-difluoropiperidin-1-yl)-5-fluoropyridin-3-yl)ethoxy)-1H-indol-3-yl)cyclopropanecarboxamide	459.2
184	 N-(5-(2-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	364.32

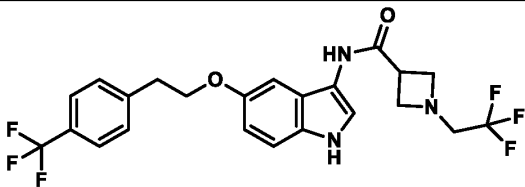
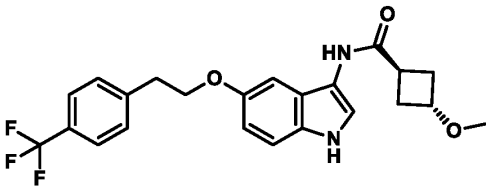
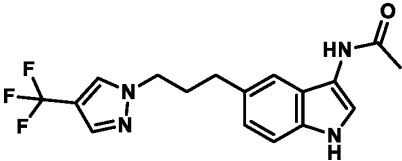
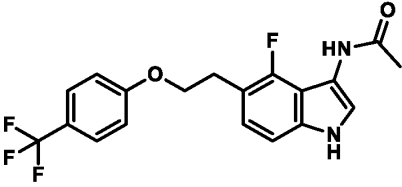
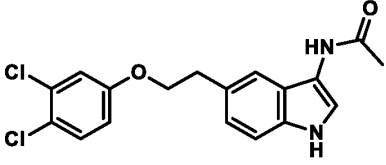
185	 1-(trifluoromethyl)-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	457.1
186	 N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)pivalamide	405.1
187	 2-cyano-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	428.1
188	 (1S,2R)-2-cyano-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	414.2
189	 3-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)tetrahydrofuran-3-carboxamide	433.2

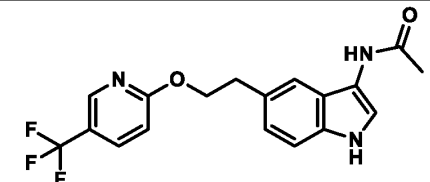
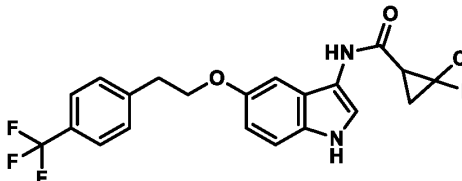
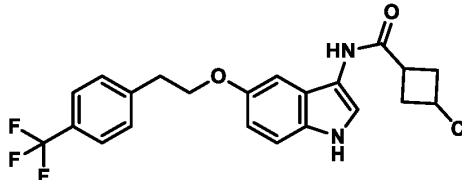
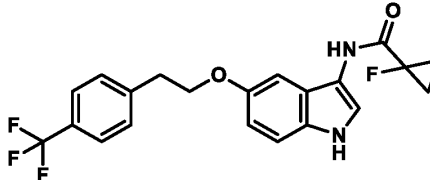
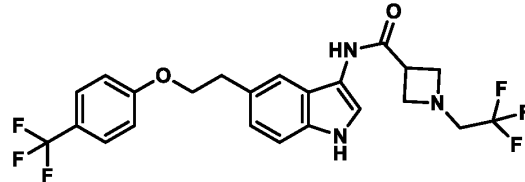
190	 cis-3-hydroxy-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	419.1
191	 2-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)tetrahydrofuran-2-carboxamide	433.2
192	 2,2-dimethyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	417.1
193	 1-cyano-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	414.2
194	 trans-3-methoxy-N-(5-(2-(6-(trifluoromethyl)pyridin-3-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	434.0

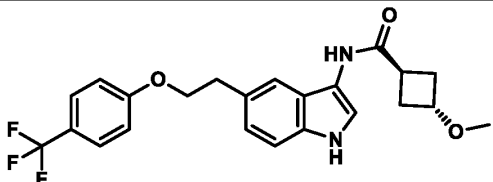
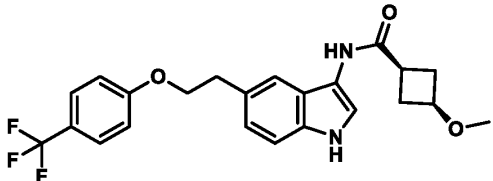
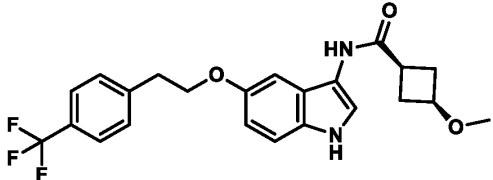
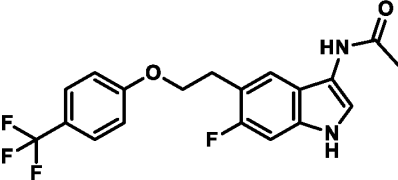
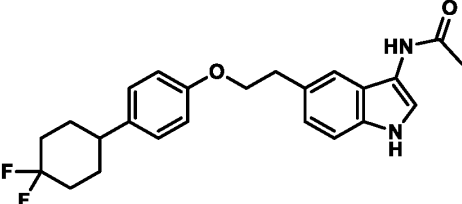
195	 1-(2,2,2-trifluoroethyl)-N-(5-(2-(6-(trifluoromethyl)pyridin-3-yl)ethoxy)-1H-indol-3-yl)azetidine-3-carboxamide	487.15
196	 N-(5-(2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)ethoxy)-1H-indol-3-yl)acetamide	351.1
197	 N-(5-(2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)ethoxy)-1H-indol-3-yl)acetamide	353.05
198	 N-(5-(2-(4-(4-methyl-1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	474.2
199	 N-(5-(2-((5-(trifluoromethyl)pyridin-2-yl)amino)ethyl)-1H-indol-3-yl)acetamide	363.05

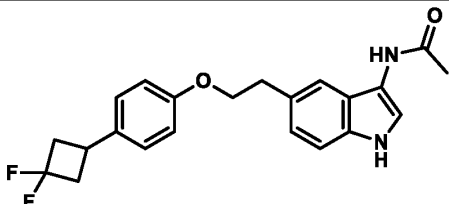
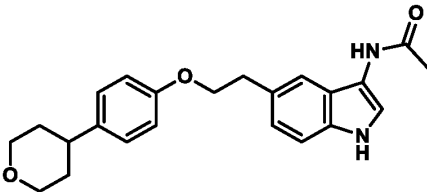
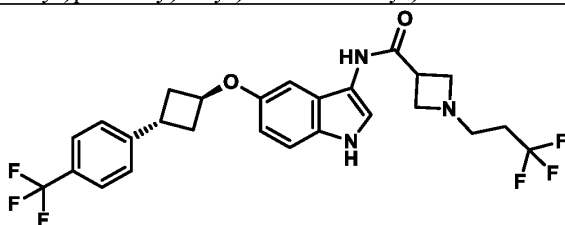
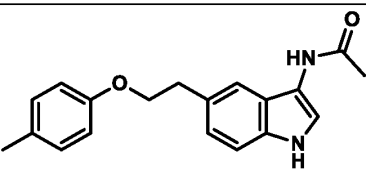
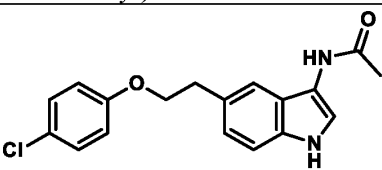
200	 (R)-N-(5-(2-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1H-indol-3-yl)cyclopropanecarboxamide	401.1
201	 (S)-N-(5-(2-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1H-indol-3-yl)cyclopropanecarboxamide	401.15
202	 3,3-dimethyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)butanamide	419.2
203	 (1S,2S)-2-cyano-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	414.2
204	 1-(methoxymethyl)-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	433.2

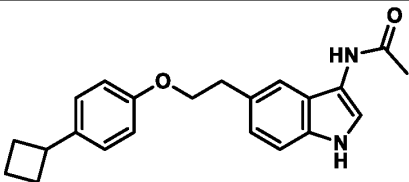
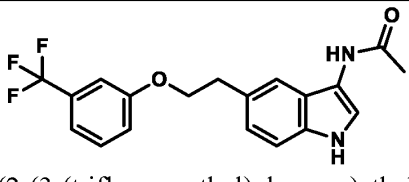
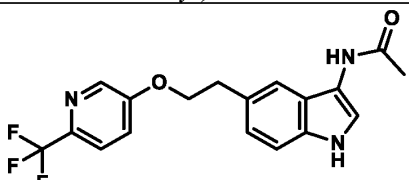
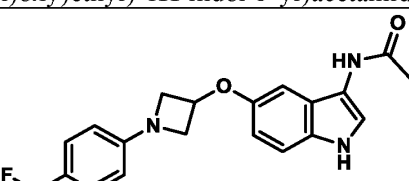
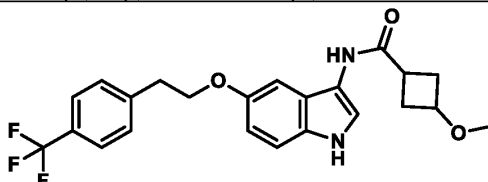
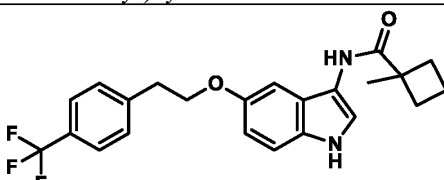
205	 trans-3-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	417.3
206	 (1S,2S)-2-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	403.2
207	 3-fluoro-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	421.2
208	 N-(5-(2-(2-(4-methyl-1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	474.25
209		401.1

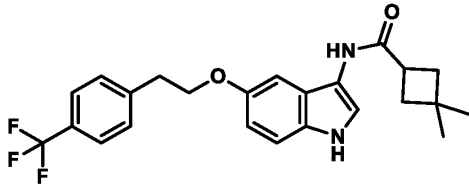
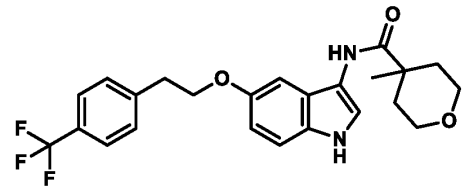
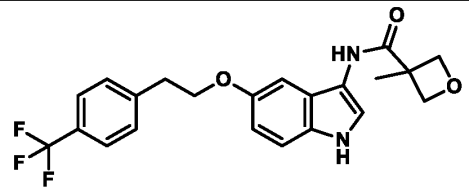
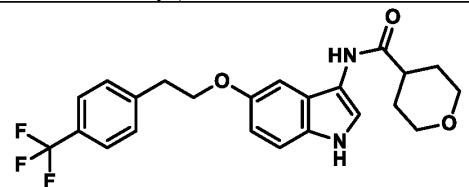
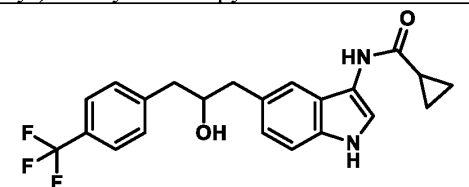
	N-(5-(1-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1H-indol-3-yl)cyclopropanecarboxamide	
210	 1-(2,2,2-trifluoroethyl)-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)azetidine-3-carboxamide	484.0
211	 trans-3-methoxy-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	431.1
212	 N-(5-(3-(4-(trifluoromethyl)-1H-pyrazol-1-yl)propyl)-1H-indol-3-yl)acetamide	350.95
213	 N-(4-fluoro-5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	379.0
214	 N-(5-(2-(3,4-dichlorophenoxy)ethyl)-1H-indol-3-yl)acetamide	363.05

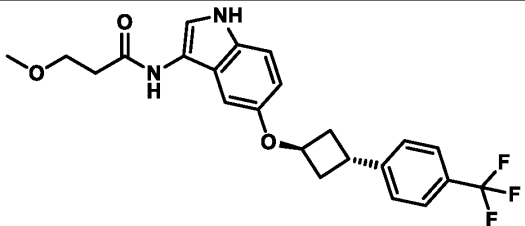
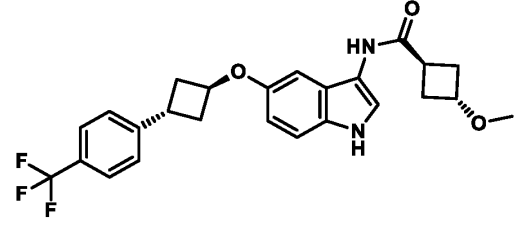
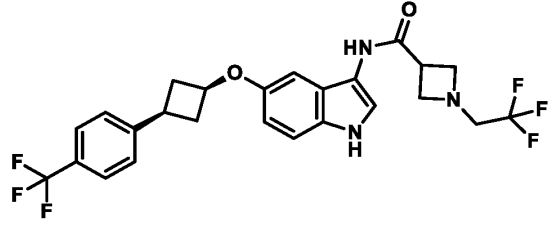
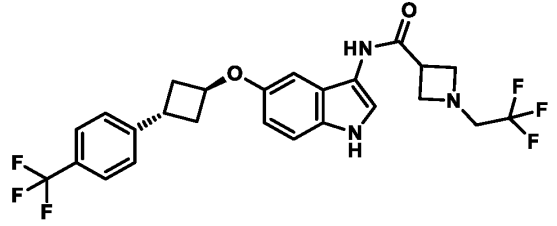
215	 N-(5-(2-((5-(trifluoromethyl)pyridin-2-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	364.1
216	 2-chloro-2-fluoro-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	441.1
217	 3-chloro-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	437.1
218	 1-fluoro-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	407.2
219	 1-(2,2,2-trifluoroethyl)-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)azetidine-3-carboxamide	486.1

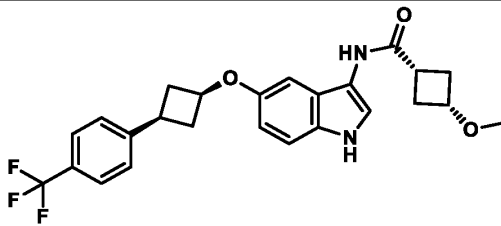
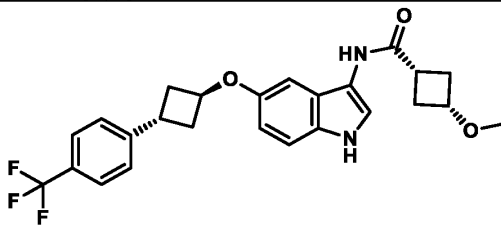
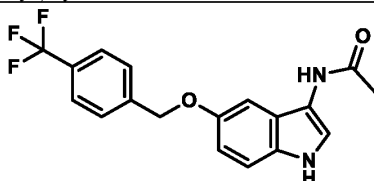
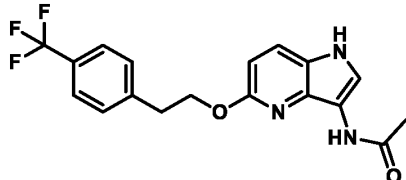
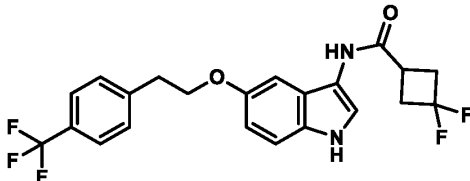
220	 trans-3-methoxy-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	431.1
221	 cis-3-methoxy-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	431.15
222	 cis-3-methoxy-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	431.1
223	 N-(6-fluoro-5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	379.1
224	 N-(5-(2-(4-(4,4-difluorocyclohexyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	411.15

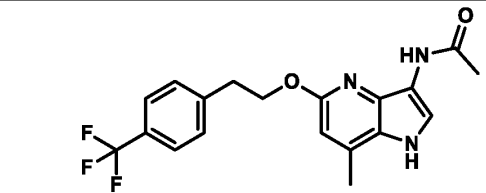
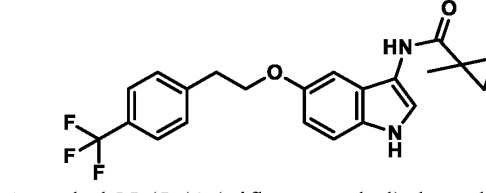
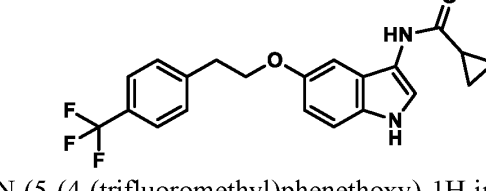
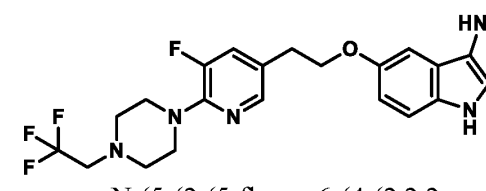
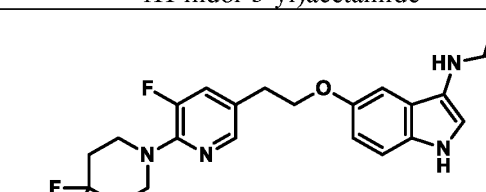
225	 N-(5-(2-(4-(3,3-difluorocyclobutyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	385.35
226	 N-(5-(2-(4-(tetrahydro-2H-pyran-4-yl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	377.0
227	 N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)-1-(3,3,3-trifluoropropyl)azetidine-3-carboxamide	524.15
228	 N-(5-(2-(p-tolyl)oxy)ethyl)-1H-indol-3-yl)acetamide	307.1
229	 N-(5-(2-(4-chlorophenoxy)ethyl)-1H-indol-3-yl)acetamide	327.05

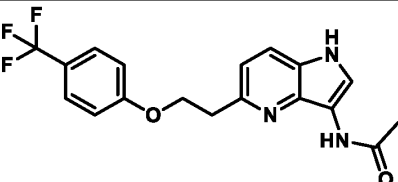
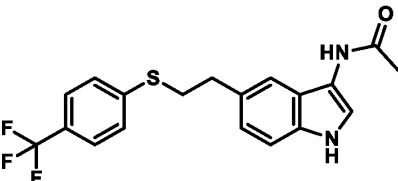
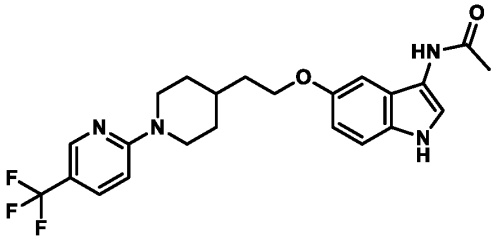
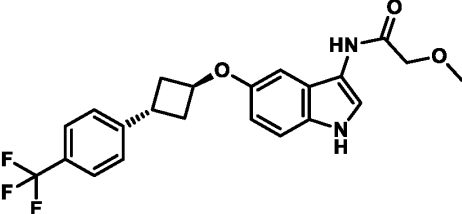
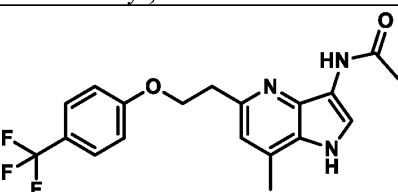
230	 N-(5-(2-(4-cyclobutylphenoxy)ethyl)-1H-indol-3-yl)acetamide	347.15
231	 N-(5-(2-(3-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	361.1
232	 N-(5-(2-((6-(trifluoromethyl)pyridin-3-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	364.1
233	 N-(5-((1-(4-(trifluoromethyl)phenyl)azetidin-3-yl)oxy)-1H-indol-3-yl)acetamide	390.1
234	 3-methoxy-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	433.2
235	 N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)-1,1-dimethylcyclobutane-1-carboxamide	417.2

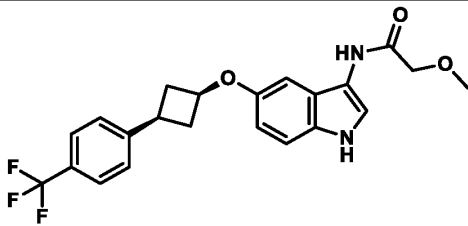
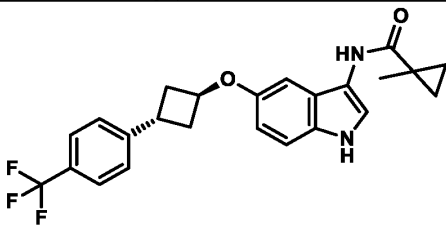
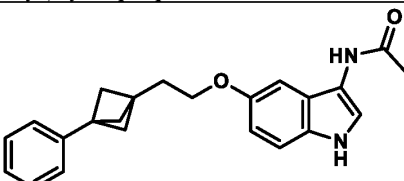
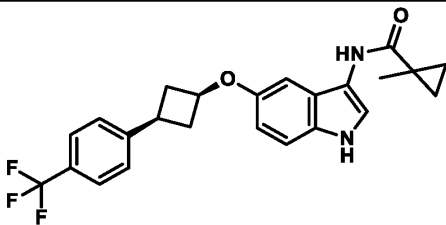
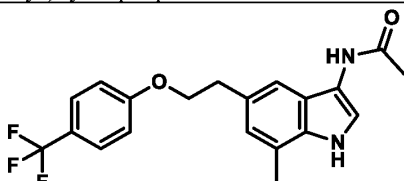
	1-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	
236	 3,3-dimethyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	431.2
237	 4-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)tetrahydro-2H-pyran-4-carboxamide	447.2
238	 3-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)oxetane-3-carboxamide	419.2
239	 N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)tetrahydro-2H-pyran-4-carboxamide	433.2
240	 N-(5-(2-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1H-indol-3-yl)cyclopropanecarboxamide	401.1

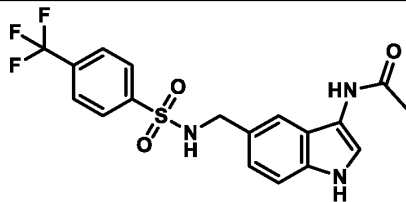
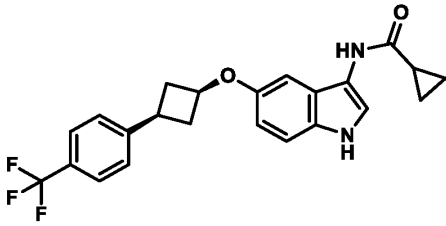
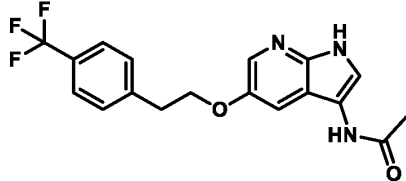
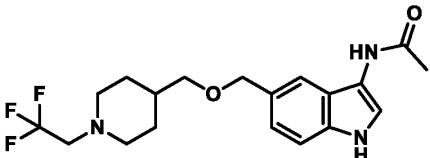
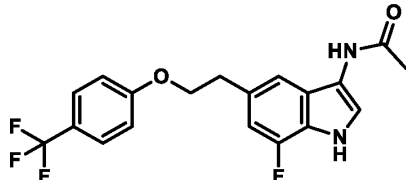
241	 3-methoxy-N-(5-((1r,3r)-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)propanamide	433.05
242	 trans-3-methoxy-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	459.3
243	 1-(2,2,2-trifluoroethyl)-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)azetidine-3-carboxamide	510.15
244	 1-(2,2,2-trifluoroethyl)-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)azetidine-3-carboxamide	510.15

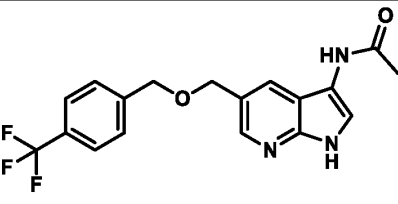
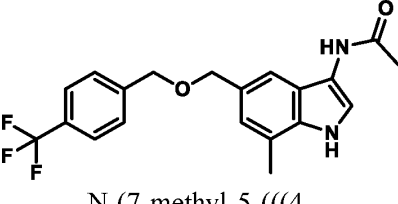
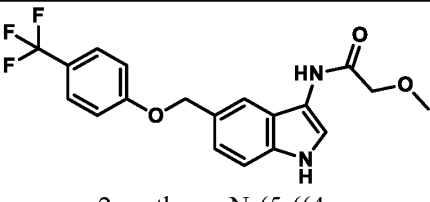
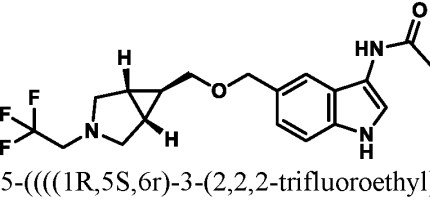
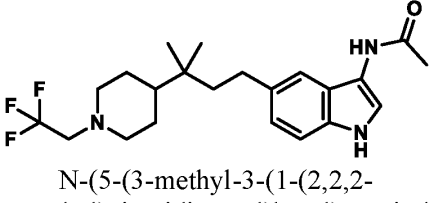
245	 cis-3-methoxy-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	459.2
246	 cis-3-methoxy-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	459.2
247	 N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)acetamide	349.0
248	 N-(5-(4-(trifluoromethyl)phenethoxy)-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamide	364.05
249	 3,3-difluoro-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	437.15

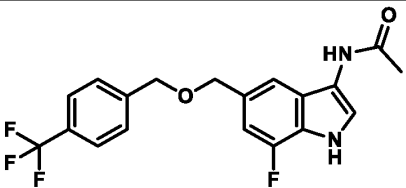
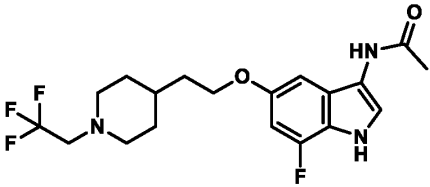
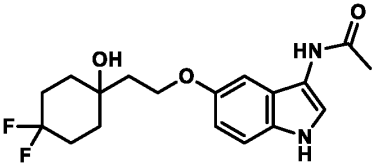
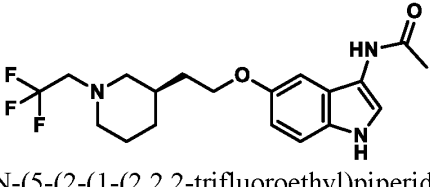
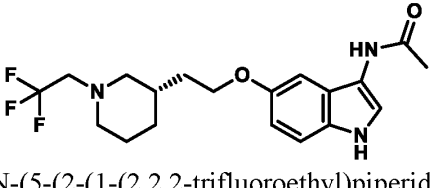
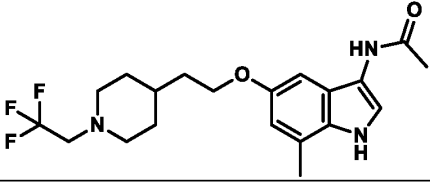
250	 N-(7-methyl-5-(4-(trifluoromethyl)phenoxy)-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamide	376.1
251	 1-methyl-N-(5-(4-(trifluoromethyl)phenoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	403.3
252	 N-(5-(4-(trifluoromethyl)phenoxy)-1H-indol-3-yl)cyclopropanecarboxamide	387.1
253	 N-(5-(2-(5-fluoro-6-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)pyridin-3-yl)ethoxy)-1H-indol-3-yl)acetamide	480.3
254	 N-(5-(2-(6-(4,4-difluoropiperidin-1-yl)-5-fluoropyridin-3-yl)ethoxy)-1H-indol-3-yl)acetamide	433.2

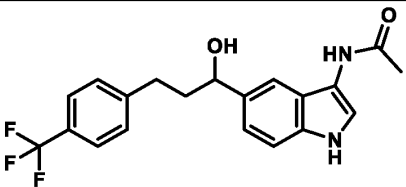
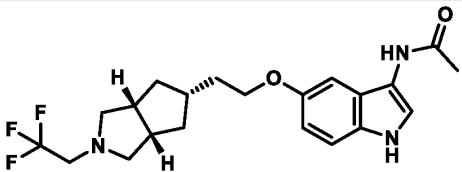
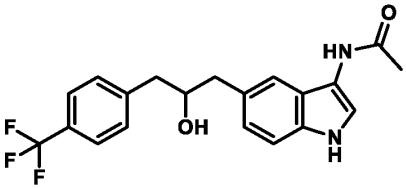
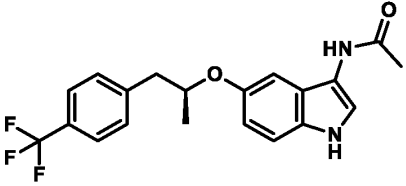
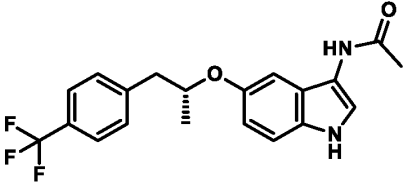
255	 N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamide	364.2
256	 N-(5-(2-((4-(trifluoromethyl)phenyl)thio)ethyl)-1H-indol-3-yl)acetamide	377.1
257	 N-(5-(2-(1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)ethoxy)-1H-indol-3-yl)acetamide	447.4
258	 2-methoxy-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)acetamide	419.1
259	 N-(7-methyl-5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamide	378.3

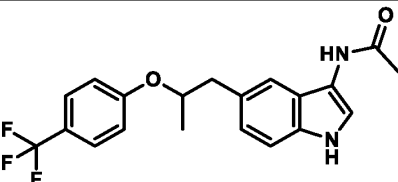
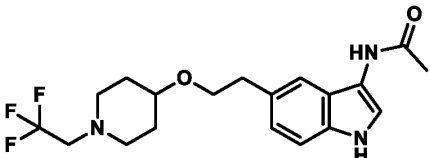
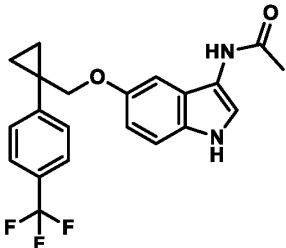
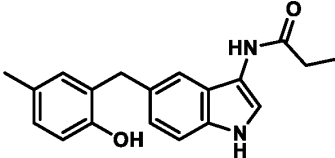
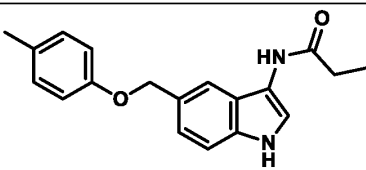
260	 2-methoxy-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)acetamide	419.2
261	 1-methyl-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	429.0
262	 N-(5-(2-(3-phenylbicyclo[1.1.1]pentan-1-yl)ethoxy)-1H-indol-3-yl)acetamide	359.2
263	 1-methyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	429.15
264	 375.15	375.15

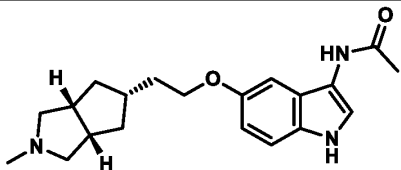
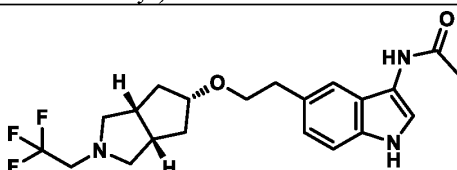
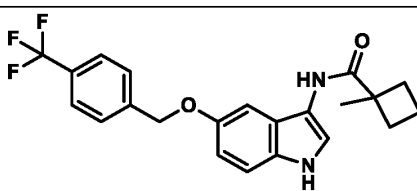
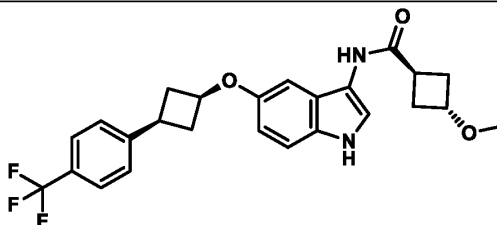
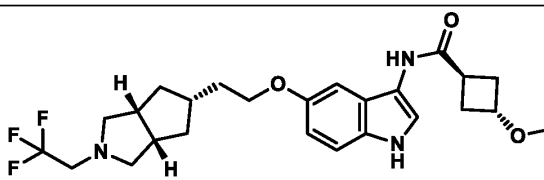
	N-(7-methyl-5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	
265	 N-(5-(((4-(trifluoromethyl)phenyl)sulfonamido)methyl)-1H-indol-3-yl)acetamide	412.1
266	 N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropanecarboxamide	415.1
267	 N-(5-(4-(trifluoromethyl)phenethoxy)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetamide	364.1
268	 N-(5-(((1-(2,2,2-trifluoroethyl)piperidin-4-yl)methoxy)methyl)-1H-indol-3-yl)acetamide	382.2
270	 N-(7-fluoro-5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	379.1

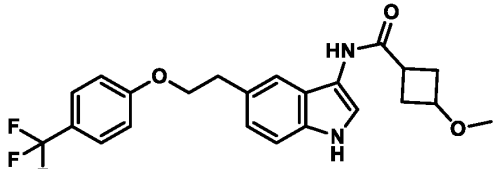
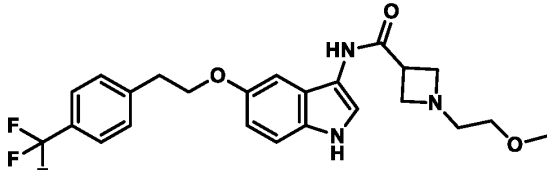
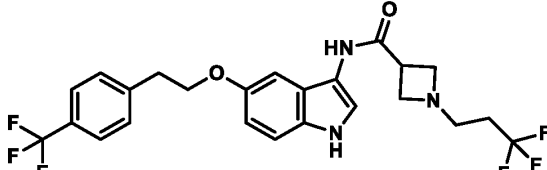
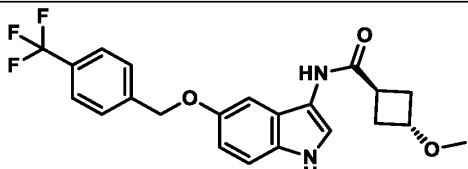
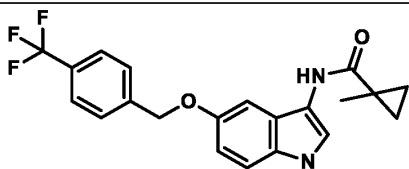
271	 N-(5-(((4-(trifluoromethyl)benzyl)oxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetamide	364.05
272	 N-(7-methyl-5-(((4-(trifluoromethyl)benzyl)oxy)methyl)-1H-indol-3-yl)acetamide	375.15
273	 2-methoxy-N-(5-(((4-(trifluoromethyl)phenoxy)methyl)-1H-indol-3-yl)acetamide	378.15
274	 N-(5-(((1R,5S,6r)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexan-6-yl)methoxy)methyl)-1H-indol-3-yl)acetamide	381.05
275	 N-(5-(3-methyl-3-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)butyl)-1H-indol-3-yl)acetamide	410.4

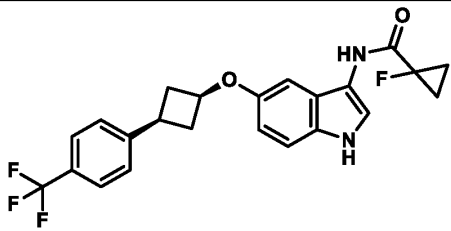
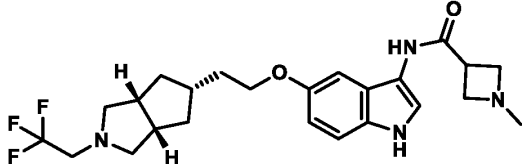
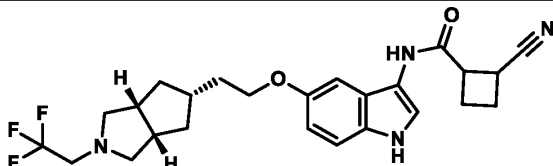
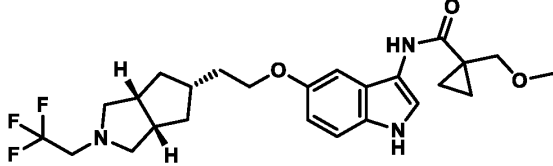
276	 N-(7-fluoro-5-(((4-(trifluoromethyl)benzyl)oxy)methyl)-1H-indol-3-yl)acetamide	379.15
277	 N-(7-fluoro-5-(2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethoxy)-1H-indol-3-yl)acetamide	402.3
278	 N-(5-(2-(4,4-difluoro-1-hydroxycyclohexyl)ethoxy)-1H-indol-3-yl)acetamide	353.15
279	 (R)-N-(5-(2-(1-(2,2,2-trifluoroethyl)piperidin-3-yl)ethoxy)-1H-indol-3-yl)acetamide	384.25
280	 (S)-N-(5-(2-(1-(2,2,2-trifluoroethyl)piperidin-3-yl)ethoxy)-1H-indol-3-yl)acetamide	384.2
281		398.3

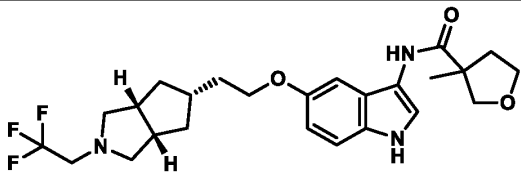
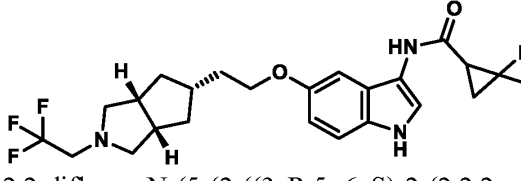
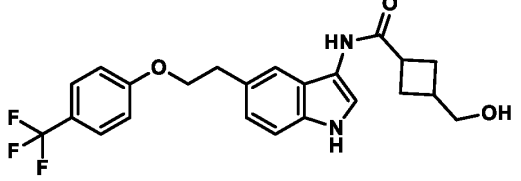
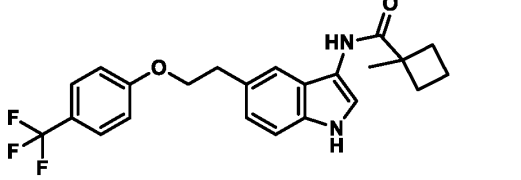
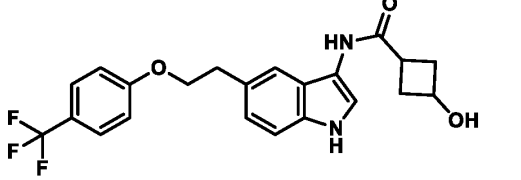
	N-(7-methyl-5-(2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethoxy)-1H-indol-3-yl)acetamide	
282	 N-(5-(1-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1H-indol-3-yl)acetamide	375.1
283	 N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)acetamide	410.2
284	 N-(5-(2-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1H-indol-3-yl)acetamide	375.1
285	 (S)-N-(5-((1-(4-(trifluoromethyl)phenyl)propan-2-yl)oxy)-1H-indol-3-yl)acetamide	377.15
286	 (R)-N-(5-((1-(4-(trifluoromethyl)phenyl)propan-2-yl)oxy)-1H-indol-3-yl)acetamide	377.15

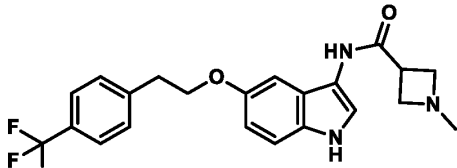
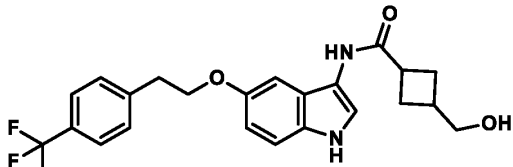
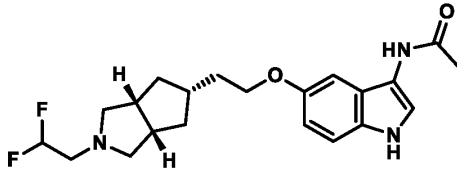
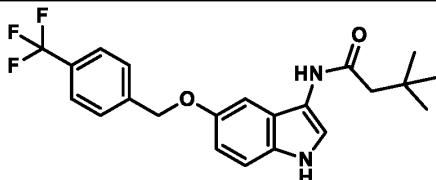
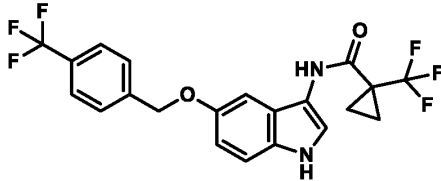
287	 N-(5-(2-(4-(trifluoromethyl)phenoxy)propyl)-1H-indol-3-yl)acetamide	375.0
288	 N-(5-(2-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	384.35
289	 N-(5-((1-(4-(trifluoromethyl)phenyl)cyclopropyl)methoxy)-1H-indol-3-yl)acetamide	389.15
290	 N-(5-(2-hydroxy-5-methylbenzyl)-1H-indol-3-yl)propionamide	308.0
291	 N-(5-((p-tolyloxy)methyl)-1H-indol-3-yl)propionamide	308.0

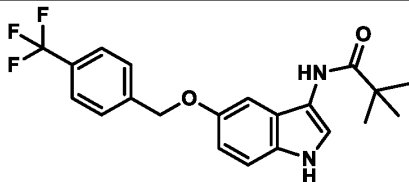
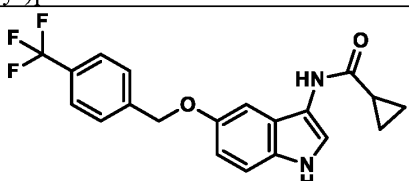
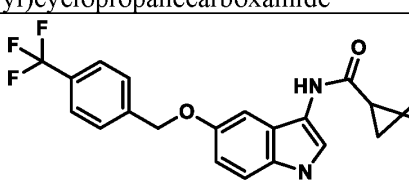
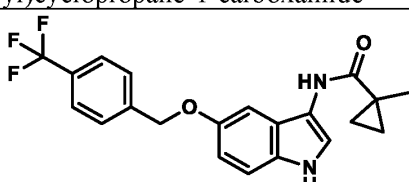
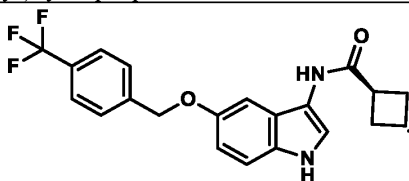
292	 N-(5-(2-((3aR,5r,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)acetamide	342.15
293	 N-(5-(2-(((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	410.2
294	 1-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	403.3
295	 trans-3-methoxy-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	459.4
296	 trans-3-methoxy-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	480.4

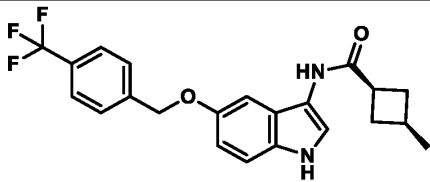
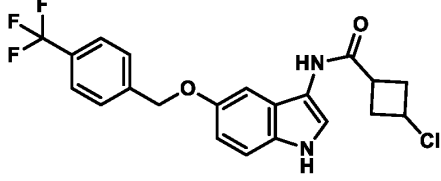
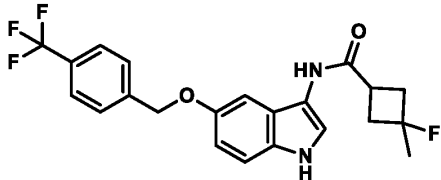
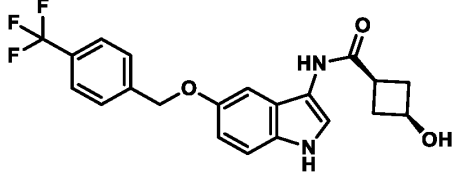
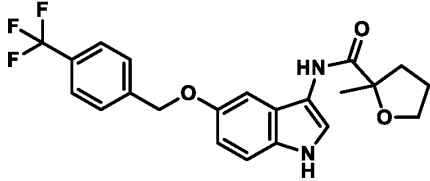
	yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	
297	 3-methoxy-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	433.2
298	 1-(2-methoxyethyl)-N-(5-(4-(trifluoromethyl)phenoxy)-1H-indol-3-yl)azetidine-3-carboxamide	462.3
299	 N-(5-(4-(trifluoromethyl)phenoxy)-1H-indol-3-yl)-1-(3,3,3-trifluoropropyl)azetidine-3-carboxamide	500.1
300	 trans-3-methoxy-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	419.3
301		389.3

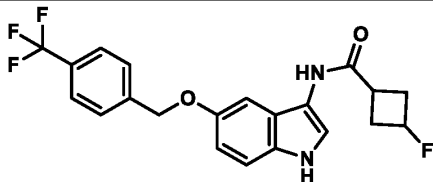
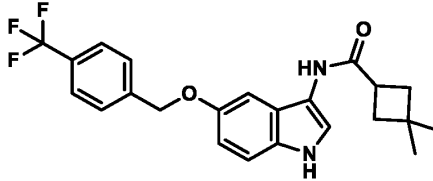
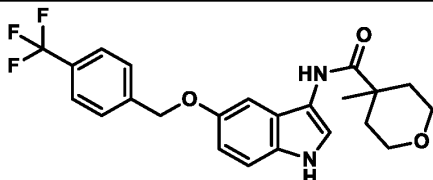
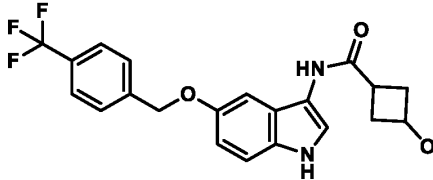
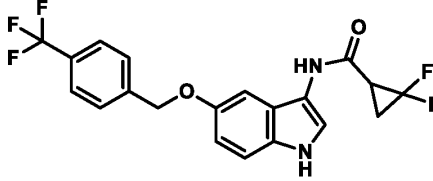
	1-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	
302	 1-fluoro-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	433.3
303	 1-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)azetidine-3-carboxamide	465.4
304	 2-cyano-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	475.4
305	 1-(methoxymethyl)-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	480.4

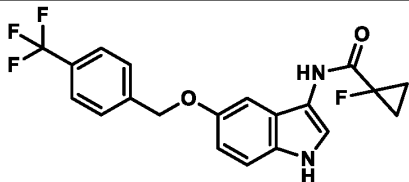
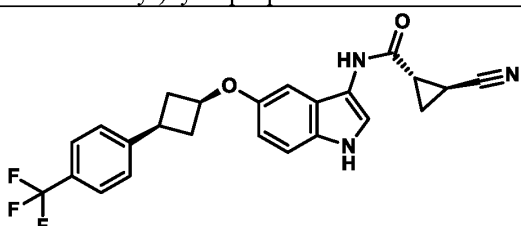
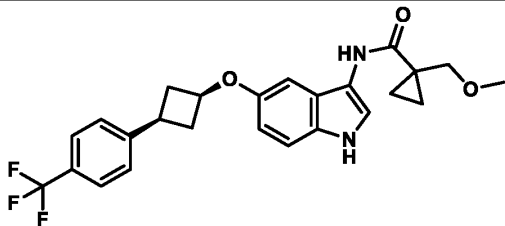
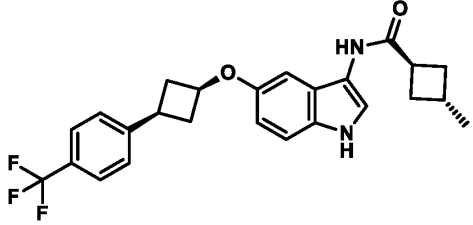
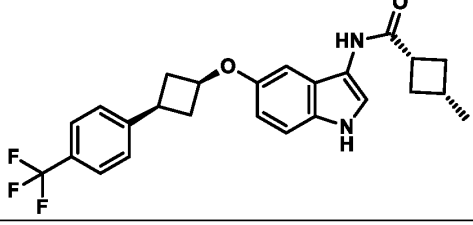
306	 3-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)tetrahydrofuran-3-carboxamide	480.4
307	 2,2-difluoro-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	472.3
308	 3-(hydroxymethyl)-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	433.3
309	 1-methyl-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	417.3
310	 3-hydroxy-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	419.0

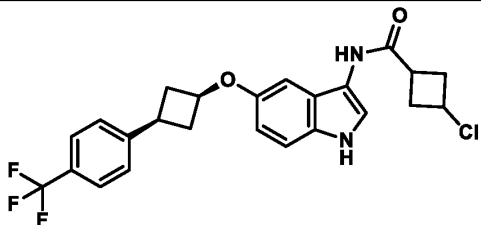
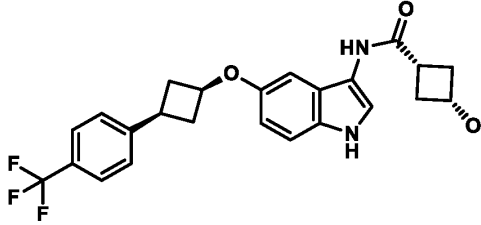
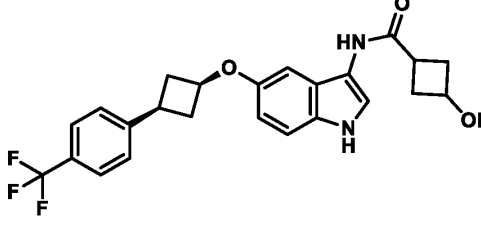
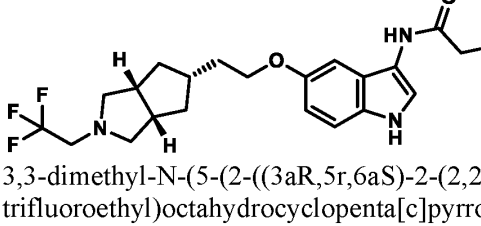
311	 1-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)azetidine-3-carboxamide	418.0
312	 3-(hydroxymethyl)-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	433.3
313	 N-(5-(2-((3aR,5r,6aS)-2-(2,2-difluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)acetamide	392.25
314	 3,3-dimethyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)butanamide	300.15
315	 1-(trifluoromethyl)-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	423.3

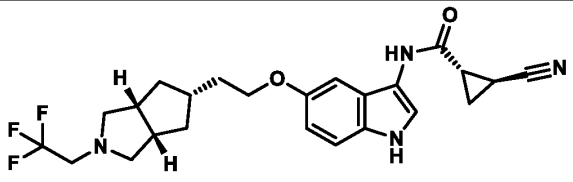
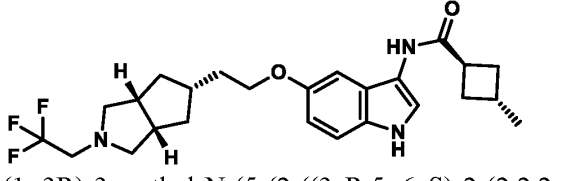
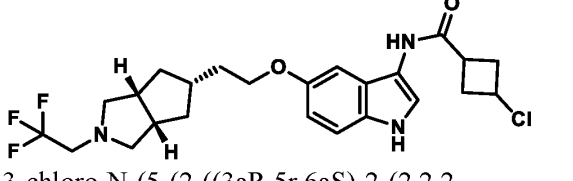
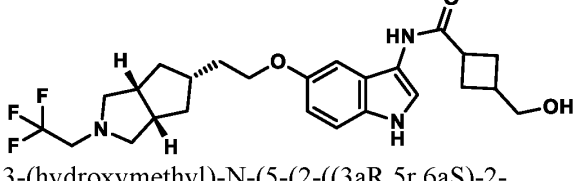
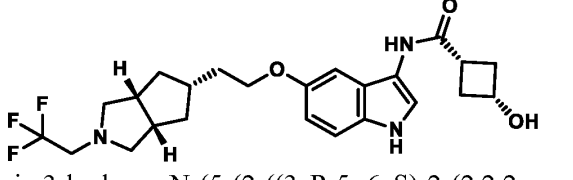
316	 N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)pivalamide	405.0
317	 N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclopropanecarboxamide	443.0
318	 2-chloro-2-fluoro-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	391.0
319	 1-(methoxymethyl)-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	375.0
320	 trans-3-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	427.2

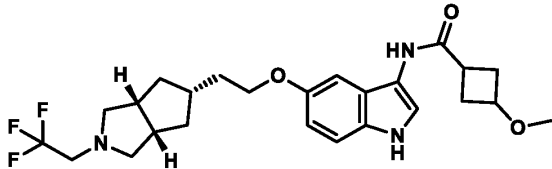
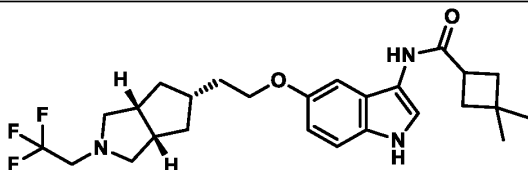
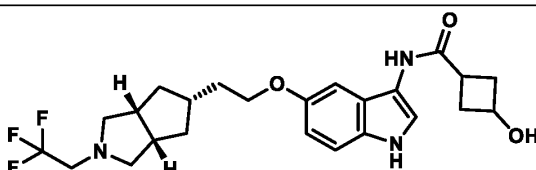
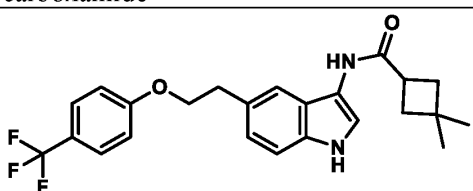
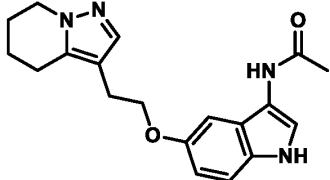
321	 cis-3-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	419.0
322	 3-chloro-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	403.3
323	 3-fluoro-3-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	403.3
324	 cis-3-hydroxy-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	423.2
325	 2-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)tetrahydrofuran-2-carboxamide	421.3

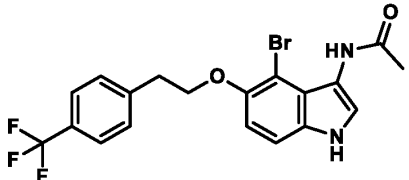
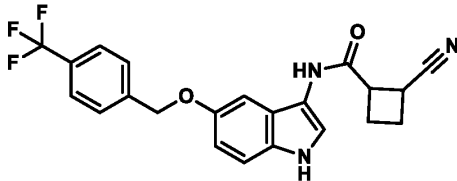
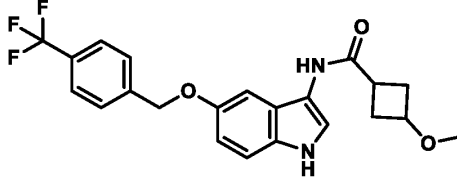
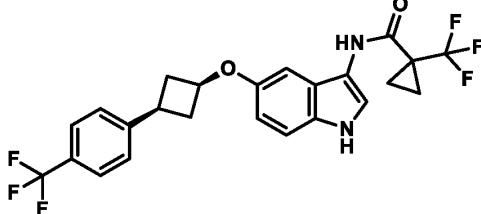
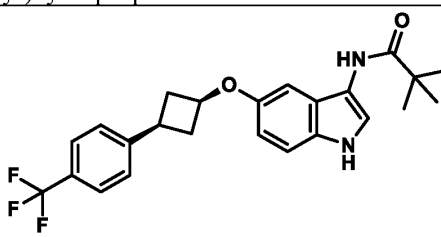
326		405.3
327		419.0
328		407.0
329		417.3
330		433.0

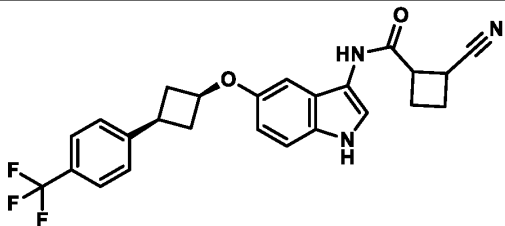
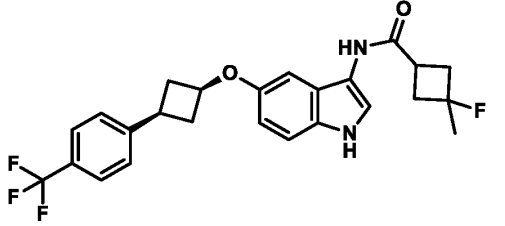
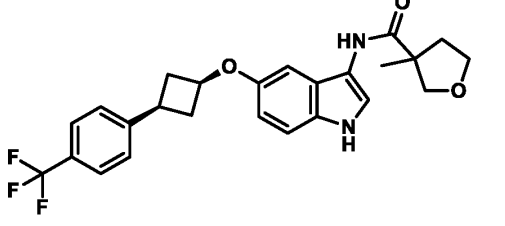
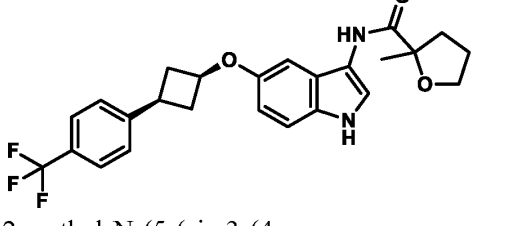
331	 1-fluoro-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	405.3
332	 cis-2-cyano-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	411.2
333	 1-(methoxymethyl)-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	393.0
334	 trans-3-methyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	440.3
335		459.1

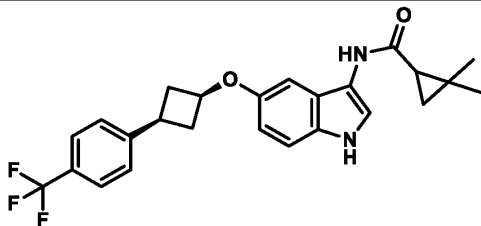
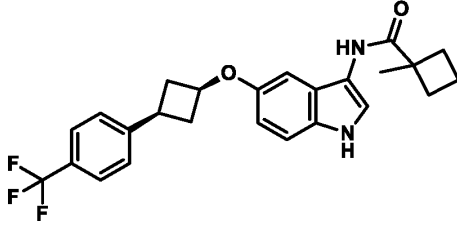
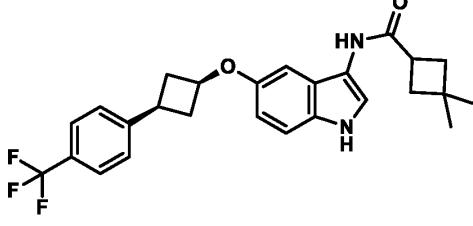
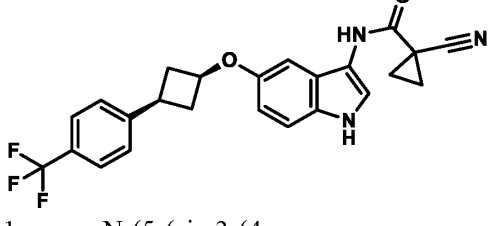
	cis-3-methyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	
336	 3-chloro-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	443.3
337	 cis-3-hydroxy-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	443.3
338	 3-hydroxy-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	463.1
339	 3,3-dimethyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)butanamide	445.3

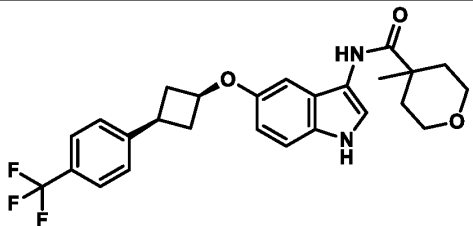
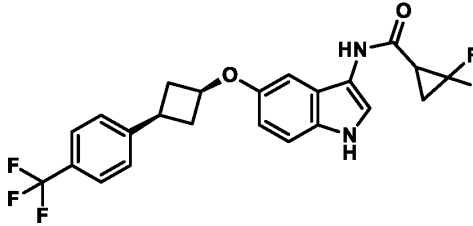
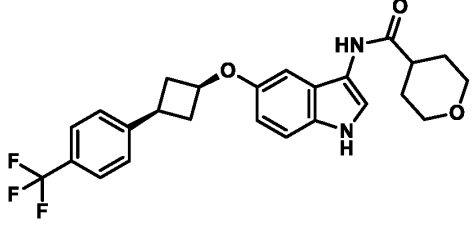
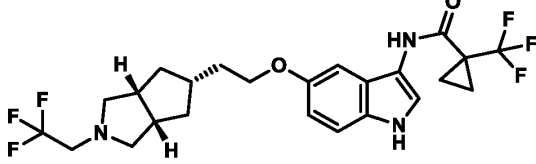
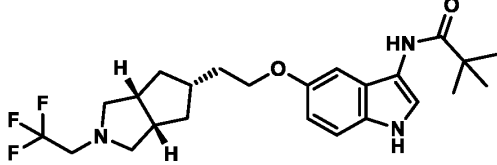
340	 (1S,2S)-2-cyano-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	445.2
341	 (1r,3R)-3-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	466.4
342	 3-chloro-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	461.4
343	 3-(hydroxymethyl)-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	464.4
344	 cis-3-hydroxy-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	484.0

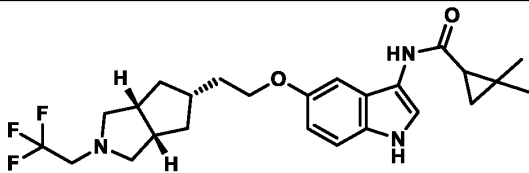
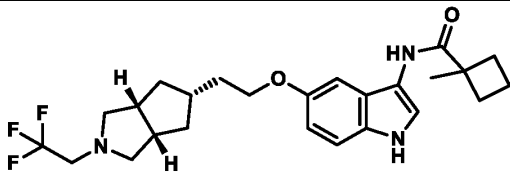
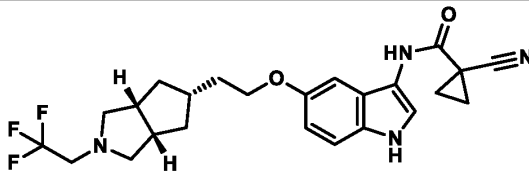
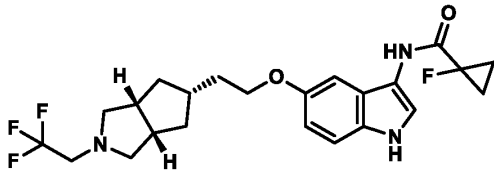
	yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	
345	 3-methoxy-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	480.3
346	 3,3-dimethyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	466.4
347	 3-hydroxy-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	480.1
348	 3,3-dimethyl-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	478.1
349		466.1

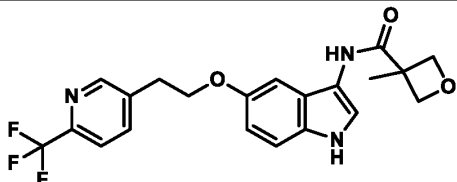
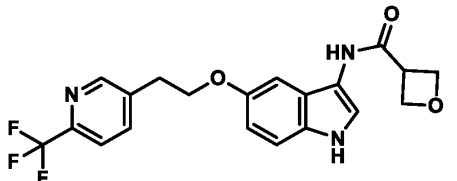
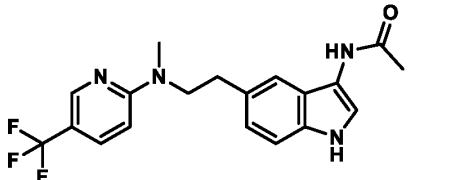
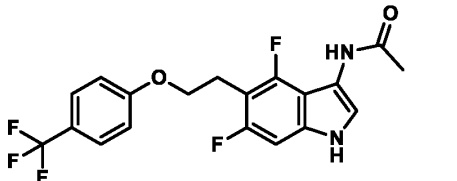
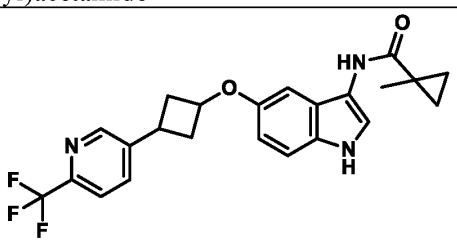
	N-(5-(2-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-yl)ethoxy)-1H-indol-3-yl)acetamide	
350	 N-(4-bromo-5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)acetamide	431.3
351	 2-cyano-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	339.1
352	 3-methoxy-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	441.0
353	 1-(trifluoromethyl)-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	414.3
354	 N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)pivalamide	419.3

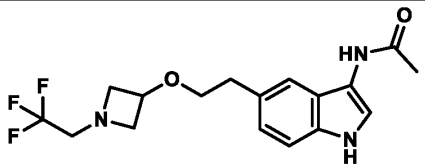
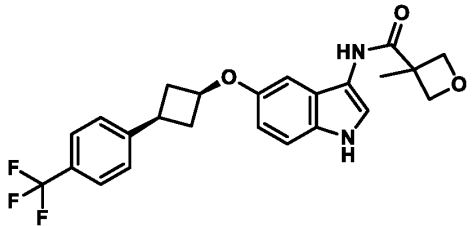
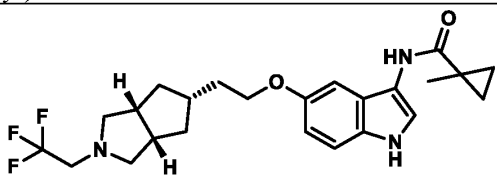
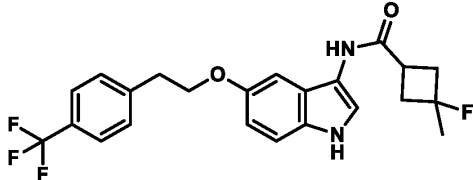
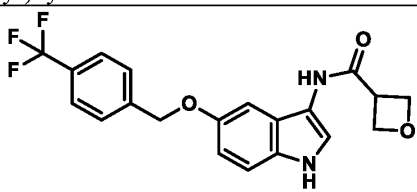
355	 2-cyano-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	483.3
356	 3-fluoro-3-methyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	431.4
357	 3-methyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)tetrahydrofuran-3-carboxamide	454.3
358	 2-methyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)tetrahydrofuran-2-carboxamide	461.3

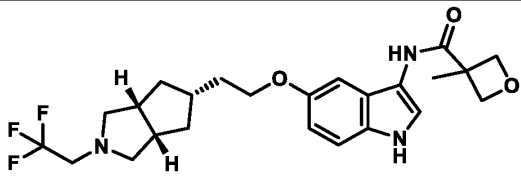
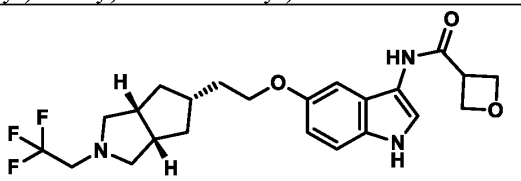
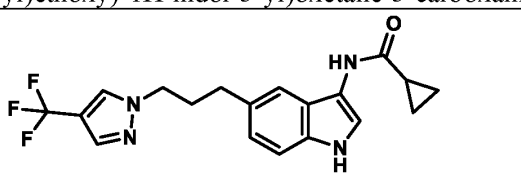
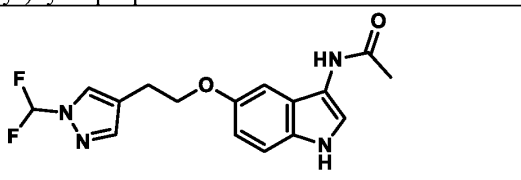
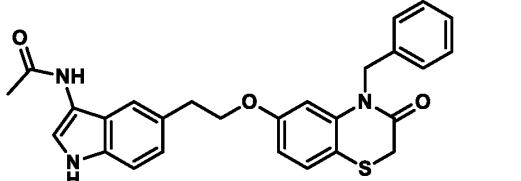
359	 2,2-dimethyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	459.3
360	 1-methyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	459.3
361	 3,3-dimethyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	443.4
362	 1-cyano-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	443.3

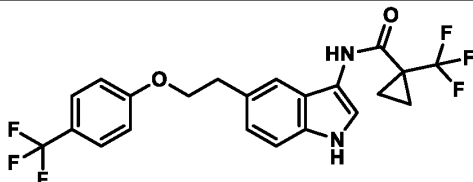
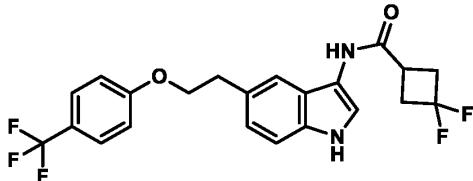
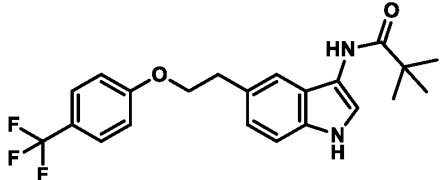
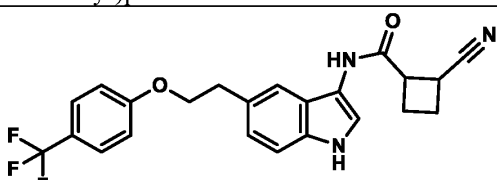
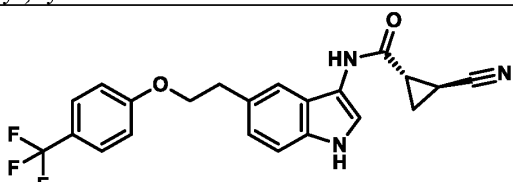
363	 4-methyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)tetrahydro-2H-pyran-4-carboxamide	457.3
364	 2,2-difluoro-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	440.3
365	 N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)tetrahydro-2H-pyran-4-carboxamide	473.3
366	 N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)-1-(trifluoromethyl)cyclopropane-1-carboxamide	451.3
367	 N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)-1-(trifluoromethyl)cyclopropane-1-carboxamide	459.3

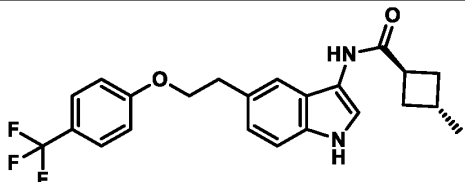
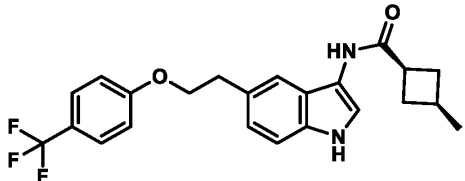
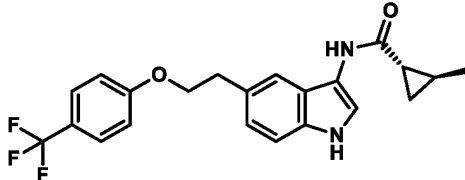
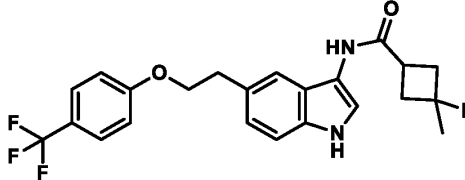
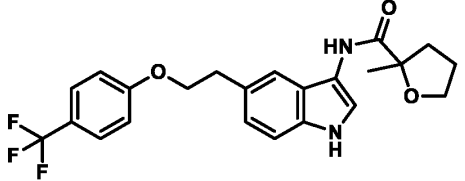
	N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)pivalamide	
368	 2,2-dimethyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	484.4
369	 1-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	504.4
370	 1-cyano-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	452.4
371	 1-fluoro-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	464.4

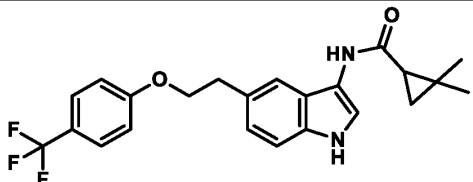
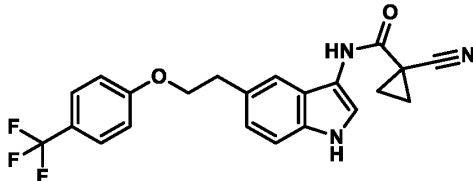
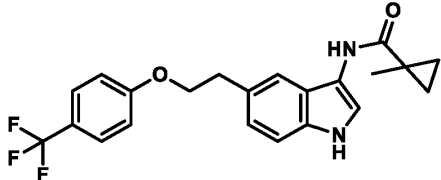
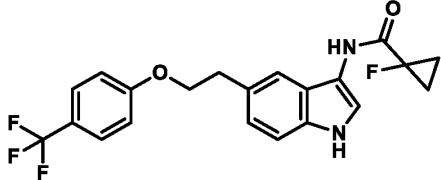
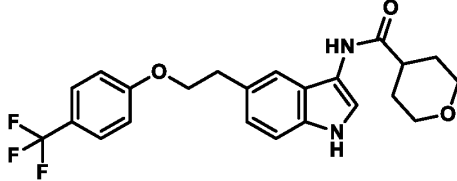
372	 3-methyl-N-(5-(2-(6-(trifluoromethyl)pyridin-3-yl)ethoxy)-1H-indol-3-yl)oxetane-3-carboxamide	464.4
373	 N-(5-(2-(6-(trifluoromethyl)pyridin-3-yl)ethoxy)-1H-indol-3-yl)oxetane-3-carboxamide	461.4
374	 N-(5-(2-(methyl(5-(trifluoromethyl)pyridin-2-yl)amino)ethyl)-1H-indol-3-yl)acetamide	454.4
375	 N-(4,6-difluoro-5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	420.05
376	 1-methyl-N-(5-(3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	406.15

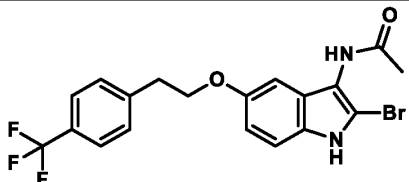
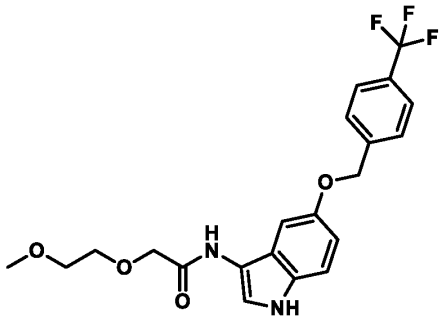
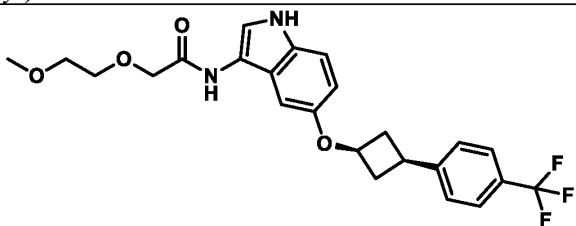
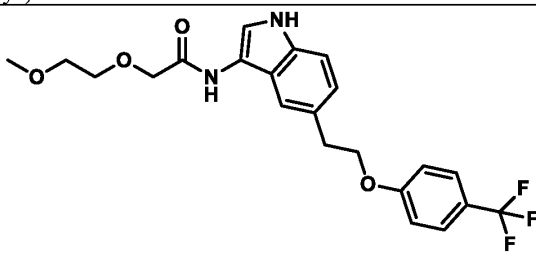
377	 N-(5-(2-((1-(2,2,2-trifluoroethyl)azetidin-3-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	377.15
378	 3-methyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)oxetane-3-carboxamide	396.9
379	 1-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	430.05
380	 3-fluoro-3-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	356.05
381	 N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)oxetane-3-carboxamide	463.3

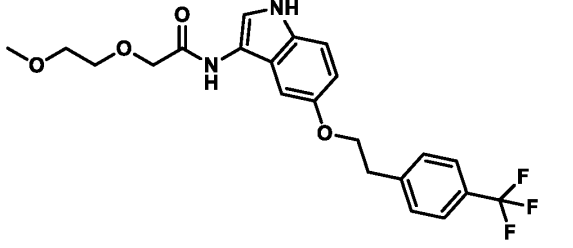
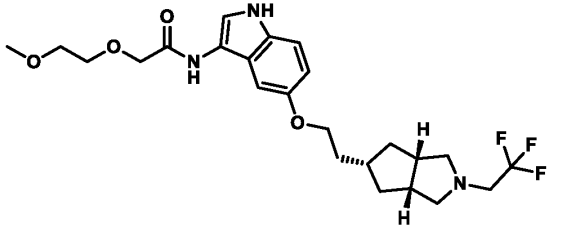
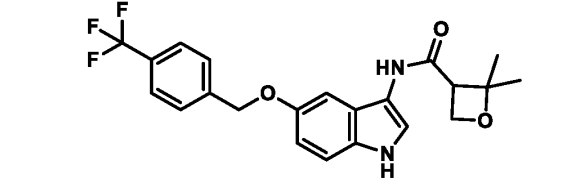
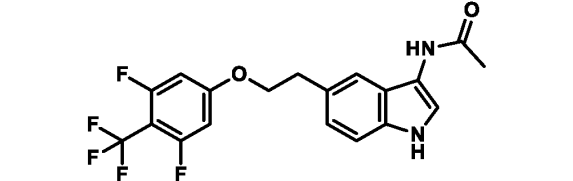
382	 3-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)oxetane-3-carboxamide	445.2
383	 N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)oxetane-3-carboxamide	450.4
384	 N-(5-(3-(4-(trifluoromethyl)-1H-pyrazol-1-yl)propyl)-1H-indol-3-yl)cyclopropanecarboxamide	435.2
385	 N-(5-(2-(1-(difluoromethyl)-1H-pyrazol-4-yl)ethoxy)-1H-indol-3-yl)acetamide	391.05
386	 N-(5-(2-((4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	466.2

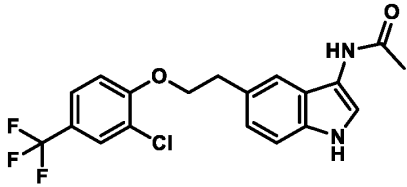
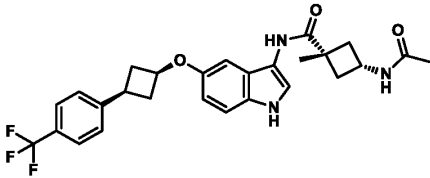
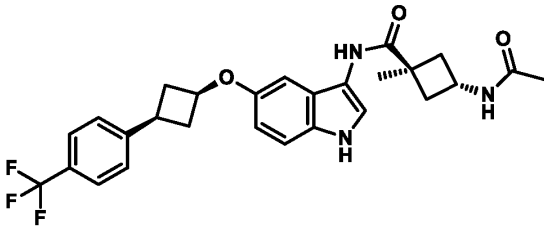
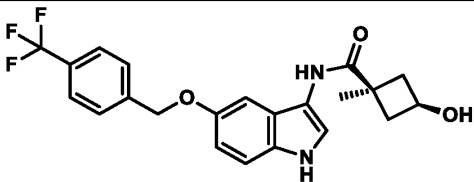
387	 1-(trifluoromethyl)-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclopropane-1-carboxamide	452.15
388	 3,3-difluoro-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	377.15
389	 N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)pivalamide	333.05
390	 2-cyano-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	470.1
391	 (1S,2S)-2-cyano-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclopropane-1-carboxamide	437.3

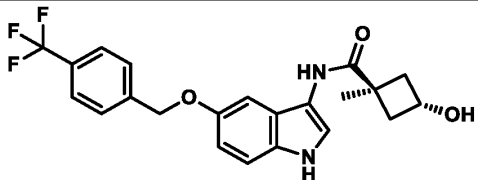
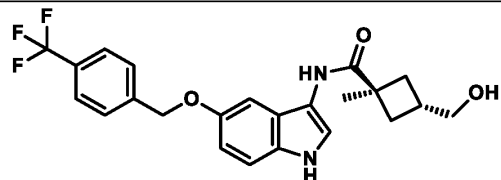
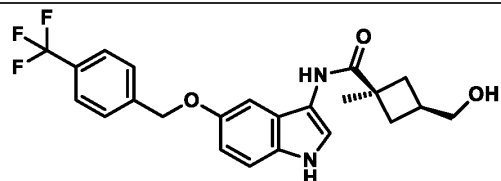
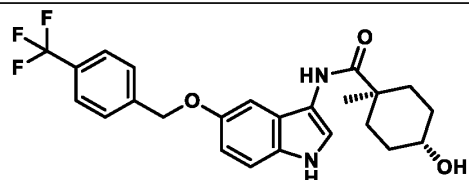
392	 trans-3-methyl-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	457.2
393	 cis-3-methyl-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	439.2
394	 (1S,2S)-2-methyl-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclopropane-1-carboxamide	405.3
395	 3-fluoro-3-methyl-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	428.2
396	 2-methyl-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)tetrahydrofuran-2-carboxamide	414.2

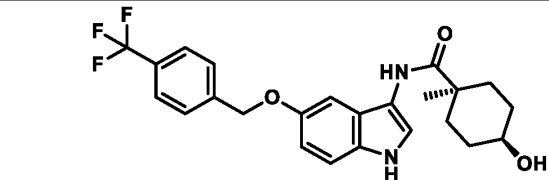
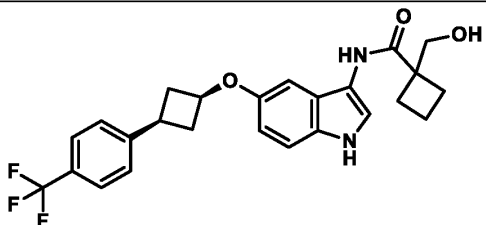
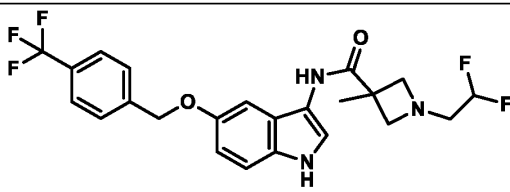
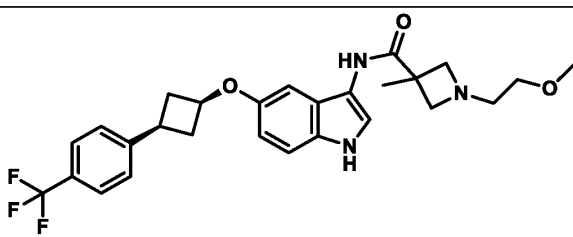
397	 2,2-dimethyl-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclopropane-1-carboxamide	417.2
398	 1-cyano-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclopropane-1-carboxamide	417.3
399	 1-methyl-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclopropane-1-carboxamide	403.2
400	 1-fluoro-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclopropane-1-carboxamide	435.3
401	 N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)tetrahydro-2H-pyran-4-carboxamide	431.2

402	 N-(2-bromo-5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)acetamide	417.3
404	 2-(2-methoxyethoxy)-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)acetamide	403.2
405	 2-(2-methoxyethoxy)-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)acetamide	407.2
406	 2-(2-methoxyethoxy)-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	433.3

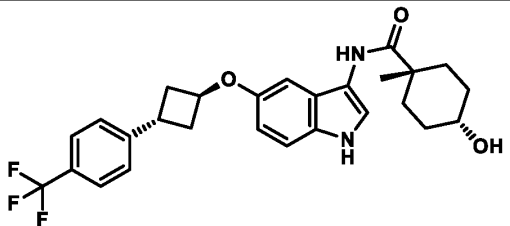
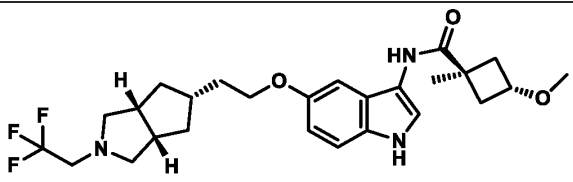
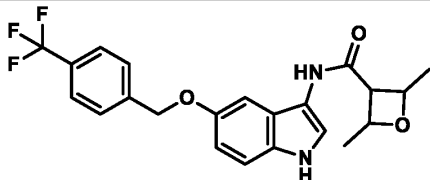
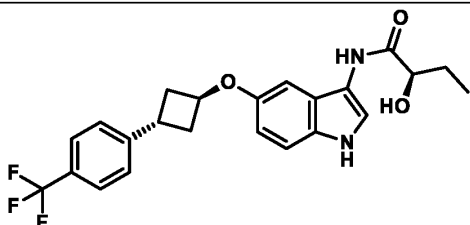
407	 2-(2-methoxyethoxy)-N-(5-(4-(trifluoromethyl)phenoxy)-1H-indol-3-yl)acetamide	437.3
408	 2-(2-methoxyethoxy)-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)acetamide	440.8
409	 2,2-dimethyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)oxetane-3-carboxamide	419.15
410	 N-(5-(2-(3,5-difluoro-4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	399.2

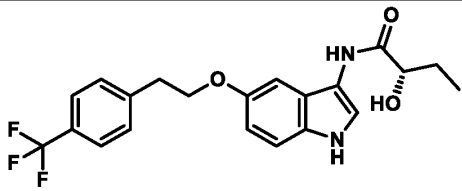
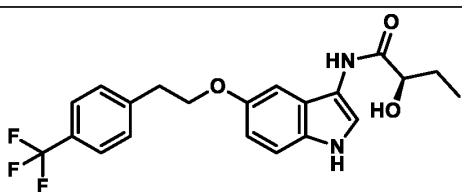
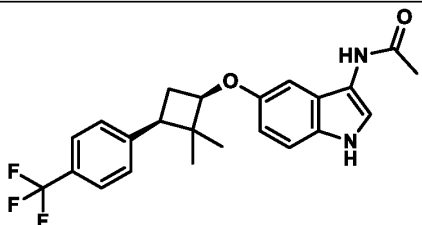
411	 N-(5-(2-(2-chloro-4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	397.1
412	 cis-3-acetamido-1-methyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	500.2
413	 trans-3-acetamido-1-methyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	500.2
414		419.15

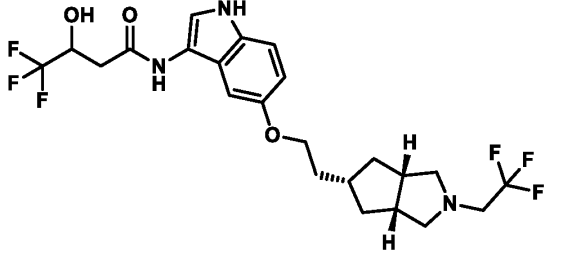
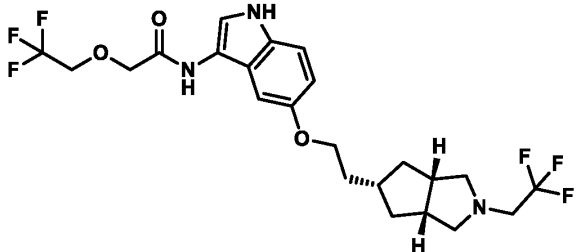
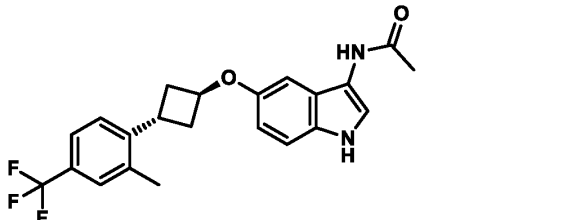
	cis-3-hydroxy-1-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	
415	 trans-3-hydroxy-1-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	419.15
416	 trans-3-(hydroxymethyl)-1-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	433.15
417	 cis-3-(hydroxymethyl)-1-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	433.25
418		447.2

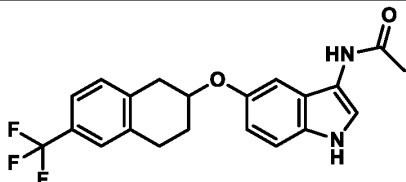
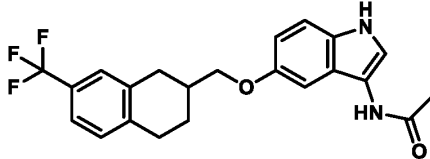
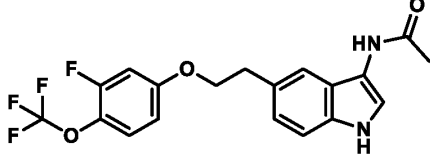
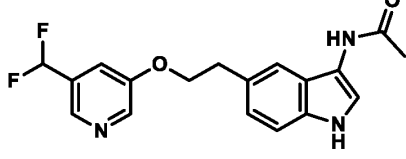
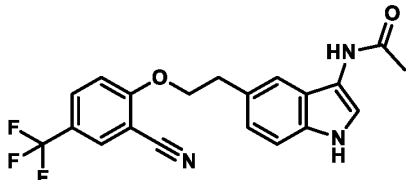
	trans-4-hydroxy-1-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclohexane-1-carboxamide	
419	 trans-4-hydroxy-1-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclohexane-1-carboxamide	447.25
420	 1-(hydroxymethyl)-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	459.15
421	 1-(2,2-difluoroethyl)-3-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)azetidine-3-carboxamide	468.1
422		502.2

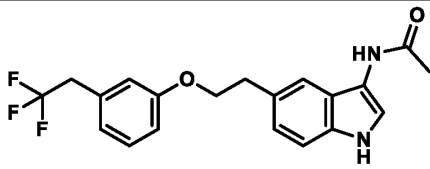
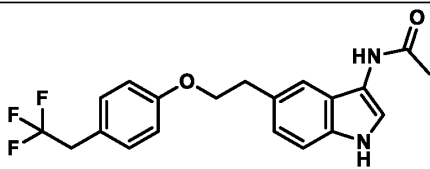
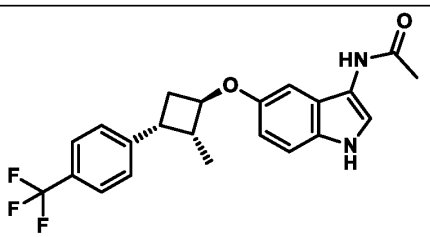
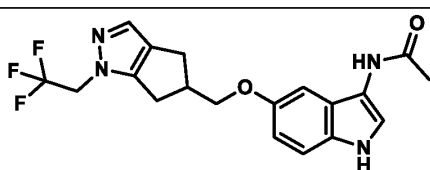
	1-(2-methoxyethyl)-3-methyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)azetidine-3-carboxamide	
423	 (2S,3R)-2-methyl-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)oxetane-3-carboxamide	445.1
424	 (2R,3R)-2-methyl-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)oxetane-3-carboxamide	445.25
425	 trans-4-hydroxy-1-methyl-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclohexane-1-carboxamide	487.2

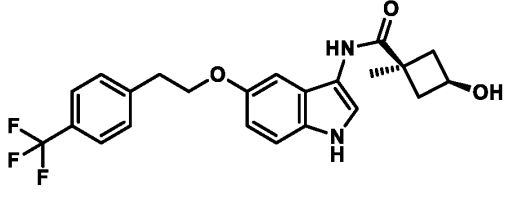
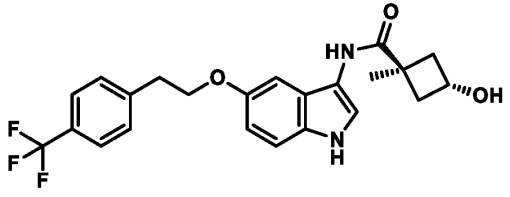
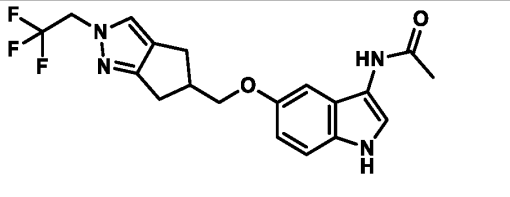
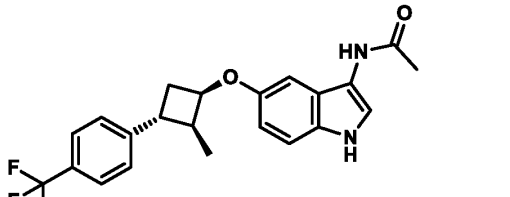
426	 cis-4-hydroxy-1-methyl-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclohexane-1-carboxamide	487.3
427	 (1r,3R)-3-methoxy-1-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	494.2
428	 2,4-dimethyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)oxetane-3-carboxamide	419.15
429		433.25

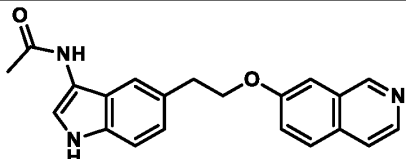
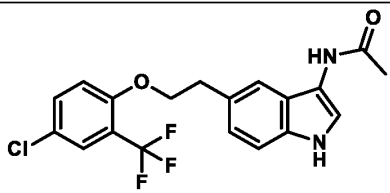
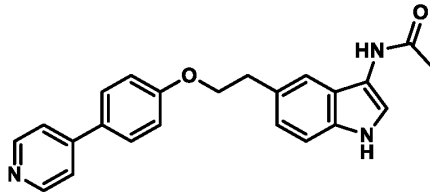
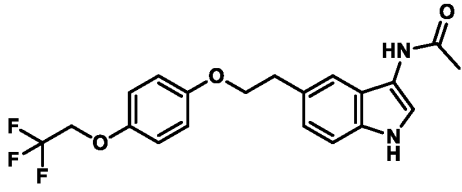
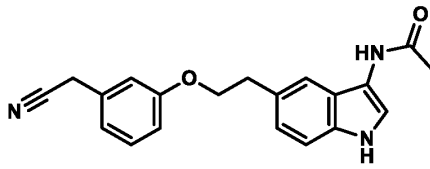
	(R)-2-hydroxy-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)butanamide	
430	 (S)-2-hydroxy-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)butanamide	407.15
431	 (R)-2-hydroxy-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)butanamide	407.2
432	 N-(5-((1R,3R)-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)acetamide	417.2

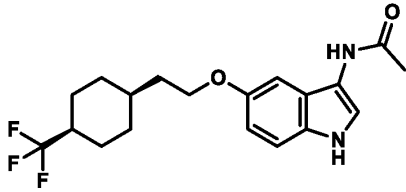
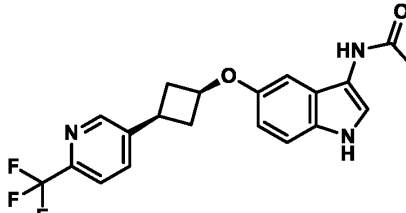
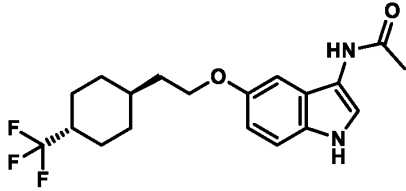
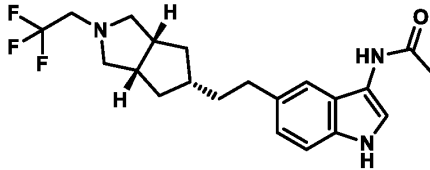
433	 4,4,4-trifluoro-3-hydroxy-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)butanamide	508.2
434	 2-(2,2,2-trifluoroethoxy)-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)acetamide	508.2
435	 N-(5-(trans-3-(2-methyl-4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)acetamide	403.15

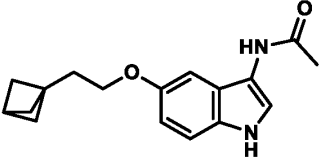
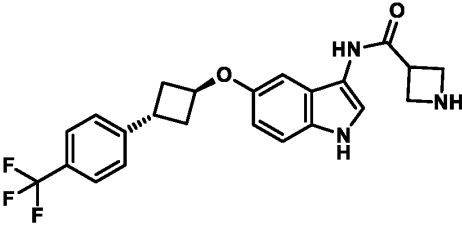
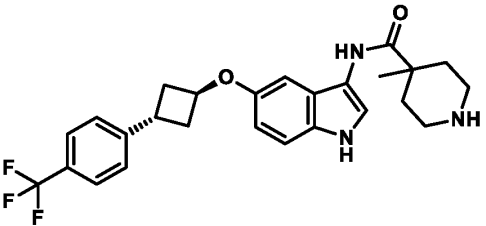
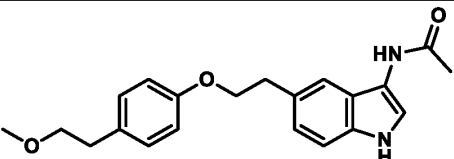
436	 N-(5-((6-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)oxy)-1H-indol-3-yl)acetamide	389.05
437	 N-(5-((7-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)methoxy)-1H-indol-3-yl)acetamide	401.1
438	 N-(5-(2-(3-fluoro-4-(trifluoromethoxy)phenoxy)ethyl)-1H-indol-3-yl)acetamide	397.3
439	 N-(5-(2-((5-(difluoromethyl)pyridin-3-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	346.2
440	 N-(5-(2-((5-(trifluoromethyl)-4-cyanophenyl)oxy)ethyl)-1H-indol-3-yl)acetamide	388.2

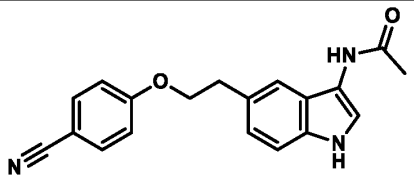
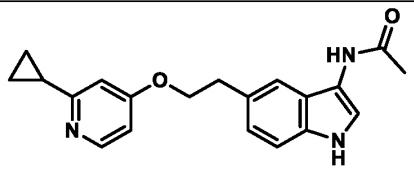
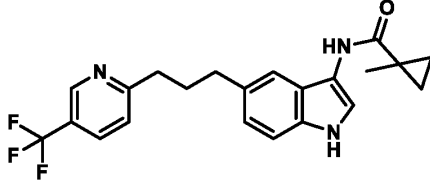
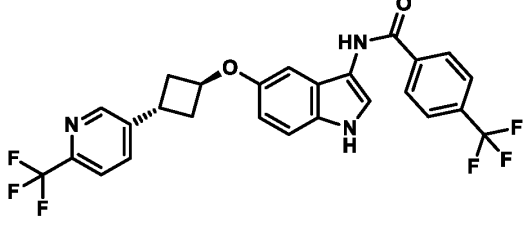
	N-(5-(2-(2-cyano-4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	
441	 N-(5-(2-(3-(2,2,2-trifluoroethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	421.2
442	 N-(5-(2-(4-(2,2,2-trifluoroethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	421.1
443	 N-(5-(((1R,2R,3R)-2-methyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)acetamide	401.1
444	 N-(5-((1-(2,2,2-trifluoroethyl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazol-5-yl)methoxy)-1H-indol-3-yl)acetamide	393.35

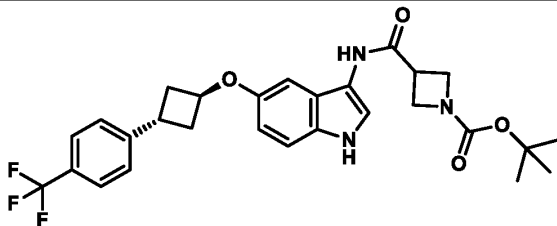
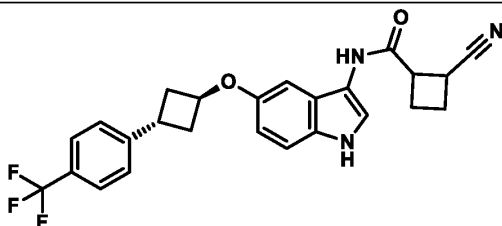
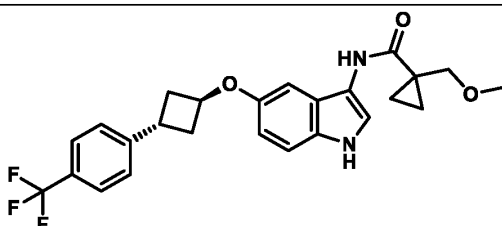
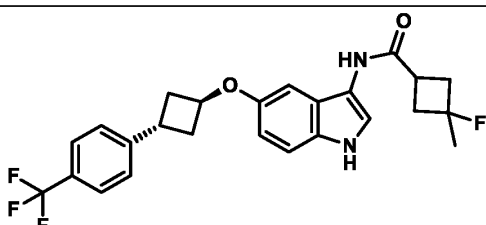
445	 (cis)-3-hydroxy-1-methyl-N-(5-(4-(trifluoromethyl)phenoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	433.15
446	 trans-3-hydroxy-1-methyl-N-(5-(4-(trifluoromethyl)phenoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	433.1
447	 N-(5-((2-(2,2,2-trifluoroethyl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-5-yl)methoxy)-1H-indol-3-yl)acetamide	393.1
448	 N-(5-((1R,2S,3R)-2-methyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)acetamide	401.1

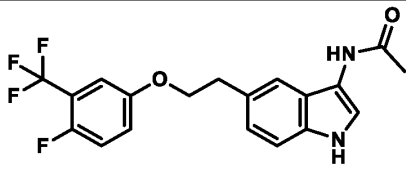
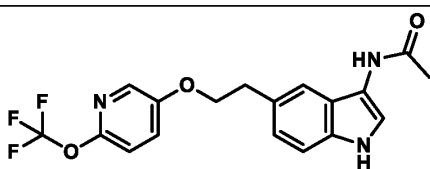
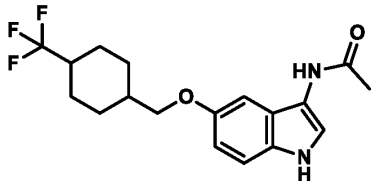
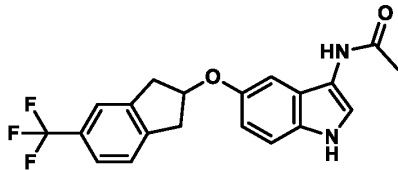
449	 N-(5-(2-(isoquinolin-7-yloxy)ethyl)-1H-indol-3-yl)acetamide	346.2
450	 N-(5-(2-(4-chloro-2-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	397.2
451	 N-(5-(2-(4-(pyridin-4-yl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	372.2
452	 N-(5-(2-(4-(2,2,2-trifluoroethoxy)phenoxy)ethyl)-1H-indol-3-yl)acetamide	393.2
453	 N-(5-(2-(4-(cyanomethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	334.3

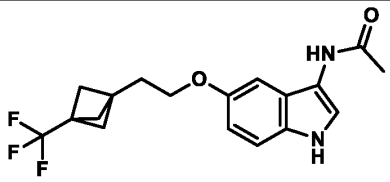
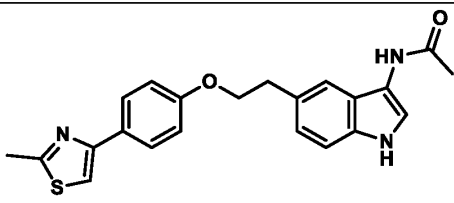
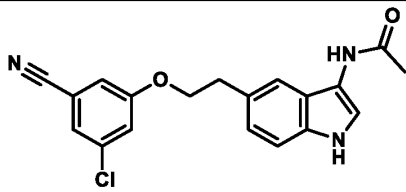
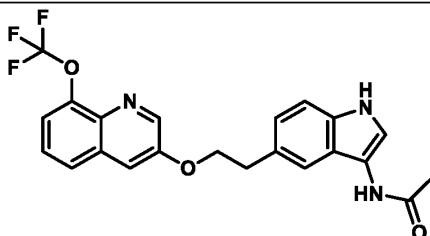
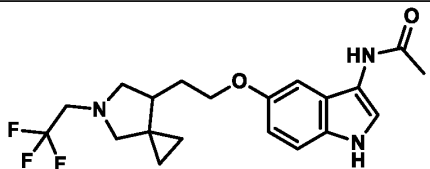
	N-(5-(2-(3-(cyanomethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	
454	 N-(5-(2-(cis-4-(trifluoromethyl)cyclohexyl)ethoxy)-1H-indol-3-yl)acetamide	369.35
455	 N-(5-(cis-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1H-indol-3-yl)acetamide	390.1
456	 N-(5-(2-(trans-4-(trifluoromethyl)cyclohexyl)ethoxy)-1H-indol-3-yl)acetamide	369.35
457	 N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethyl)-1H-indol-3-yl)acetamide	394.15

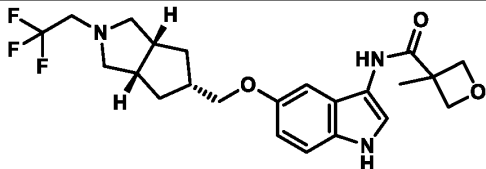
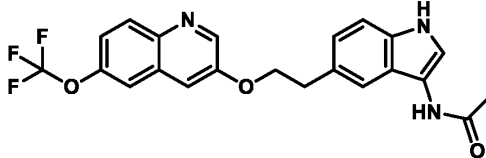
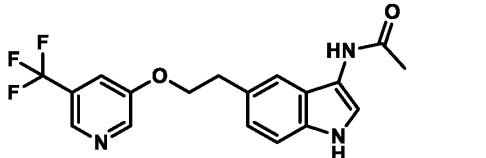
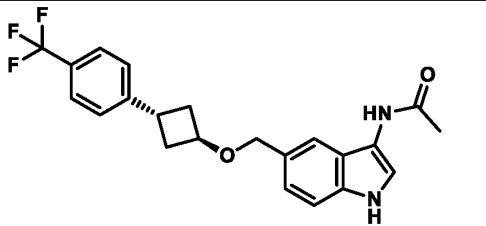
458	 N-(5-(2-(bicyclo[1.1.1]pentan-1-yl)ethoxy)-1H-indol-3-yl)acetamide	285.15
459	 N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)azetidine-3-carboxamide	430.3
460	 4-methyl-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)piperidine-4-carboxamide	472.3
461	 N-(5-(2-(4-(2-methoxyethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	353.3

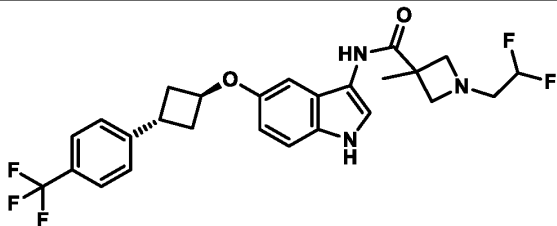
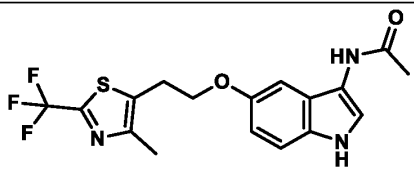
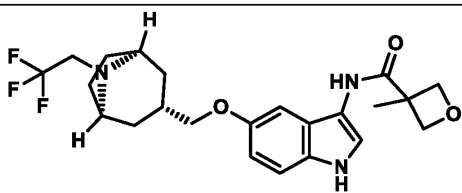
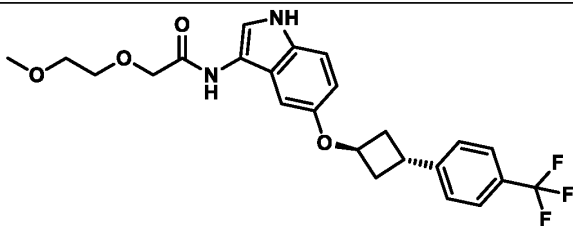
462	 N-(5-(2-(4-cyanophenoxy)ethyl)-1H-indol-3-yl)acetamide	320.2
463	 N-(5-(2-((2-cyclopropylpyridin-4-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	336.3
464	 1-methyl-N-(5-(3-(5-(trifluoromethyl)pyridin-2-yl)propyl)-1H-indol-3-yl)cyclopropane-1-carboxamide	402.1
465	 4-(trifluoromethyl)-N-(5-(trans-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1H-indol-3-yl)benzamide	518.1

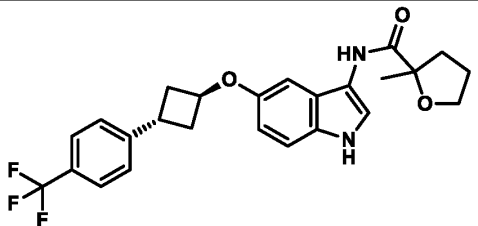
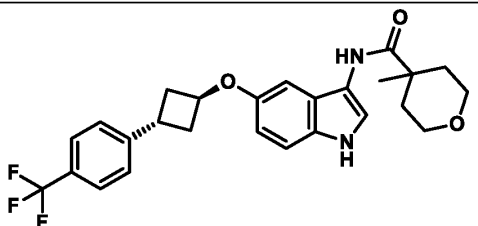
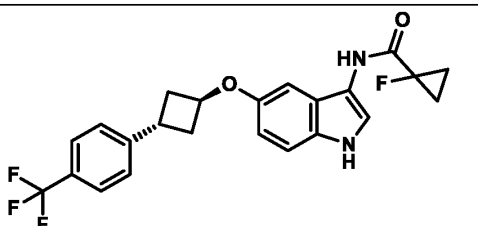
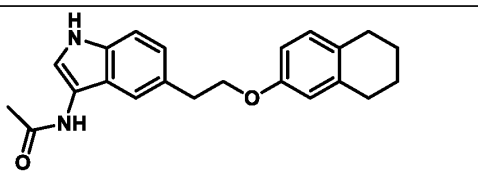
466	 tert-butyl 3-((5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)carbamoyl)azetidine-1-carboxylate	529.3
467	 2-cyano-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	454.3
468	 1-(methoxymethyl)-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	459.3
469	 2-fluoro-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	461.3

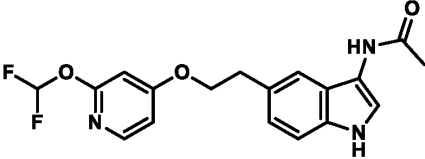
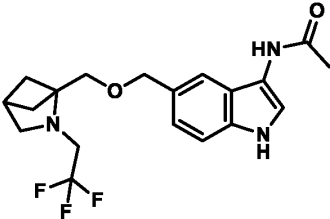
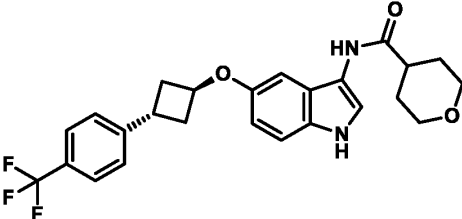
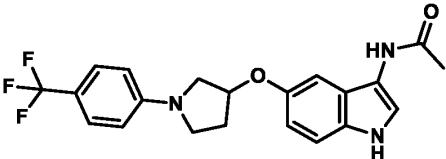
	3-fluoro-3-methyl-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	
470	 N-(5-(2-(4-fluoro-3-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	381.2
471	 N-(5-(2-((6-(trifluoromethoxy)pyridin-3-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	380.2
472	 N-(5-((4-(trifluoromethyl)cyclohexyl)methoxy)-1H-indol-3-yl)acetamide	355.25
473	 N-(5-((5-(trifluoromethyl)-2,3-dihydro-1H-inden-2-yl)oxy)-1H-indol-3-yl)acetamide	375.25

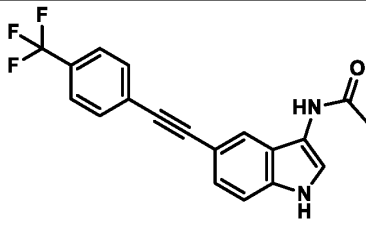
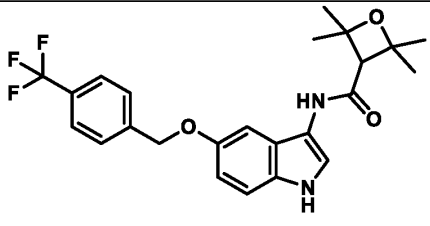
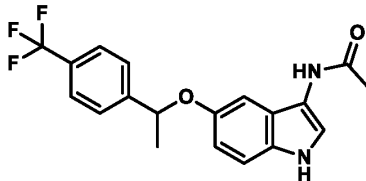
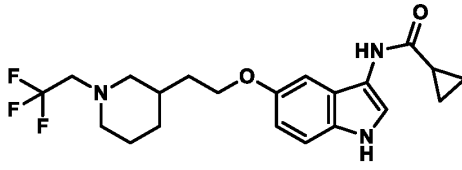
474	 N-(5-(2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)ethoxy)-1H-indol-3-yl)acetamide	353.15
475	 N-(5-(2-(4-(2-methylthiazol-4-yl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	392.2
476	 N-(5-(2-(3-chloro-5-cyanophenoxy)ethyl)-1H-indol-3-yl)acetamide	354.2
477	 N-(5-(2-((8-(trifluoromethoxy)quinolin-3-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	430.3
478	 N-(5-(2-(1-(trifluoromethyl)adamantan-1-yl)ethoxy)-1H-indol-3-yl)acetamide	396.1

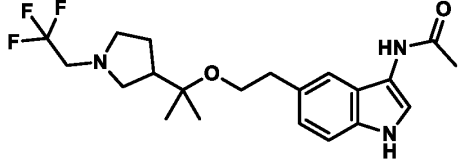
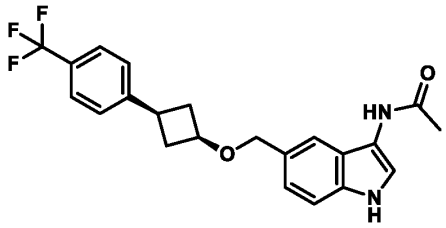
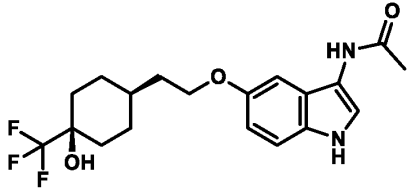
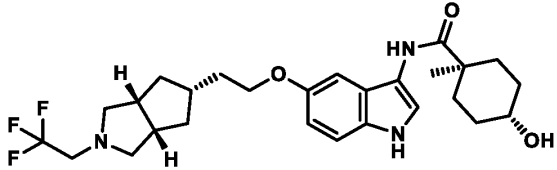
	N-(5-(2-(5-(2,2,2-trifluoroethyl)-5-azaspiro[2.4]heptan-7-yl)ethoxy)-1H-indol-3-yl)acetamide	
479	 3-methyl-N-(5-(((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)methoxy)-1H-indol-3-yl)oxetane-3-carboxamide	452.15
480	 N-(5-(2-(((6-(trifluoromethoxy)quinolin-3-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	430.3
481	 N-(5-(2-((5-(trifluoromethyl)pyridin-3-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	364.2
482	 N-(5-(((trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)methyl)-1H-indol-3-yl)acetamide	401.1

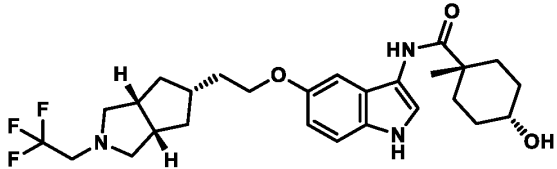
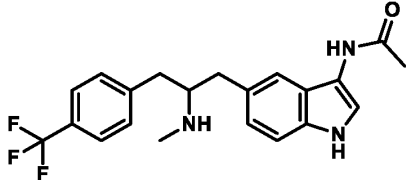
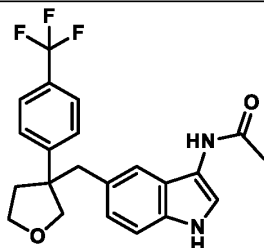
483	 1-(2,2-difluoroethyl)-3-methyl-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)azetidine-3-carboxamide	508.2
484	 N-(5-(2-(4-methyl-2-(trifluoromethyl)thiazol-5-yl)ethoxy)-1H-indol-3-yl)acetamide	382.05
485	 3-methyl-N-(5-(((1R,3s,5S)-8-(2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octan-3-yl)methoxy)-1H-indol-3-yl)oxetane-3-carboxamide	452.1
486	 2-(2-methoxyethoxy)-N-(5-((trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)acetamide	463.3

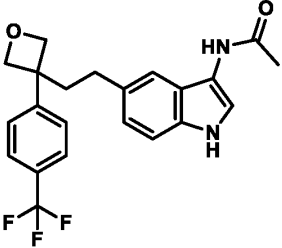
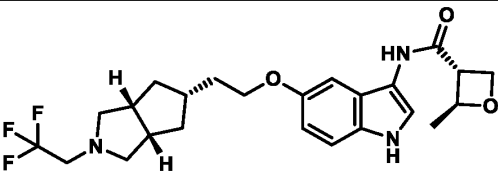
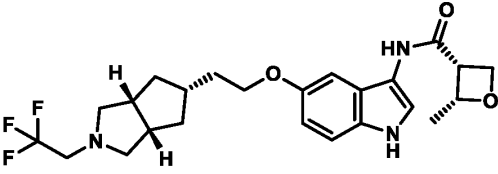
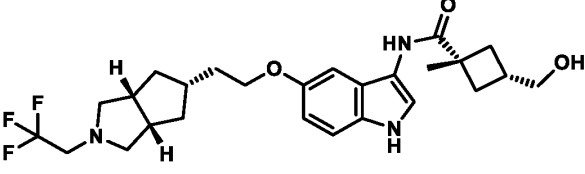
487	 2-methyl-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)tetrahydrofuran-2-carboxamide	459.3
488	 4-methyl-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)tetrahydro-2H-pyran-4-carboxamide	473.4
489	 1-fluoro-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	433.2
490	 N-(5-(2-((5,6,7,8-tetrahydronaphthalen-2-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	349.3

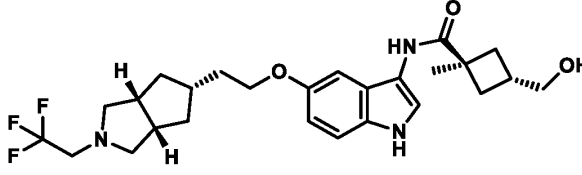
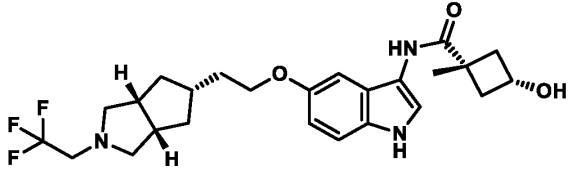
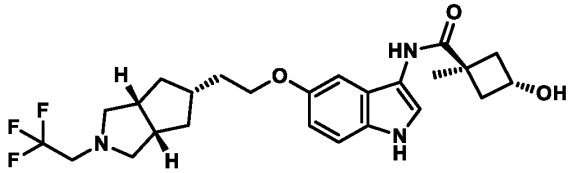
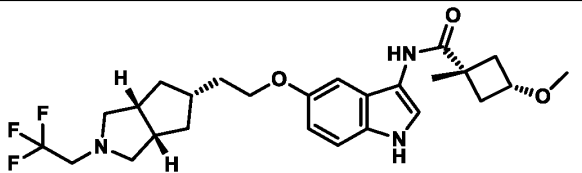
491	 N-(5-(2-((2-(difluoromethoxy)pyridin-4-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	362.2
492	 N-(5-(((2-(2,2,2-trifluoroethyl)-2-azabicyclo[2.1.1]hexan-1-yl)methoxy)methyl)-1H-indol-3-yl)acetamide	382.05
493	 N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)tetrahydro-2H-pyran-4-carboxamide	459.3
494	 N-(5-((1-(4-(trifluoromethyl)phenyl)pyrrolidin-3-yl)oxy)-1H-indol-3-yl)acetamide	404.05

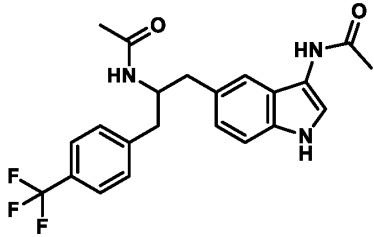
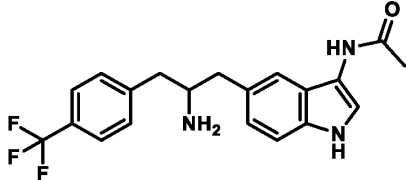
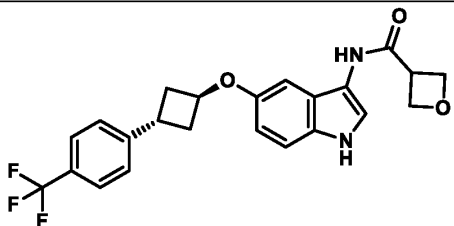
495	 N-(5-((4-(trifluoromethyl)phenyl)ethynyl)-1H-indol-3-yl)acetamide	341.05
496	 2,2,4,4-tetramethyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)oxetane-3-carboxamide	445.1
497	 N-(5-(1-(4-(trifluoromethyl)phenyl)ethoxy)-1H-indol-3-yl)acetamide	361.05
498	 N-(5-(2-(1-(2,2,2-trifluoroethyl)piperidin-3-yl)ethoxy)-1H-indol-3-yl)cyclopropanecarboxamide	410.15

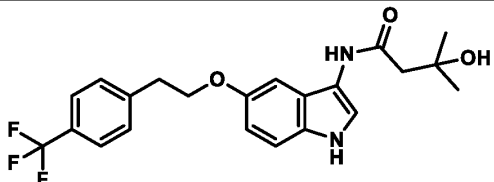
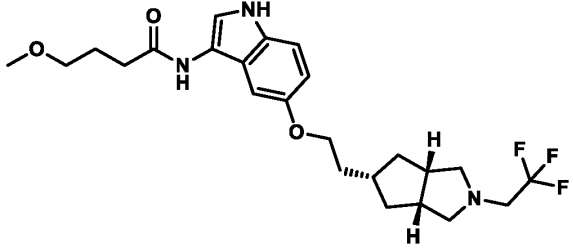
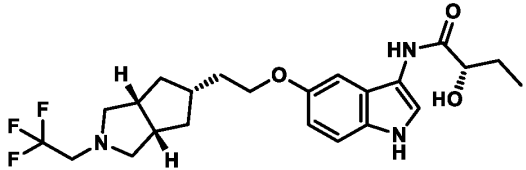
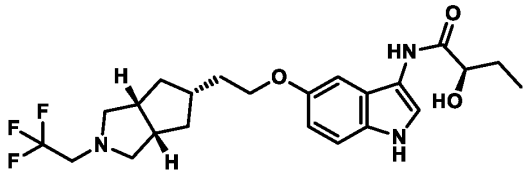
499	 N-(5-(2-((2-(1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)propan-2-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	412.2
500	 N-(5-((cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)methyl)-1H-indol-3-yl)acetamide	401.1
501	 N-(5-(2-(trans-4-hydroxy-4-(trifluoromethyl)cyclohexyl)ethoxy)-1H-indol-3-yl)acetamide	385.05
504	 (1r,4R)-4-hydroxy-1-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)oxy)methyl)-1H-indol-3-yl)acetamide	508.2

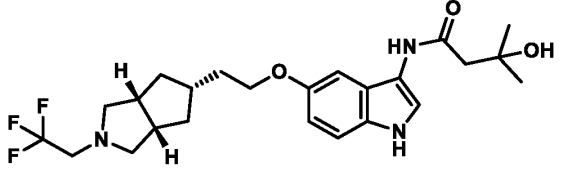
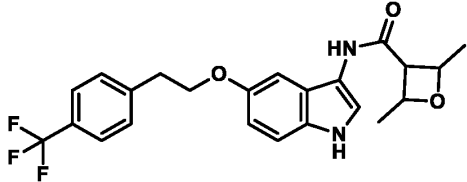
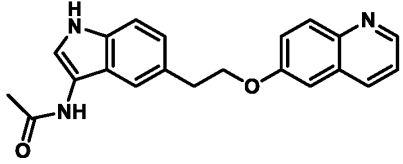
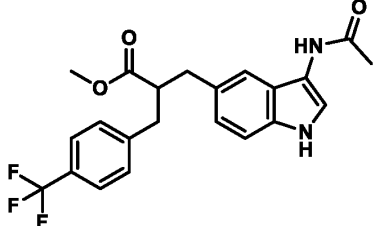
	yl)ethoxy)-1H-indol-3-yl)cyclohexane-1-carboxamide	
505	 (1s,4S)-4-hydroxy-1-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclohexane-1-carboxamide	508.2
506	 N-(5-(2-(methylamino)-3-(4-(trifluoromethyl)phenyl)propyl)-1H-indol-3-yl)acetamide	390.15
507	 N-(5-((3-(4-(trifluoromethyl)phenyl)tetrahydrofuran-3-yl)methyl)-1H-indol-3-yl)acetamide	403.05

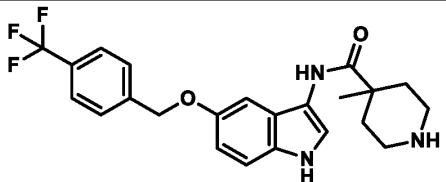
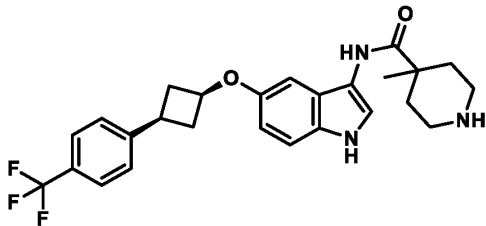
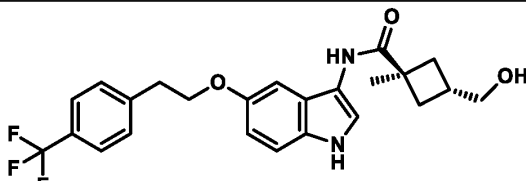
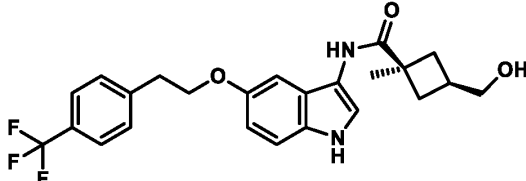
508	 N-(5-(2-(3-(4-(trifluoromethyl)phenyl)oxetan-3-yl)ethyl)-1H-indol-3-yl)acetamide	403.05
509	 (2S,3R)-2-methyl-N-(5-(2-(((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)oxetane-3-carboxamide	466.2
510	 (2R,3R)-2-methyl-N-(5-(2-(((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)oxetane-3-carboxamide	466.2
511	 (1s,3S)-3-(hydroxymethyl)-1-methyl-N-(5-(2-(((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	494.2

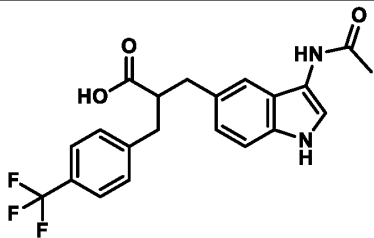
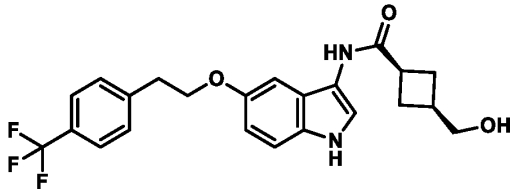
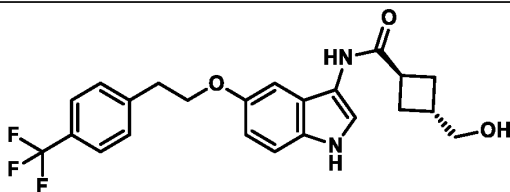
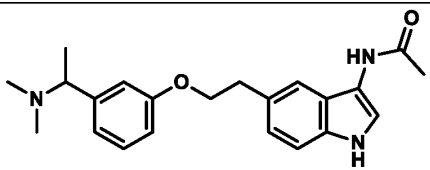
512	 (1r,3R)-3-(hydroxymethyl)-1-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	494.2
513	 (1s,3S)-3-hydroxy-1-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	480.2
514	 (1r,3R)-3-hydroxy-1-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	480.2
515	 (1r,3R)-3-(methoxymethyl)-1-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	494.2

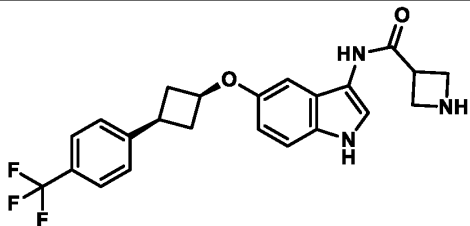
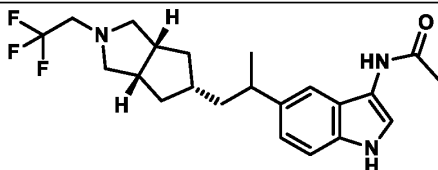
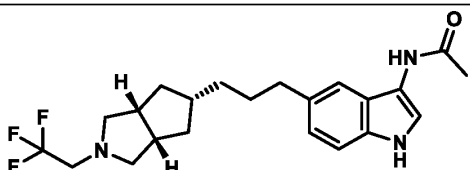
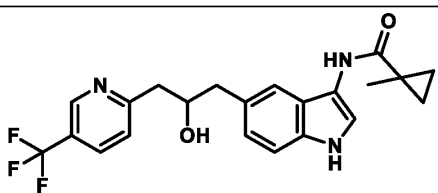
	(1 <i>s</i> ,3 <i>S</i>)-3-methoxy-1-methyl-N-(5-(2-((3 <i>aR</i> ,5 <i>r</i> ,6 <i>aS</i>)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[<i>c</i>]pyrrol-5-yl)ethoxy)-1 <i>H</i> -indol-3-yl)cyclobutane-1-carboxamide	
516	 N-(1-(3-acetamido-1<i>H</i>-indol-5-yl)-3-(4-(trifluoromethyl)phenyl)propan-2-yl)acetamide	418.15
517	 N-(5-(2-amino-3-(4-(trifluoromethyl)phenyl)propyl)-1<i>H</i>-indol-3-yl)acetamide	376.1
518	 N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1<i>H</i>-indol-3-yl)oxetane-3-carboxamide	431.1

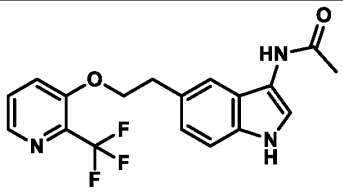
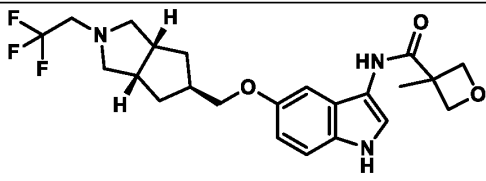
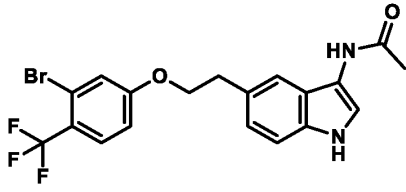
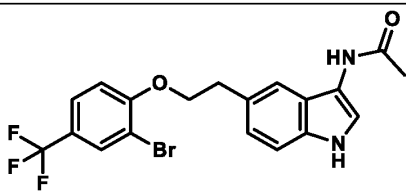
519	 3-hydroxy-3-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)butanamide	421.15
520	 4-methoxy-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)butanamide	468.25
521	 (S)-2-hydroxy-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)butanamide	454.2
522	 (R)-2-hydroxy-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)butanamide	454.2

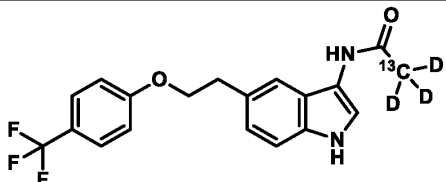
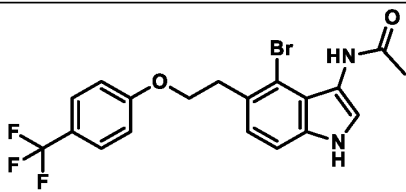
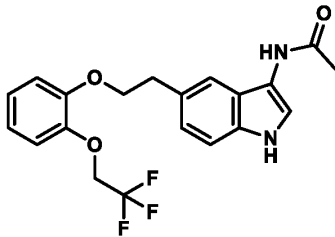
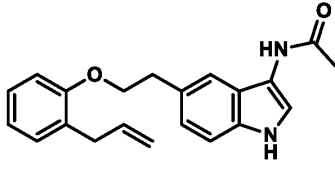
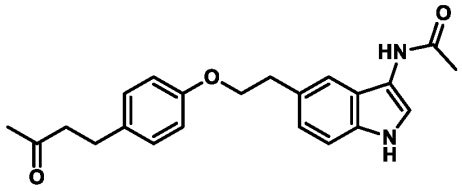
523	 3-hydroxy-3-methyl-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)butanamide	468.15
525	 2,4-dimethyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)oxetane-3-carboxamide	433.1
526	 N-(5-(2-(quinolin-6-yloxy)ethyl)-1H-indol-3-yl)acetamide	346.2
527	 methyl 3-(3-acetamido-1H-indol-5-yl)-2-(4-(trifluoromethyl)benzyl)propanoate	419.3

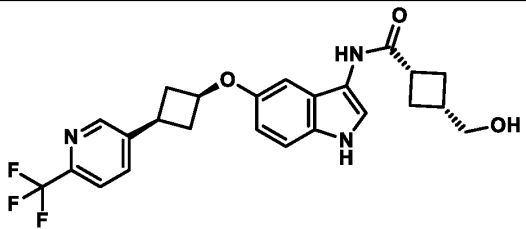
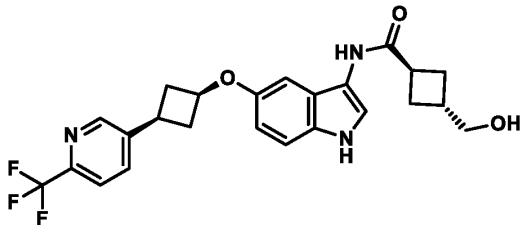
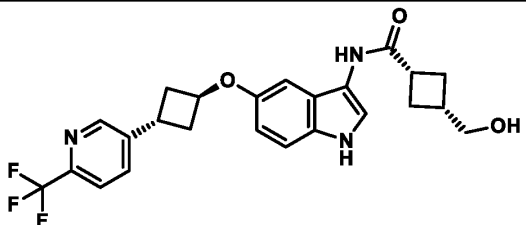
528	 4-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)piperidine-4-carboxamide	432.4
529	 4-methyl-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)piperidine-4-carboxamide	472.3
530	 trans-3-(hydroxymethyl)-1-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	447.2
531	 cis-3-(hydroxymethyl)-1-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	447.15

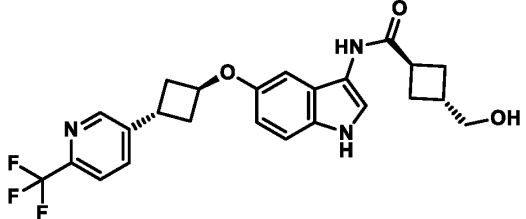
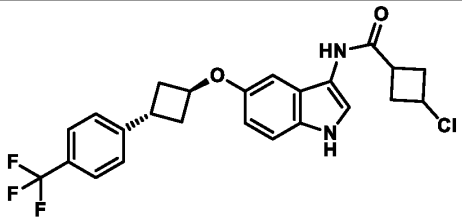
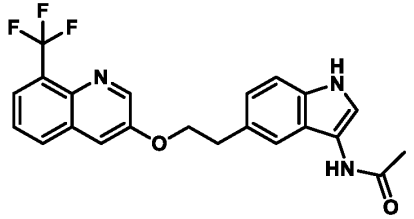
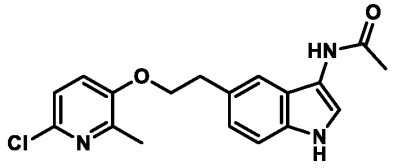
532	 3-(3-acetamido-1H-indol-5-yl)-2-(4-(trifluoromethyl)benzyl)propanoic acid	403.0
533	 cis-3-(hydroxymethyl)-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	433.1
534	 trans-3-(hydroxymethyl)-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	433.15
536	 N-(5-(2-(3-(1-(dimethylamino)ethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	366.3

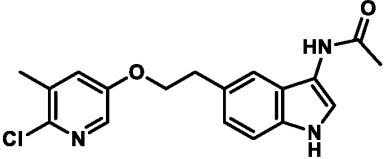
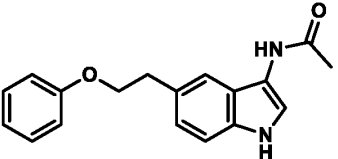
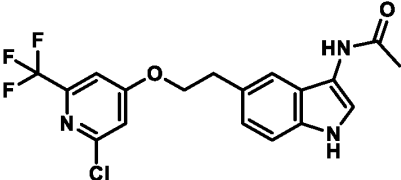
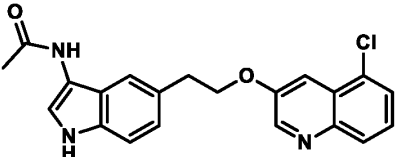
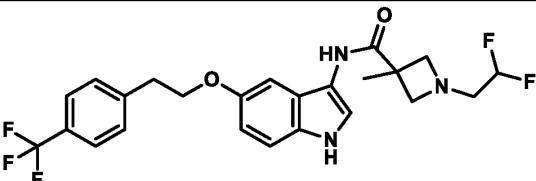
537	 N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)azetidine-3-carboxamide	430.3
538	 N-(5-(1-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)propan-2-yl)-1H-indol-3-yl)acetamide	408.2
539	 N-(5-(3-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)propyl)-1H-indol-3-yl)acetamide	408.2
540	 N-(5-(2-hydroxy-3-(5-(trifluoromethyl)pyridin-2-yl)propyl)-1H-indol-3-yl)-1-methylcyclopropane-1-carboxamide	418.2

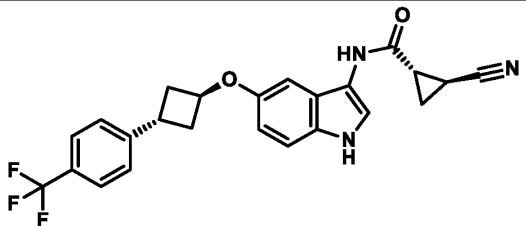
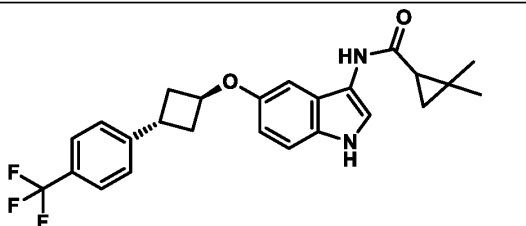
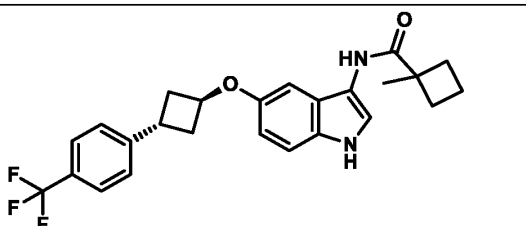
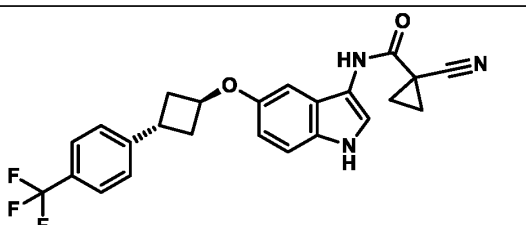
541	 N-(5-(2-((2-(trifluoromethyl)pyridin-3-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	364.3
542	 3-methyl-N-(5-(((3aR,5s,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)methoxy)-1H-indol-3-yl)oxetane-3-carboxamide	452.15
543	 N-(5-(2-(3-bromo-4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	439.0
544	 N-(5-(2-(2-bromo-4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	438.95

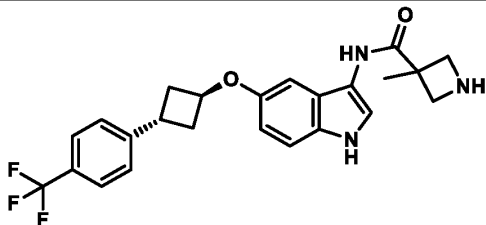
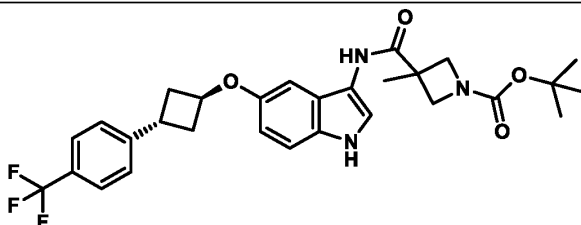
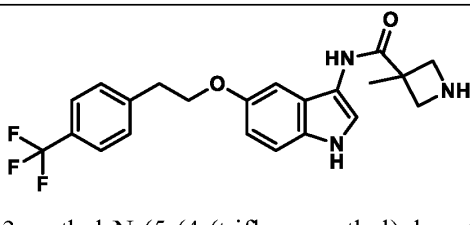
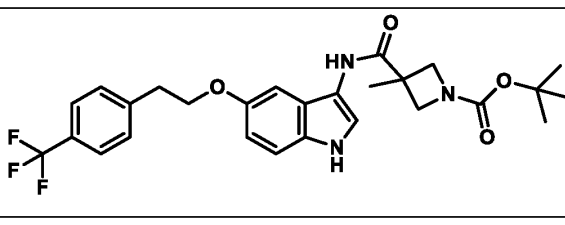
545	 N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide-2-¹³C-2,2,2-d₃	365.0
546	 N-(4-bromo-5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	441.05
547	 N-(5-(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)-1H-indol-3-yl)acetamide	393.3
548	 N-(5-(2-(2-allylphenoxy)ethyl)-1H-indol-3-yl)acetamide	335.3
549	 N-(5-(2-(4-(4-oxopentyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	365.3

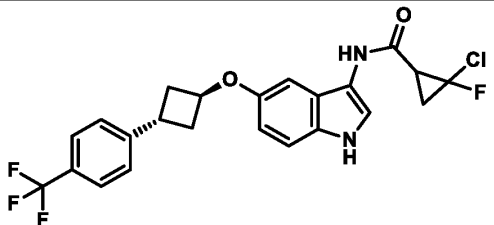
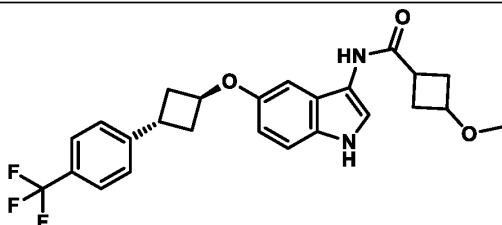
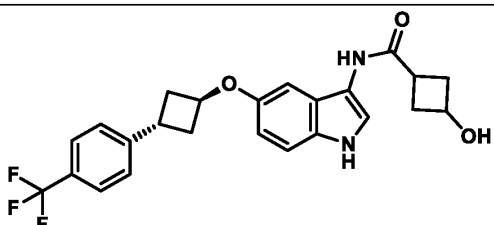
	N-(5-(2-(4-(3-oxobutyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	
550	 cis-3-(hydroxymethyl)-N-(5-(cis-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	460.1
551	 trans-3-(hydroxymethyl)-N-(5-(cis-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	460.1
552	 cis-3-(hydroxymethyl)-N-(5-(trans-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	458.1

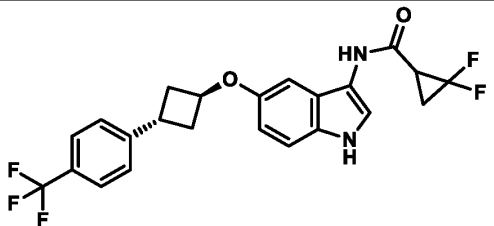
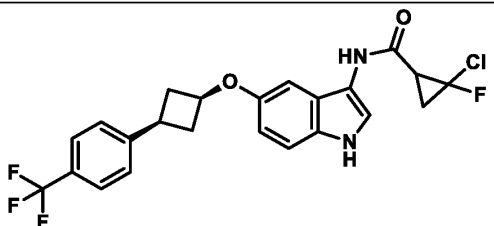
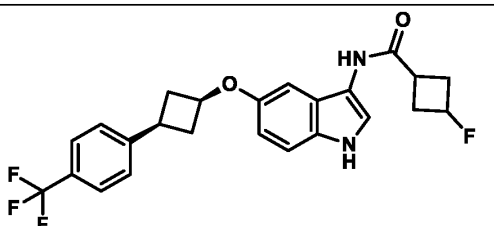
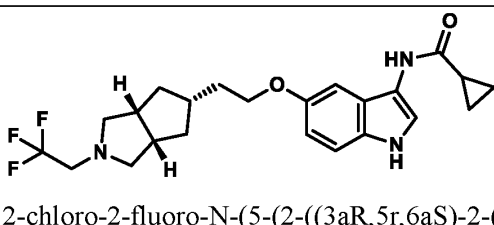
553	 trans-3-(hydroxymethyl)-N-(5-(trans-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	458.1
554	 3-chloro-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	463.2
555	 N-(5-(2-((8-(trifluoromethyl)quinolin-3-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	414.3
556	 N-(5-(2-((6-chloro-2-methylpyridin-3-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	344.2

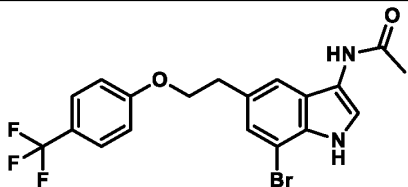
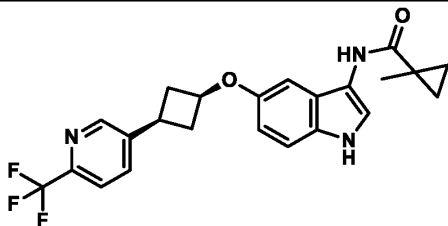
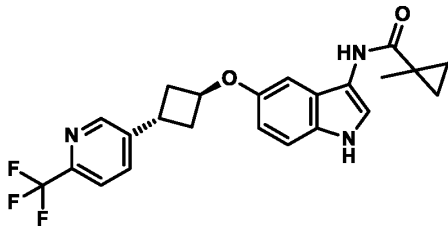
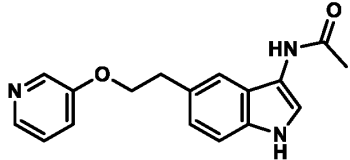
557	 N-(5-(2-((6-chloro-5-methylpyridin-3-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	344.2
558	 N-(5-(2-phenoxyethyl)-1H-indol-3-yl)acetamide	295.2
559	 N-(5-(2-((2-chloro-6-(trifluoromethyl)pyridin-4-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	398.2
560	 N-(5-(2-((5-chloroquinolin-3-yl)oxy)ethyl)-1H-indol-3-yl)acetamide	380.2
561	 1-(2,2-difluoroethyl)-3-methyl-N-(5-(4-(trifluoromethyl)phenoxy)-1H-indol-3-yl)azetidine-3-carboxamide	480.15

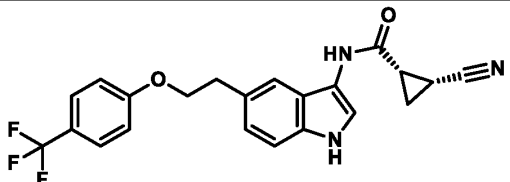
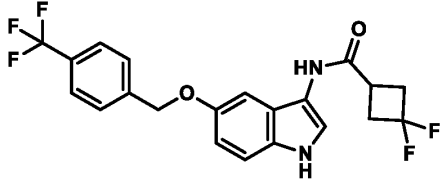
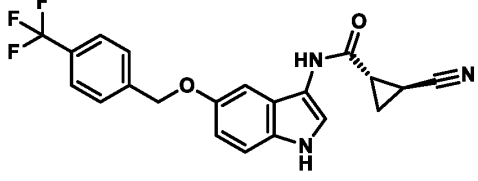
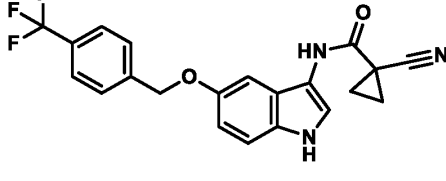
562	 (1s,2s)-2-cyano-N-(5-((trans)-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	440.2
563	 2,2-dimethyl-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	443.3
564	 1-methyl-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	443.3
565	 (1s,2s)-2-cyano-N-(5-((trans)-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	440.3

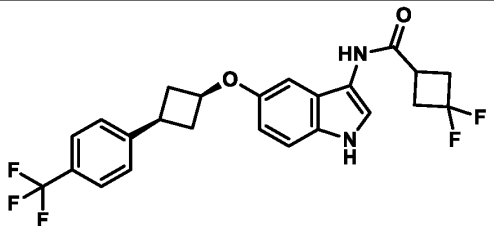
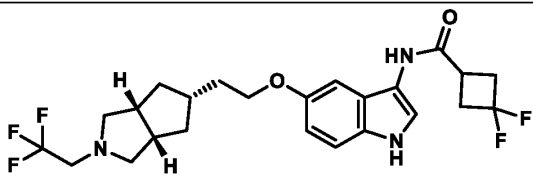
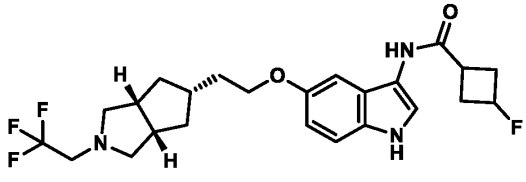
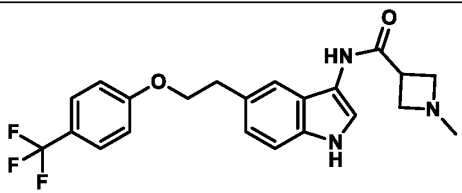
	1-cyano-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	
567	 3-methyl-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)azetidine-3-carboxamide	444.25
568	 tert-butyl 3-methyl-3-((5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)carbamoyl)azetidine-1-carboxylate	542.15
569	 3-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)azetidine-3-carboxamide	418.15
570		516.15

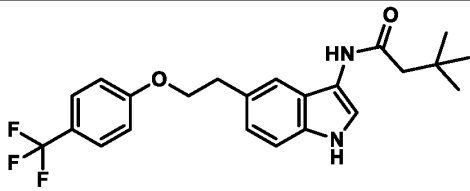
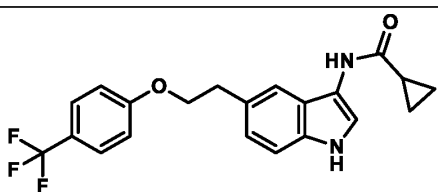
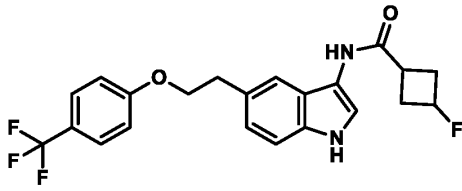
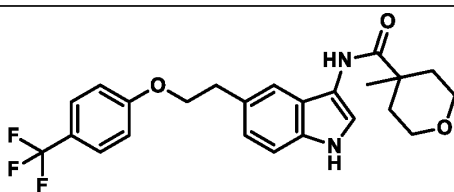
	tert-butyl 3-methyl-3-((5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)carbamoyl)azetidine-1-carboxylate	
571	 2-chloro-2-fluoro-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	467.2
572	 3-methoxy-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	459.2
573	 3-hydroxy-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	445.2

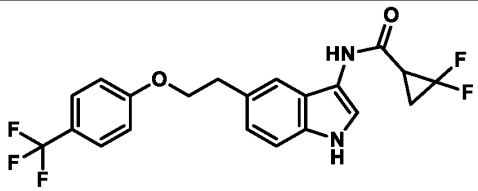
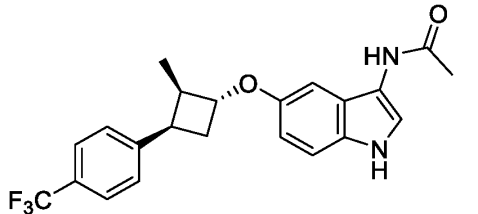
574	 2,2-difluoro-N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	451.2
575	 2-chloro-2-fluoro-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	467.3
576	 3-fluoro-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	447.2
577	 2-chloro-2-fluoro-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	488.3

	yl)ethoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	
578	 N-(7-bromo-5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)acetamide	440.8
579	 1-methyl-N-(5-(cis-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	430.15
580	 1-methyl-N-(5-(cis-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	430.15
581	 N-(5-(2-(pyridin-3-yloxy)ethyl)-1H-indol-3-yl)acetamide	296.2

582	 (1S,2R)-2-cyano-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclopropane-1-carboxamide	412.1
584	 3,3-difluoro-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	425.3
585	 (1S,2S)-2-cyano-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	400.3
586	 1-cyano-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclopropane-1-carboxamide	400.3

587	 3,3-difluoro-N-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	465.3
588	 3,3-difluoro-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	486.4
589	 3-fluoro-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	468.3
590	 3,3-difluoro-N-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethoxy)-1H-indol-3-yl)cyclobutane-1-carboxamide	418.3

	1-methyl-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)azetidine-3-carboxamide	
591	 3,3-dimethyl-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)butanamide	419.3
592	 N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclopropanecarboxamide	389.2
593	 3-fluoro-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclobutane-1-carboxamide	421.2
594		447.3

	4-methyl-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)tetrahydro-2H-pyran-4-carboxamide	
595	 2,2-difluoro-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclopropane-1-carboxamide	425.2
596		401.1

Pharmaceutical Compositions and Administration

5

General

In some embodiments, a chemical entity (e.g., a compound that inhibits (e.g., antagonizes) STING, or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination thereof) is administered as a pharmaceutical composition that includes the chemical entity and one or more pharmaceutically acceptable excipients, and optionally one or more additional therapeutic agents as described herein.

In some embodiments, the chemical entities can be administered in combination with one or more conventional pharmaceutical excipients. Pharmaceutically acceptable excipients include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d- α -tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, poloxamers or other similar polymeric delivery matrices, serum proteins, such

as human serum albumin, buffer substances such as phosphates, tris, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium-chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, and wool fat. Cyclodextrins such as α -, β , and γ -cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl- β -cyclodextrins, or other solubilized derivatives can also be used to enhance delivery of compounds described herein. Dosage forms or compositions containing a chemical entity as described herein in the range of 0.005% to 100% with the balance made up from non-toxic excipient may be prepared. The contemplated compositions may contain 0.001%-100% of a chemical entity provided herein, in one embodiment 0.1-95%, in another embodiment 75-85%, in a further embodiment 20-80%. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 22nd Edition (Pharmaceutical Press, London, UK. 2012).

Routes of Administration and Composition Components

In some embodiments, the chemical entities described herein or a pharmaceutical composition thereof can be administered to subject in need thereof by any accepted route of administration. Acceptable routes of administration include, but are not limited to, buccal, cutaneous, endocervical, endosinusal, endotracheal, enteral, epidural, interstitial, intra-abdominal, intra-arterial, intrabronchial, intrabursal, intracerebral, intracisternal, intracoronary, intradermal, intraductal, intraduodenal, intradural, intraepidermal, intraesophageal, intragastric, intragingival, intraileal, intralymphatic, intramedullary, intrameningeal, intramuscular, intraovarian, intraperitoneal, intraprostatic, intrapulmonary, intrasinal, intraspinal, intrasynovial, intratesticular, intrathecal, intratubular, intratumoral, intrauterine, intravascular, intravenous, nasal, nasogastric, oral, parenteral, percutaneous, peridural, rectal, respiratory (inhalation), subcutaneous, sublingual, submucosal, topical, transdermal, transmucosal, transtracheal, ureteral, urethral

and vaginal. In certain embodiments, a preferred route of administration is parenteral (e.g., intratumoral).

Compositions can be formulated for parenteral administration, e.g., formulated for injection via the intravenous, intramuscular, sub-cutaneous, or even intraperitoneal routes.

5 Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for use to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified. The preparation of such formulations will be known to those of skill in the art in light of the present disclosure.

10 The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil, or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that it may be easily injected. It also should be stable under the conditions of
15 manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

The carrier also can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can
20 be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for
25 example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients
30 enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle

which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient, plus any additional desired
5 ingredient from a previously sterile-filtered solution thereof.

Intratumoral injections are discussed, e.g., in Lammers, et al., *“Effect of Intratumoral Injection on the Biodistribution and the Therapeutic Potential of HPMA Copolymer-Based Drug Delivery Systems” Neoplasia*. **2006**, *10*, 788–795.

Pharmacologically acceptable excipients usable in the rectal composition as a gel,
10 cream, enema, or rectal suppository, include, without limitation, any one or more of cocoa butter glycerides, synthetic polymers such as polyvinylpyrrolidone, PEG (like PEG ointments), glycerine, glycerinated gelatin, hydrogenated vegetable oils, poloxamers, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol Vaseline, anhydrous lanolin, shark liver oil, sodium saccharinate,
15 menthol, sweet almond oil, sorbitol, sodium benzoate, anoxid SBN, vanilla essential oil, aerosol, parabens in phenoxyethanol, sodium methyl p-oxybenzoate, sodium propyl p-oxybenzoate, diethylamine, carbomers, carbopol, methoxybenzoate, macrogol cetostearyl ether, cocoyl caprylocaprates, isopropyl alcohol, propylene glycol, liquid paraffin, xanthan gum, carboxy-metabisulfite, sodium edetate, sodium benzoate, potassium metabisulfite, grapefruit seed extract, methyl sulfonyl methane (MSM), lactic acid,
20 glycine, vitamins, such as vitamin A and E and potassium acetate.

In certain embodiments, suppositories can be prepared by mixing the chemical entities described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature
25 but liquid at body temperature and therefore melt in the rectum and release the active compound. In other embodiments, compositions for rectal administration are in the form of an enema.

In other embodiments, the compounds described herein or a pharmaceutical composition thereof are suitable for local delivery to the digestive or GI tract by way of
30 oral administration (e.g., solid or liquid dosage forms.).

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the chemical entity is mixed with one or more pharmaceutically acceptable excipients, such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

In one embodiment, the compositions will take the form of a unit dosage form such as a pill or tablet and thus the composition may contain, along with a chemical entity provided herein, a diluent such as lactose, sucrose, dicalcium phosphate, or the like; a lubricant such as magnesium stearate or the like; and a binder such as starch, gum acacia, polyvinylpyrrolidine, gelatin, cellulose, cellulose derivatives or the like. In another solid dosage form, a powder, granule, solution or suspension (*e.g.*, in propylene carbonate, vegetable oils, PEG's, poloxamer 124 or triglycerides) is encapsulated in a capsule (gelatin or cellulose base capsule). Unit dosage forms in which one or more chemical entities provided herein or additional active agents are physically separated are also contemplated; *e.g.*, capsules with granules (or tablets in a capsule) of each drug; two-layer tablets; two-compartment gel caps, etc. Enteric coated or delayed release oral dosage forms are also contemplated.

Other physiologically acceptable compounds include wetting agents, emulsifying agents, dispersing agents or preservatives that are particularly useful for preventing the

growth or action of microorganisms. Various preservatives are well known and include, for example, phenol and ascorbic acid.

In certain embodiments the excipients are sterile and generally free of undesirable matter. These compositions can be sterilized by conventional, well-known sterilization techniques. For various oral dosage form excipients such as tablets and capsules sterility is not required. The USP/NF standard is usually sufficient.

In certain embodiments, solid oral dosage forms can further include one or more components that chemically and/or structurally predispose the composition for delivery of the chemical entity to the stomach or the lower GI; e.g., the ascending colon and/or transverse colon and/or distal colon and/or small bowel. Exemplary formulation techniques are described in, e.g., Filipski, K.J., et al., *Current Topics in Medicinal Chemistry*, **2013**, *13*, 776-802, which is incorporated herein by reference in its entirety.

Examples include upper-GI targeting techniques, e.g., Accordion Pill (Intec Pharma), floating capsules, and materials capable of adhering to mucosal walls.

Other examples include lower-GI targeting techniques. For targeting various regions in the intestinal tract, several enteric/pH-responsive coatings and excipients are available. These materials are typically polymers that are designed to dissolve or erode at specific pH ranges, selected based upon the GI region of desired drug release. These materials also function to protect acid labile drugs from gastric fluid or limit exposure in cases where the active ingredient may be irritating to the upper GI (e.g., hydroxypropyl methylcellulose phthalate series, Coateric (polyvinyl acetate phthalate), cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate, Eudragit series (methacrylic acid-methyl methacrylate copolymers), and Marcoat). Other techniques include dosage forms that respond to local flora in the GI tract, Pressure-controlled colon delivery capsule, and Pulsincap.

Ocular compositions can include, without limitation, one or more of any of the following: viscosogens (e.g., Carboxymethylcellulose, Glycerin, Polyvinylpyrrolidone, Polyethylene glycol); Stabilizers (e.g., Pluronic (triblock copolymers), Cyclodextrins); Preservatives (e.g., Benzalkonium chloride, ETDA, SofZia (boric acid, propylene glycol, sorbitol, and zinc chloride; Alcon Laboratories, Inc.), Purite (stabilized oxychloro complex; Allergan, Inc.)).

Topical compositions can include ointments and creams. Ointments are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. Creams containing the selected active agent are typically viscous liquid or semisolid emulsions, often either oil-in-water or water-in-oil. Cream bases are typically water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also sometimes called the “internal” phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and non-sensitizing.

In any of the foregoing embodiments, pharmaceutical compositions described herein can include one or more one or more of the following: lipids, interbilayer crosslinked multilamellar vesicles, biodegradable poly(D,L-lactic-co-glycolic acid) [PLGA]-based or poly anhydride-based nanoparticles or microparticles, and nanoporous particle-supported lipid bilayers.

Dosages

The dosages may be varied depending on the requirement of the patient, the severity of the condition being treating and the particular compound being employed. Determination of the proper dosage for a particular situation can be determined by one skilled in the medical arts. The total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery.

In some embodiments, the compounds described herein are administered at a dosage of from about 0.001 mg/Kg to about 500 mg/Kg (e.g., from about 0.01 mg/Kg to about 100 mg/Kg; from about 0.01 mg/Kg to about 10 mg/Kg; from about 0.01 mg/Kg to about 1 mg/Kg; from from about 0.01 mg/Kg to about 0.1 mg/Kg; from about 0. 1 mg/Kg to about 100 mg/Kg; from about 0. 1 mg/Kg to about 10 mg/Kg).

Regimens

The foregoing dosages can be administered on a daily basis (e.g., as a single dose or as two or more divided doses) or non-daily basis (e.g., every other day, every two days, every three days, once weekly, twice weeks, once every two weeks, once a month).

In some embodiments, the period of administration of a compound described herein is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In a further embodiment, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In an embodiment, a therapeutic compound is administered to an individual for a period of time followed by a separate period of time. In another embodiment, a therapeutic compound is administered for a first period and a second period following the first period, with administration stopped during the second period, followed by a third period where administration of the therapeutic compound is started and then a fourth period following the third period where administration is stopped. In an aspect of this embodiment, the period of administration of a therapeutic compound followed by a period where administration is stopped is repeated for a determined or undetermined period of time. In a further embodiment, a period of administration is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In a further embodiment, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more.

Methods of Treatment

In some embodiments, methods for treating a subject having condition, disease or disorder in which increased (e.g., excessive) STING activity (e.g., , e.g., STING signaling) contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., immune disorders, cancer) are provided.

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Indications

In some embodiments, the condition, disease or disorder is cancer. Non-limiting examples of cancer include melanoma, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include
10 breast cancer, colon cancer, rectal cancer, colorectal cancer, kidney or renal cancer, clear cell cancer lung cancer including small-cell lung cancer, non- small cell lung cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, squamous cell cancer (e.g. epithelial squamous cell cancer), cervical cancer, ovarian cancer, prostate cancer, prostatic neoplasms, liver cancer, bladder cancer, cancer of the peritoneum, hepatocellular
15 cancer, gastric or stomach cancer including gastrointestinal cancer, gastrointestinal stromal tumor, pancreatic cancer, head and neck cancer, glioblastoma, retinoblastoma, astrocytoma, thecomas, arrhenoblastomas, hepatoma, hematologic malignancies including non-Hodgkins lymphoma (NHL), multiple myeloma, myelodysplasia disorders, myeloproliferative disorders, chronic myelogenous leukemia, and acute hematologic
20 malignancies, endometrial or uterine carcinoma, endometriosis, endometrial stromal sarcoma, fibrosarcomas, choriocarcinoma, salivary gland carcinoma, vulval cancer, thyroid cancer, esophageal carcinomas, hepatic carcinoma, anal carcinoma, penile carcinoma, nasopharyngeal carcinoma, laryngeal carcinomas, Kaposi's sarcoma, mast cell sarcoma, ovarian sarcoma, uterine sarcoma, melanoma, malignant mesothelioma, skin
25 carcinomas, Schwannoma, oligodendroglioma, neuroblastomas, neuroectodermal tumor, rhabdomyosarcoma, osteogenic sarcoma, leiomyosarcomas, Ewing Sarcoma, peripheral primitive neuroectodermal tumor, urinary tract carcinomas, thyroid carcinomas, Wilm's tumor, as well as abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), and Meigs' syndrome. In some cases, the cancer
30 is melanoma.

In some embodiments, the condition, disease or disorder is a neurological disorder, which includes disorders that involve the central nervous system (brain, brainstem and cerebellum), the peripheral nervous system (including cranial nerves), and the autonomic nervous system (parts of which are located in both central and peripheral nervous system).

- 5 Non-limiting examples of neurological disorders include acquired epileptiform aphasia; acute disseminated encephalomyelitis; adrenoleukodystrophy; age-related macular degeneration; agenesis of the corpus callosum; agnosia; Aicardi syndrome; Alexander disease; Alpers' disease; alternating hemiplegia; Alzheimer's disease; Vascular dementia; amyotrophic lateral sclerosis; anencephaly; Angelman syndrome; angiomas; anoxia;
- 10 aphasia; apraxia; arachnoid cysts; arachnoiditis; Arnold-Chiari malformation; arteriovenous malformation; Asperger syndrome; ataxia telangiectasia; attention deficit hyperactivity disorder; autism; autonomic dysfunction; back pain; Batten disease; Behcet's disease; Bell's palsy; benign essential blepharospasm; benign focal; amyotrophy; benign intracranial hypertension; Binswanger's disease; blepharospasm; Bloch Sulzberger
- 15 syndrome; brachial plexus injury; brain abscess; brain injury; brain tumors (including glioblastoma multiforme); spinal tumor; Brown-Sequard syndrome; Canavan disease; carpal tunnel syndrome; causalgia; central pain syndrome; central pontine myelinolysis; cephalic disorder; cerebral aneurysm; cerebral arteriosclerosis; cerebral atrophy; cerebral gigantism; cerebral palsy; Charcot-Marie-Tooth disease; chemotherapy-induced
- 20 neuropathy and neuropathic pain; Chiari malformation; chorea; chronic inflammatory demyelinating polyneuropathy; chronic pain; chronic regional pain syndrome; Coffin Lowry syndrome; coma, including persistent vegetative state; congenital facial diplegia; corticobasal degeneration; cranial arteritis; craniosynostosis; Creutzfeldt-Jakob disease; cumulative trauma disorders; Cushing's syndrome; cytomegalic inclusion body disease;
- 25 cytomegalovirus infection; dancing eyes-dancing feet syndrome; Dandy-Walker syndrome; Dawson disease; De Morsier's syndrome; Dejerine-Klumpke palsy; dementia; dermatomyositis; diabetic neuropathy; diffuse sclerosis; dysautonomia; dysgraphia; dyslexia; dystonias; early infantile epileptic encephalopathy; empty sella syndrome; encephalitis; encephaloceles; encephalotrigeminal angiomas; epilepsy; Erb's palsy;
- 30 essential tremor; Fabry's disease; Fahr's syndrome; fainting; familial spastic paralysis; febrile seizures; Fisher syndrome; Friedreich's ataxia; fronto-temporal dementia and other

“tauopathies”; Gaucher's disease; Gerstmann's syndrome; giant cell arteritis; giant cell inclusion disease; globoid cell leukodystrophy; Guillain-Barre syndrome; HTLV-1-associated myelopathy; Hallervorden-Spatz disease; head injury; headache; hemifacial spasm; hereditary spastic paraplegia; hereditary ataxia polyneuritis; herpes zoster
 5 oticus; herpes zoster; Hirayama syndrome; HIV-associated dementia and neuropathy (also neurological manifestations of AIDS); holoprosencephaly; Huntington's disease and other polyglutamine repeat diseases; hydranencephaly; hydrocephalus; hypercortisolism; hypoxia; immune-mediated encephalomyelitis; inclusion body myositis; incontinentia pigmenti; infantile phytanic acid storage disease; infantile Refsum disease; infantile spasms;
 10 inflammatory myopathy; intracranial cyst; intracranial hypertension; Joubert syndrome; Kearns-Sayre syndrome; Kennedy disease; Kinsbourne syndrome; Klippel Feil syndrome; Krabbe disease; Kugelberg-Welander disease; kuru; Lafora disease; Lambert-Eaton myasthenic syndrome; Landau-Kleffner syndrome; lateral medullary (Wallenberg) syndrome; learning disabilities; Leigh's disease; Lennox-Gustaut syndrome; Lesch-Nyhan
 15 syndrome; leukodystrophy; Lewy body dementia; Lissencephaly; locked-in syndrome; Lou Gehrig's disease (i.e., motor neuron disease or amyotrophic lateral sclerosis); lumbar disc disease; Lyme disease—neurological sequelae; Machado-Joseph disease; macrencephaly; megalencephaly; Melkersson-Rosenthal syndrome; Meniere's disease; meningitis; Menkes disease; metachromatic leukodystrophy; microcephaly; migraine;
 20 Miller Fisher syndrome; mini-strokes; mitochondrial myopathies; Mobius syndrome; monomelic amyotrophy; motor neuron disease; Moyamoya disease; mucopolysaccharidoses; multi-infarct dementia; multifocal motor neuropathy; multiple sclerosis and other demyelinating disorders; multiple system atrophy with postural hypotension; p muscular dystrophy; myasthenia gravis; myelinoclastic diffuse sclerosis;
 25 myoclonic encephalopathy of infants; myoclonus; myopathy; myotonia congenita; narcolepsy; neurofibromatosis; neuroleptic malignant syndrome; neurological manifestations of AIDS; neurological sequelae of lupus; neuromyotonia; neuronal ceroid lipofuscinosis; neuronal migration disorders; Niemann-Pick disease; O'Sullivan-McLeod syndrome; occipital neuralgia; occult spinal dysraphism sequence; Ohtahara syndrome;
 30 olivopontocerebellar atrophy; opsoclonus myoclonus; optic neuritis; orthostatic hypotension; overuse syndrome; paresthesia; Parkinson's disease; paramyotonia

congenital; paraneoplastic diseases; paroxysmal attacks; Parry Romberg syndrome; Pelizaeus-Merzbacher disease; periodic paralyses; peripheral neuropathy; painful neuropathy and neuropathic pain; persistent vegetative state; pervasive developmental disorders; photic sneeze reflex; phytanic acid storage disease; Pick's disease; pinched
5 nerve; pituitary tumors; polymyositis; porencephaly; post-polio syndrome; postherpetic neuralgia; postinfectious encephalomyelitis; postural hypotension; Prader-Willi syndrome; primary lateral sclerosis; prion diseases; progressive hemifacial atrophy; progressive multifocal leukoencephalopathy; progressive sclerosing poliodystrophy; progressive supranuclear palsy; pseudotumor cerebri; Ramsay-Hunt syndrome (types I and II);
10 Rasmussen's encephalitis; reflex sympathetic dystrophy syndrome; Refsum disease; repetitive motion disorders; repetitive stress injuries; restless legs syndrome; retrovirus-associated myelopathy; Rett syndrome; Reye's syndrome; Saint Vitus dance; Sandhoff disease; Schilder's disease; schizencephaly; septo-optic dysplasia; shaken baby syndrome; shingles; Shy-Drager syndrome; Sjögren's syndrome; sleep apnea; Soto's syndrome;
15 spasticity; spina bifida; spinal cord injury; spinal cord tumors; spinal muscular atrophy; Stiff-Person syndrome; stroke; Sturge-Weber syndrome; subacute sclerosing panencephalitis; subcortical arteriosclerotic encephalopathy; Sydenham chorea; syncope; syringomyelia; tardive dyskinesia; Tay-Sachs disease; temporal arteritis; tethered spinal cord syndrome; Thomsen disease; thoracic outlet syndrome; Tic Douloureux; Todd's
20 paralysis; Tourette syndrome; transient ischemic attack; transmissible spongiform encephalopathies; transverse myelitis; traumatic brain injury; tremor; trigeminal neuralgia; tropical spastic paraparesis; tuberous sclerosis; vascular dementia (multi-infarct dementia); vasculitis including temporal arteritis; Von Hippel-Lindau disease; Wallenberg's syndrome; Werdnig-Hoffman disease; West syndrome; whiplash; Williams syndrome;
25 Wildon's disease; amyotrophic lateral sclerosis and Zellweger syndrome.

In some embodiments, the condition, disease or disorder is STING-associated conditions, e.g., type I interferonopathies (e.g., STING-associated vasculopathy with onset in infancy (SAVI)), Aicardi-Goutières Syndrome (AGS), genetic forms of lupus, and inflammation-associated disorders such as systemic lupus erythematosus, and rheumatoid
30 arthritis. In certain embodiments, the condition, disease or disorder is an autoimmune disease (e.g., a cytosolic DNA-triggered autoinflammatory disease). Non-limiting

examples include rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel diseases (IBDs) comprising Crohn disease (CD) and ulcerative colitis (UC), which are chronic inflammatory conditions with polygenic susceptibility. In certain embodiments, the condition is an inflammatory bowel disease. In certain embodiments, the condition is Crohn's disease, autoimmune colitis, iatrogenic autoimmune colitis, ulcerative colitis, colitis induced by one or more chemotherapeutic agents, colitis induced by treatment with adoptive cell therapy, colitis associated by one or more alloimmune diseases (such as graft-vs-host disease, e.g., acute graft vs. host disease and chronic graft vs. host disease), radiation enteritis, collagenous colitis, lymphocytic colitis, microscopic colitis, and radiation enteritis. In certain of these embodiments, the condition is alloimmune disease (such as graft-vs-host disease, e.g., acute graft vs. host disease and chronic graft vs. host disease), celiac disease, irritable bowel syndrome, rheumatoid arthritis, lupus, scleroderma, psoriasis, cutaneous T-cell lymphoma, uveitis, and mucositis (e.g., oral mucositis, esophageal mucositis or intestinal mucositis).

In some embodiments, modulation of the immune system by STING provides for the treatment of diseases, including diseases caused by foreign agents. Exemplary infections by foreign agents which may be treated and/or prevented by the method of the present invention include an infection by a bacterium (e.g., a Gram-positive or Gram-negative bacterium), an infection by a fungus, an infection by a parasite, and an infection by a virus. In one embodiment of the present invention, the infection is a bacterial infection (e.g., infection by *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella spp.*, *Staphylococcus aureus*, *Streptococcus spp.*, or vancomycin-resistant enterococcus), or sepsis. In another embodiment, the infection is a fungal infection (e.g. infection by a mould, a yeast, or a higher fungus). In still another embodiment, the infection is a parasitic infection (e.g., infection by a single-celled or multicellular parasite, including *Giardia duodenalis*, *Cryptosporidium parvum*, *Cyclospora cayetanensis*, and *Toxoplasma gondii*). In yet another embodiment, the infection is a viral infection (e.g., infection by a virus associated with AIDS, avian flu, chickenpox, cold sores, common cold, gastroenteritis, glandular fever, influenza, measles, mumps, pharyngitis, pneumonia, rubella, SARS, lower or upper respiratory tract infection (e.g., respiratory syncytial virus), Ebola, Zika, and SARS-CoV-2 (COVID19)).

In some embodiments, the condition, disease or disorder is hepatitis B (see, e.g., WO 2015/061294).

In some embodiments, the condition, disease or disorder is selected from cardiovascular diseases (including e.g., myocardial infarction).

5 In some embodiments, the condition, disease or disorder is age-related macular degeneration.

In some embodiments, the condition, disease or disorder is mucositis, also known as stomatitis, which can occur as a result of chemotherapy or radiation therapy, either alone or in combination as well as damage caused by exposure to radiation outside of the
10 context of radiation therapy.

In some embodiments, the condition, disease or disorder is uveitis, which is inflammation of the uvea (e.g., anterior uveitis, e.g., iridocyclitis or iritis; intermediate uveitis (also known as pars planitis); posterior uveitis; or chorioretinitis, e.g., pan-uveitis).

In some embodiments, the condition, disease or disorder is selected from the group
15 consisting of a cancer, a neurological disorder, an autoimmune disease, hepatitis B, uveitis, a cardiovascular disease, age-related macular degeneration, and mucositis.

In some embodiments, the condition, disease or disorder is selected from the group consisting of Familial Chilblain Lupus, RVCL (autosomal dominant retinal vasculopathy with cerebral leukodystrophy), lupus nephritis (LN), Sjogren's Syndrome (SS), lung
20 inflammation, acute lung inflammation, idiopathic pulmonary fibrosis, liver and renal fibrosis, nonalcoholic steatohepatitis (NASH), cirrhosis, endomyocardial fibrosis, acute and chronic kidney injury, APOL1 -associated podocytopathy, acute pancreatitis, chronic obstructive pulmonary disease (COPD), senescence, and aging.

Still other examples can include those indications discussed herein and below in
25 contemplated combination therapy regimens.

Combination therapy

This disclosure contemplates both monotherapy regimens as well as combination therapy regimens.

30 In some embodiments, the methods described herein can further include administering one or more additional therapies (e.g., one or more additional therapeutic

agents and/or one or more therapeutic regimens) in combination with administration of the compounds described herein.

In certain embodiments, the methods described herein can further include administering one or more additional cancer therapies.

5 The one or more additional cancer therapies can include, without limitation, surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy, cancer vaccines (e.g., HPV vaccine, hepatitis B vaccine, Oncophage, Provenge) and gene therapy, as well as combinations thereof. Immunotherapy, including, without limitation, adoptive cell therapy, the derivation of stem cells and/or dendritic cells, blood transfusions, lavages, and/or other treatments, including, without limitation, freezing a tumor.

In some embodiments, the one or more additional cancer therapies is chemotherapy, which can include administering one or more additional chemotherapeutic agents.

In certain embodiments, the additional chemotherapeutic agent is an immunomodulatory moiety, e.g., an immune checkpoint inhibitor. In certain of these
 15 embodiments, the immune checkpoint inhibitor targets an immune checkpoint receptor selected from the group consisting of CTLA-4, PD-1, PD-L1, PD-1 – PD-L1, PD-1 – PD-L2, interleukin-2 (IL-2), indoleamine 2,3-dioxygenase (IDO), IL-10, transforming growth factor- β (TGF β), T cell immunoglobulin and mucin 3 (TIM3 or HAVCR2), Galectin 9 – TIM3, Phosphatidylserine – TIM3, lymphocyte activation gene 3 protein (LAG3), MHC
 20 class II – LAG3, 4-1BB–4-1BB ligand, OX40–OX40 ligand, GITR, GITR ligand – GITR, CD27, CD70–CD27, TNFRSF25, TNFRSF25–TL1A, CD40L, CD40–CD40 ligand, HVEM–LIGHT–LTA, HVEM, HVEM – BTLA, HVEM – CD160, HVEM – LIGHT, HVEM–BTLA–CD160, CD80, CD80 – PDL-1, PDL2 – CD80, CD244, CD48 – CD244, CD244, ICOS, ICOS–ICOS ligand, B7-H3, B7-H4, VISTA, TMIGD2, HHLA2–
 25 TMIGD2, Butyrophilins, including BTNL2, Siglec family, TIGIT and PVR family members, KIRs, ILTs and LIRs, NKG2D and NKG2A, MICA and MICB, CD244, CD28, CD86 – CD28, CD86 – CTLA, CD80 – CD28, CD39, CD73 Adenosine–CD39–CD73, CXCR4–CXCL12, Phosphatidylserine, TIM3, Phosphatidylserine – TIM3, SIRPA–CD47,

VEGF, Neuropilin, CD160, CD30, and CD155; e.g., CTLA-4 or PD1 or PD-L1). See, e.g., Postow, M. J. *Clin. Oncol.* **2015**, 33, 1.

In certain of these embodiments, the immune checkpoint inhibitor is selected from the group consisting of: Urelumab, PF-05082566, MEDI6469, TRX518, Varlilumab, CP-870893, Pembrolizumab (PD1), Nivolumab (PD1), Atezolizumab (formerly MPDL3280A) (PDL1), MEDI4736 (PD-L1), Avelumab (PD-L1), PDR001 (PD1), BMS-986016, MGA271, Lirilumab, IPH2201, Emactuzumab, INCB024360, Galunisertib, Ulocuplumab, BKT140, Bavituximab, CC-90002, Bevacizumab, and MNRP1685A, and MGA271.

In certain embodiments, the additional chemotherapeutic agent is an alkylating agent. Alkylating agents are so named because of their ability to alkylate many nucleophilic functional groups under conditions present in cells, including, but not limited to cancer cells. In a further embodiment, an alkylating agent includes, but is not limited to, Cisplatin, carboplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide and/or oxaliplatin. In an embodiment, alkylating agents can function by impairing cell function by forming covalent bonds with the amino, carboxyl, sulfhydryl, and phosphate groups in biologically important molecules or they can work by modifying a cell's DNA. In a further embodiment an alkylating agent is a synthetic, semisynthetic or derivative.

In certain embodiments, the additional chemotherapeutic agent is an anti-metabolite. Anti-metabolites masquerade as purines or pyrimidines, the building-blocks of DNA and in general, prevent these substances from becoming incorporated in to DNA during the "S" phase (of the cell cycle), stopping normal development and division. Anti-metabolites can also affect RNA synthesis. In an embodiment, an antimetabolite includes, but is not limited to azathioprine and/or mercaptopurine. In a further embodiment an anti-metabolite is a synthetic, semisynthetic or derivative.

In certain embodiments, the additional chemotherapeutic agent is a plant alkaloid and/or terpenoid. These alkaloids are derived from plants and block cell division by, in general, preventing microtubule function. In an embodiment, a plant alkaloid and/or

terpenoid is a vinca alkaloid, a podophyllotoxin and/or a taxane. Vinca alkaloids, in general, bind to specific sites on tubulin, inhibiting the assembly of tubulin into microtubules, generally during the M phase of the cell cycle. In an embodiment, a vinca alkaloid is derived, without limitation, from the Madagascar periwinkle, *Catharanthus roseus* (formerly known as *Vinca rosea*). In an embodiment, a vinca alkaloid includes, without limitation, Vincristine, Vinblastine, Vinorelbine and/or Vindesine. In an embodiment, a taxane includes, but is not limited, to Taxol, Paclitaxel and/or Docetaxel. In a further embodiment a plant alkaloid or terpenoid is a synthetic, semisynthetic or derivative. In a further embodiment, a podophyllotoxin is, without limitation, an etoposide and/or teniposide. In an embodiment, a taxane is, without limitation, docetaxel and/or ortataxel. [021] In an embodiment, a cancer therapeutic is a topoisomerase. Topoisomerases are essential enzymes that maintain the topology of DNA. Inhibition of type I or type II topoisomerases interferes with both transcription and replication of DNA by upsetting proper DNA supercoiling. In a further embodiment, a topoisomerase is, without limitation, a type I topoisomerase inhibitor or a type II topoisomerase inhibitor. In an embodiment a type I topoisomerase inhibitor is, without limitation, a camptothecin. In another embodiment, a camptothecin is, without limitation, exatecan, irinotecan, lurtotecan, topotecan, BNP 1350, CKD 602, DB 67 (AR67) and/or ST 1481. In an embodiment, a type II topoisomerase inhibitor is, without limitation, epipodophyllotoxin. In a further embodiment an epipodophyllotoxin is, without limitation, an amsacrine, etoposid, etoposide phosphate and/or teniposide. In a further embodiment a topoisomerase is a synthetic, semisynthetic or derivative, including those found in nature such as, without limitation, epipodophyllotoxins, substances naturally occurring in the root of American Mayapple (*Podophyllum peltatum*).

In certain embodiments, the additional chemotherapeutic agent is a stilbenoid. In a further embodiment, a stilbenoid includes, but is not limited to, Resveratrol, Piceatannol, Pinosylvin, Pterostilbene, Alpha-Viniferin, Ampelopsin A, Ampelopsin E, Diptoindonesin C, Diptoindonesin F, Epsilon- Viniferin, Flexuosol A, Gnetin H, Hemsleyanol D, Hopeaphenol, Trans-Diptoindonesin B, Astringin, Piceid and Diptoindonesin A. In a further embodiment a stilbenoid is a synthetic, semisynthetic or derivative.

In certain embodiments, the additional chemotherapeutic agent is a cytotoxic antibiotic. In an embodiment, a cytotoxic antibiotic is, without limitation, an actinomycin, an anthracenedione, an anthracycline, thalidomide, dichloroacetic acid, nicotinic acid, 2-deoxyglucose and/or chlofazimine. In an embodiment, an actinomycin is, without limitation, actinomycin D, bacitracin, colistin (polymyxin E) and/or polymyxin B. In another embodiment, an anthracenedione is, without limitation, mitoxantrone and/or pixantrone. In a further embodiment, an anthracycline is, without limitation, bleomycin, doxorubicin (Adriamycin), daunorubicin (daunomycin), epirubicin, idarubicin, mitomycin, plicamycin and/or valrubicin. In a further embodiment a cytotoxic antibiotic is a synthetic, semisynthetic or derivative.

In certain embodiments, the additional chemotherapeutic agent is selected from endostatin, angiogenin, angiostatin, chemokines, angioarrestin, angiostatin (plasminogen fragment), basement-membrane collagen-derived anti-angiogenic factors (tumstatin, canstatin, or arrestin), anti-angiogenic antithrombin III, signal transduction inhibitors, cartilage-derived inhibitor (CDI), CD59 complement fragment, fibronectin fragment, gro-beta, heparinases, heparin hexasaccharide fragment, human chorionic gonadotropin (hCG), interferon alpha/beta/gamma, interferon inducible protein (IP-10), interleukin-12, kringle 5 (plasminogen fragment), metalloproteinase inhibitors (TIMPs), 2-methoxyestradiol, placental ribonuclease inhibitor, plasminogen activator inhibitor, platelet factor-4 (PF4), prolactin 16 kD fragment, proliferin-related protein (PRP), various retinoids, tetrahydrocortisol-S, thrombospondin-1 (TSP-1), transforming growth factor-beta (TGF- β), vasculostatin, vasostatin (calreticulin fragment) and the like.

In certain embodiments, the additional chemotherapeutic agent is selected from abiraterone acetate, altretamine, anhydrovinblastine, auristatin, bexarotene, bicalutamide, BMS 184476, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)benzene sulfonamide, bleomycin, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, cachectin, cemadotin, chlorambucil, cyclophosphamide, 3',4'-didehydro-4'-deoxy-8'-norvin-cal leukoblastine, docetaxol, doxorubicin, cyclophosphamide, carboplatin, carmustine, cisplatin, cryptophycin, cyclophosphamide, cytarabine, dacarbazine (DTIC), dactinomycin, daunorubicin, decitabine, dolastatin, doxorubicin (adriamycin), etoposide, 5-fluorouracil, finasteride, flutamide, hydroxyurea and hydroxyureataxanes, ifosfamide,

liarozole, lonidamine, lomustine (CCNU), MDV3100, mechlorethamine (nitrogen mustard), melphalan, mivobulin isethionate, rhizoxin, serteneff, streptozocin, mitomycin, methotrexate, taxanes, nilutamide, onapristone, paclitaxel, prednimustine, procarbazine, RPR109881, stramustine phosphate, tamoxifen, tasonermin, taxol, tretinoin, vinblastine, vincristine, vindesine sulfate, and vinflunine.

In certain embodiments, the additional chemotherapeutic agent is platinum, cisplatin, carboplatin, oxaliplatin, mechlorethamine, cyclophosphamide, chlorambucil, azathioprine, mercaptopurine, vincristine, vinblastine, vinorelbine, vindesine, etoposide and teniposide, paclitaxel, docetaxel, irinotecan, topotecan, amsacrine, etoposide, etoposide phosphate, teniposide, 5-fluorouracil, leucovorin, methotrexate, gemcitabine, taxane, leucovorin, mitomycin C, tegafur-uracil, idarubicin, fludarabine, mitoxantrone, ifosfamide and doxorubicin. Additional agents include inhibitors of mTOR (mammalian target of rapamycin), including but not limited to rapamycin, everolimus, temsirolimus and deforolimus.

In still other embodiments, the additional chemotherapeutic agent can be selected from those delineated in U.S. Patent 7,927,613, which is incorporated herein by reference in its entirety.

In some embodiments, the additional therapeutic agent and/or regimen are those that can be used for treating other STING-associated conditions, e.g., type I interferonopathies (e.g., STING-associated vasculopathy with onset in infancy (SAVI)), Aicardi-Goutières Syndrome (AGS), genetic forms of lupus, and inflammation-associated disorders such as systemic lupus erythematosus, and rheumatoid arthritis and the like.

Non-limiting examples of additional therapeutic agents and/or regimens for treating rheumatoid arthritis include non-steroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen and naproxen), corticosteroids (e.g., prednisone), disease-modifying antirheumatic drugs (DMARDs; e.g., methotrexate (Trexall®, Otrexup®, Rasuvo®, Rheumatrex®), leflunomide (Arava®), hydroxychloroquine (Plaquenil), PF-06650833, iguratimod, tofacitinib (Xeljanz®), ABBV-599, evobrutinib, and sulfasalazine (Azulfidine®)), and biologics (e.g., abatacept (Orencia®), adalimumab (Humira®), anakinra (Kineret®), certolizumab (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®), infliximab (Remicade®), rituximab (Rituxan®), tocilizumab (Actemra®),

vobarilizumab, sarilumab (Kevzara®), secukinumab, ABP 501, CHS-0214, ABC-3373, and tocilizumab (ACTEMRA®).

Non-limiting examples of additional therapeutic agents and/or regimens for treating lupus include steroids, topical immunomodulators (e.g., tacrolimus ointment (Protopic®) and pimecrolimus cream (Elidel®)), thalidomide (Thalomid®), non-steroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen and naproxen), antimalarial drugs (e.g., Hydroxychloroquine (Plaquenil®)), corticosteroids (e.g., prednisone) and immunomodulators (e.g., evobrutinib, iberdomide, voclosporin, cenerimod, azathioprine (Imuran®), cyclophosphamide (Cytoxan®, Neosar®, Endoxan®), and cyclosporine (Neoral, Sandimmune®, Gengraf®), and mycophenolate mofetil) baricitinb, iguratimod, filogotinib, GS-9876, rapamycin, and PF-06650833), and biologics (e.g., belimumab (Benlysta®), anifrolumab, prezalumab, MEDI0700, obinutuzumab, vobarilizumab, lulizumab, atacicept, PF-06823859, and lupizor, rituximab, BT063, BI655064, BIIB059, aldesleukin (Proleukin®), dapirolizumab, edratide, IFN- α -kinoid, OMS721, RC18, RSLV-132, theralizumab, XmaB5871, and ustekinumab (Stelara®)). For example, non-limiting treatments for systemic lupus erythematosus include non-steroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen and naproxen), antimalarial drugs (e.g., Hydroxychloroquine (Plaquenil®)), corticosteroids (e.g., prednisone) and immunomodulators (e.g., iberdomide, voclosporin, azathioprine (Imuran®), cyclophosphamide (Cytoxan®, Neosar®, Endoxan®), and cyclosporine (Neoral, Sandimmune®, Gengraf®), and mycophenolate mofetil, baricitinb, filogotinib, and PF-06650833), and biologics (e.g., belimumab (Benlysta®), anifrolumab, prezalumab, MEDI0700, vobarilizumab, lulizumab, atacicept, PF-06823859, lupizor, rituximab, BT063, BI655064, BIIB059, aldesleukin (Proleukin®), dapirolizumab, edratide, IFN- α -kinoid, RC18, RSLV-132, theralizumab, XmaB5871, and ustekinumab (Stelara®)). As another example, non-limiting examples of treatments for cutaneous lupus include steroids, immunomodulators (e.g., tacrolimus ointment (Protopic®) and pimecrolimus cream (Elidel®)), GS-9876, filogotinib, and thalidomide (Thalomid®). Agents and regimens for treating drug-induced and/or neonatal lupus can also be administered.

Non-limiting examples of additional therapeutic agents and/or regimens for treating STING-associated vasculopathy with onset in infancy (SAVI) include JAK inhibitors (e.g., tofacitinib, ruxolitinib, filgotinib, and baricitinib).

5 Non-limiting examples of additional therapeutic agents and/or regimens for treating Aicardi-Goutières Syndrome (AGS) include physiotherapy, treatment for respiratory complications, anticonvulsant therapies for seizures, tube-feeding, nucleoside reverse transcriptase inhibitors (e.g., emtricitabine (e.g., Emtriva®), tenofovir (e.g., Viread®), emtricitabine/tenofovir (e.g., Truvada®), zidovudine, lamivudine, and abacavir), and JAK inhibitors (e.g., tofacitinib, ruxolitinib, filgotinib, and baricitinib).

10 Non-limiting examples of additional therapeutic agents and/or regimens for treating IBDs include 6-mercaptopurine, AbGn-168H, ABX464, ABT-494, adalimumab, AJM300, alicaforsen, AMG139, anrukinzumab, apremilast, ATR-107 (PF0530900), autologous CD34-selected peripheral blood stem cells transplant, azathioprine, bertilimumab, BI 655066, BMS-936557, certolizumab pegol (Cimzia®), cobitolimod, corticosteroids (e.g.,
15 prednisone, Methylprednisolone, prednisone), CP-690,550, CT-P13, cyclosporine, DIMS0150, E6007, E6011, etrasimod, etrolizumab, fecal microbial transplantation, figlotinib, fingolimod, firategrast (SB-683699) (formerly T-0047), GED0301, GLPG0634, GLPG0974, guselkumab, golimumab, GSK1399686, HMPL-004 (*Andrographis paniculata* extract), IMU-838, infliximab, Interleukin 2 (IL-2), Janus kinase (JAK)
20 inhibitors, laquinimod, masitinib (AB1010), matrix metalloproteinase 9 (MMP 9) inhibitors (e.g., GS-5745), MEDI2070, mesalamine, methotrexate, mirikizumab (LY3074828), natalizumab, NNC 0142-0000-0002, NNC0114-0006, ozanimod, peficitinib (JNJ-54781532), PF-00547659, PF-04236921, PF-06687234, QAX576, RHB-104, rifaximin, risankizumab, RPC1063, SB012, SHP647, sulfasalazine, TD-1473,
25 thalidomide, tildrakizumab (MK 3222), TJ301, TNF-Kinoid®, tofacitinib, tralokinumab, TRK-170, upadacitinib, ustekinumab, UTTR1147A, V565, vatelizumab, VB-201, vedolizumab, and vidofludimus.

Non-limiting examples of additional therapeutic agents and/or regimens for treating irritable bowel syndrome include alosetron, bile acid sequestrants (e.g., cholestyramine,
30 colestipol, colesevelam), chloride channel activators (e.g., lubiprostone), coated peppermint oil capsules, desipramine, dicyclomine, ebastine, eluxadoline, farnesoid X

receptor agonist (e.g., obeticholic acid), fecal microbiota transplantation, fluoxetine, gabapentin, guanylate cyclase-C agonists (e.g., linaclotide, plecanatide), ibodutant, imipramine, JCM-16021, loperamide, lubiprostone, nortriptyline, ondansetron, opioids, paroxetine, pinaverium, polyethylene glycol, pregabalin, probiotics, ramosetron, rifaximin, and tanpanor.

Non-limiting examples of additional therapeutic agents and/or regimens for treating scleroderma include non-steroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen and naproxen), corticosteroids (e.g., prednisone), immunomodulators (e.g., azathioprine, methotrexate (Trexall®, Otrexup®, Rasuvo®, Rheumatrex®), cyclophosphamide (Cytoxan®, Neosar®, Endoxan®), and cyclosporine (Neoral®, Sandimmune®, Gengraf®), antithymocyte globulin, mycophenolate mofetil, intravenous immunoglobulin, rituximab, sirolimus, and alefacept), calcium channel blockers (e.g., nifedipine), alpha blockers, serotonin receptor antagonists, angiotensin II receptor inhibitors, statins, local nitrates, iloprost, phosphodiesterase 5 inhibitors (e.g., sildenafil), bosentan, tetracycline antibiotics, endothelin receptor antagonists, prostanoids, and tyrosine kinase inhibitors (e.g., imatinib, nilotinib and dasatinib).

Non-limiting examples of additional therapeutic agents and/or regimens for treating Crohn's Disease (CD) include adalimumab, autologous CD34-selected peripheral blood stem cells transplant, 6-mercaptopurine, azathioprine, certolizumab pegol (Cimzia®), corticosteroids (e.g., prednisone), etrolizumab, E6011, fecal microbial transplantation, figlotinib, guselkumab, infliximab, IL-2, JAK inhibitors, matrix metalloproteinase 9 (MMP 9) inhibitors (e.g., GS-5745), MEDI2070, mesalamine, methotrexate, natalizumab, ozanimod, RHB-104, rifaximin, risankizumab, SHP647, sulfasalazine, thalidomide, upadacitinib, V565, and vedolizumab.

Non-limiting examples of additional therapeutic agents and/or regimens for treating UC include AbGn-168H, ABT-494, ABX464, apremilast, PF-00547659, PF-06687234, 6-mercaptopurine, adalimumab, azathioprine, bertilimumab, brazikumab (MEDI2070), cobitolimod, certolizumab pegol (Cimzia®), CP-690,550, corticosteroids (e.g., multimax budesonide, Methylprednisolone), cyclosporine, E6007, etrasimod, etrolizumab, fecal microbial transplantation, figlotinib, guselkumab, golimumab, IL-2, IMU-838, infliximab, matrix metalloproteinase 9 (MMP9) inhibitors (e.g., GS-5745), mesalamine, mesalamine,

mirikizumab (LY3074828), RPC1063, risankizumab (BI 6555066), SHP647, sulfasalazine, TD-1473, TJ301, tildrakizumab (MK 3222), tofacitinib, tofacitinib, ustekinumab, UTTR1147A, and vedolizumab.

5 Non-limiting examples of additional therapeutic agents and/or regimens for treating autoimmune colitis include corticosteroids (e.g., budesonide, prednisone, prednisolone, Beclometasone dipropionate), diphenoxylate/atropine, infliximab, loperamide, mesalamine, TIP60 inhibitors (see, e.g., U.S. Patent Application Publication No. 2012/0202848), and vedolizumab.

10 Non-limiting examples of additional therapeutic agents and/or regimens for treating iatrogenic autoimmune colitis include corticosteroids (e.g., budesonide, prednisone, prednisolone, Beclometasone dipropionate), diphenoxylate/atropine, infliximab, loperamide, TIP60 inhibitors (see, e.g., U.S. Patent Application Publication No. 2012/0202848), and vedolizumab.

15 Non-limiting examples of additional therapeutic agents and/or regimens for treating colitis induced by one or more chemotherapeutics agents include corticosteroids (e.g., budesonide, prednisone, prednisolone, beclometasone dipropionate), diphenoxylate/atropine, infliximab, loperamide, mesalamine, TIP60 inhibitors (see, e.g., U.S. Patent Application Publication No. 2012/0202848), and vedolizumab.

20 Non-limiting examples of additional therapeutic agents and/or regimens for treating colitis induced by treatment with adoptive cell therapy include corticosteroids (e.g., budesonide, prednisone, prednisolone, beclometasone dipropionate), diphenoxylate/atropine, infliximab, loperamide, TIP60 inhibitors (see, e.g., U.S. Patent Application Publication No. 2012/0202848), and vedolizumab.

25 Non-limiting examples of additional therapeutic agents and/or regimens for treating colitis associated with one or more alloimmune diseases include corticosteroids (e.g., budesonide, prednisone, prednisolone, beclometasone dipropionate), sulfasalazine, and eicopentaenoic acid.

30 Non-limiting examples of additional therapeutic agents and/or regimens for treating radiation enteritis include teduglutide, amifostine, angiotensin-converting enzyme (ACE) inhibitors (e.g., benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril), probiotics, selenium supplementation,

statins (e.g., atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin), sucralfate, and vitamin E.

Non-limiting examples of additional therapeutic agents and/or regimens for treating collagenous colitis include 6-mercaptopurine, azathioprine, bismuth subsalicylate, *Boswellia serrata* extract, cholestyramine, colestipol, corticosteroids (e.g., budesonide, prednisone, prednisolone, beclometasone dipropionate), loperamide, mesalamine, methotrexate, probiotics, and sulfasalazine.

Non-limiting examples of additional therapeutic agents and/or regimens for treating lymphocytic colitis include 6-mercaptopurine, azathioprine, bismuth subsalicylate, cholestyramine, colestipol, corticosteroids (e.g., budesonide, prednisone, prednisolone, beclometasone dipropionate), loperamide, mesalamine, methotrexate, and sulfasalazine.

Non-limiting examples of additional therapeutic agents and/or regimens for treating microscopic colitis include 6-mercaptopurine, azathioprine, bismuth subsalicylate, *Boswellia serrata* extract, cholestyramine, colestipol, corticosteroids (e.g., budesonide, prednisone, prednisolone, beclometasone dipropionate), fecal microbial transplantation, loperamide, mesalamine, methotrexate, probiotics, and sulfasalazine.

Non-limiting examples of additional therapeutic agents and/or regimens for treating alloimmune disease include intrauterine platelet transfusions, intravenous immunoglobulin, maternal steroids, abatacept, alemtuzumab, alpha1-antitrypsin, AMG592, antithymocyte globulin, baricitinib, basiliximab, bortezomib, brentuximab, cannabidiol, corticosteroids (e.g., methylprednisone, prednisone), cyclosporine, dacilizumab, defibrotide, denileukin diftitox, glasdegib, ibrutinib, IL-2, infliximab, itacitinib, LBH589, maraviroc, mycophenolate mofetil, natalizumab, neihulizumab, pentostatin, pevonedistat, photobiomodulation, photopheresis, ruxolitinib, sirolimus, sonidegib, tacrolimus, tocilizumab, and vismodegib.

Non-limiting examples of additional therapeutic agents and/or regimens for treating multiple sclerosis (MS) include alemtuzumab (Lemtrada®), ALKS 8700, amiloride, ATX-MS-1467, azathioprine, baclofen (Lioresal®), beta interferons (e.g., IFN- β -1a, IFN- β -1b), cladribine, corticosteroids (e.g., methylprednisolone), daclizumab, dimethyl fumarate (Tecfidera®), fingolimod (Gilenya®), fluoxetine, glatiramer acetate (Copaxone®), hydroxychloroquine, ibudilast, idebenone, laquinimod, lipoic acid, losartan, masitinib,

MD1003 (biotin), mitoxantrone, montelukast, natalizumab (Tysabri®), NeuroVax™, ocrelizumab, ofatumumab, pioglitazone, and RPC1063.

Non-limiting examples of additional therapeutic agents and/or regimens for treating graft-vs-host disease include abatacept, alemtuzumab, alpha1-antitrypsin, AMG592, antithymocyte globulin, barcitinib, basiliximab, bortezomib, brentuximab, cannabidiol, corticosteroids (e.g., methylprednisone, prednisone), cyclosporine, dacilzumab, defibrotide, denileukin diftitox, glasdegib, ibrutinib, IL-2, imatinib, infliximab, itacitinib, LBH589, maraviroc, mycophenolate mofetil, natalizumab, neihulizumab, pentostatin, pevonedistat, photobiomodulation, photopheresis, ruxolitinib, sirolimus, sonidegib, tacrolimus, tocilizumab, and vismodegib.

Non-limiting examples of additional therapeutic agents and/or regimens for treating acute graft-vs-host disease include alemtuzumab, alpha-1 antitrypsin, antithymocyte globulin, basiliximab, brentuximab, corticosteroids (e.g., methylprednisone, prednisone), cyclosporine, dacilzumab, defibrotide, denileukin diftitox, ibrutinib, infliximab, itacitinib, LBH589, mycophenolate mofetil, natalizumab, neihulizumab, pentostatin, photopheresis, ruxolitinib, sirolimus, tacrolimus, and tocilizumab.

Non-limiting examples of additional therapeutic agents and/or regimens for treating chronic graft vs. host disease include abatacept, alemtuzumab, AMG592, antithymocyte globulin, basiliximab, bortezomib, corticosteroids (e.g., methylprednisone, prednisone), cyclosporine, dacilzumab, denileukin diftitox, glasdegib, ibrutinib, IL-2, imatinib, infliximab, mycophenolate mofetil, pentostatin, photobiomodulation, photopheresis, ruxolitinib, sirolimus, sonidegib, tacrolimus, tocilizumab, and vismodegib.

Non-limiting examples of additional therapeutic agents and/or regimens for treating celiac disease include AMG 714, AMY01, *Aspergillus niger* prolyl endoprotease, BL-7010, CALY-002, GBR 830, Hu-Mik-Beta-1, IMGX003, KumaMax, Larazotide Acetate, Nexvan2®, pancrelipase, TIMP-GLIA, vedolizumab, and ZED1227.

Non-limiting examples of additional therapeutic agents and/or regimens for treating psoriasis include topical corticosteroids, topical crisaborole/AN2728, topical SNA-120, topical SAN021, topical tapinarof, topical tofacitinib, topical IDP-118, topical M518101, topical calcipotriene and betamethasone dipropionate (e.g., MC2-01 cream and

Taclonex®), topical P-3073, topical LEO 90100 (Enstilar®), topical betamethasone dipropionate (Sernivo®), halobetasol propionate (Ultravate®), vitamin D analogues (e.g., calcipotriene (Dovonex®) and calcitriol (Vectical®)), anthralin (e.g., Dritho-scalp® and Dritho-crème®), topical retinoids (e.g., tazarotene (e.g., Tazorac® and Avage®)),

5 calcineurin inhibitors (e.g., tacrolimus (Prograf®) and pimecrolimus (Elidel®)), salicylic acid, coal tar, moisturizers, phototherapy (e.g., exposure to sunlight, UVB phototherapy, narrow band UVB phototherapy, Goeckerman therapy, psoralen plus ultraviolet A (PUVA) therapy, and excimer laser), retinoids (e.g., acitretin (Soriatane®)), methotrexate (Trexall®, Otrexup®, Rasuvo®, Rheumatrex®), Apo805K1, baricitinib, FP187, KD025,

10 prurisol, VTP-43742, XP23829, ZPL-389, CF101 (piclidenoson), LAS41008, VPD-737 (serlopitant), upadacitinib (ABT-494), aprmilast, tofacitinib, cyclosporine (Neoral®, Sandimmune®, Gengraf®), biologics (e.g., etanercept (Enbrel®), entanercept-szzs (Elrezi®), infliximab (Remicade®), adalimumab (Humira®), adalimumab-adbm (Cyltezo®), ustekinumab (Stelara®), golimumab (Simponi®), apremilast (Otezla®),

15 secukinumab (Cosentyx®), certolixumab pegol, secukinumab, tildrakizumab-asmn, infliximab-dyyb, abatacept, ixekizumab (Taltz®), ABP 710, BCD-057, BI695501, bimekizumab (UCB4940), CHS-1420, GP2017, guselkumab (CNTO 1959), HD203, M923, MSB11022, Mirikizumab (LY3074828), PF-06410293, PF-06438179, risankizumab (BI655066), SB2, SB4, SB5, siliq (brodalumab), namilumab (MT203,

20 tildrakizumab (MK-3222), and ixekizumab (Taltz®)), thioguanine, and hydroxyurea (e.g., Droxia® and Hydrea®).

Non-limiting examples of additional therapeutic agents and/or regimens for treating cutaneous T-cell lymphoma include phototherapy (e.g., exposure to sunlight, UVB

25 phototherapy, narrow band UVB phototherapy, Goeckerman therapy, psoralen plus ultraviolet A (PUVA) therapy, and excimer laser), extracorporeal photopheresis, radiation therapy (e.g., spot radiation and total skin body electron beam therapy), stem cell transplant, corticosteroids, imiquimod, bexarotene gel, topical bis-chloroethyl-nitrourea, mechlorethamine gel, vorinostat (Zolinza®), romidepsin (Istodax®), pralatrexate (Foloty®) biologics (e.g., alemtuzumab (Campath®), brentuximab vedotin (SGN-35),

30 mogamulizumab, and IPH4102).

Non-limiting examples of additional therapeutic agents and/or regimens for treating uveitis include corticosteroids (e.g., intravitreal triamcinolone acetonide injectable suspensions), antibiotics, antivirals (e.g., acyclovir), dexamethasone, immunomodulators (e.g., tacrolimus, leflunomide, cyclophosphamide (Cytosan®, Neosar®, Endoxan®), and cyclosporine (Neoral®, Sandimmune®, Gengraf®), chlorambucil, azathioprine, methotrexate, and mycophenolate mofetil), biologics (e.g., infliximab (Remicade®), adalimumab (Humira®), etanercept (Enbrel®), golimumab (Simponi®), certolizumab (Cimzia®), rituximab (Rituxan®), abatacept (Orencia®), basiliximab (Simulect®), anakinra (Kineret®), canakinumab (Ilaris®), gevokixumab (XOMA052), tocilizumab (Actemra®), alemtuzumab (Campath®), efalizumab (Raptiva®), LFG316, sirolimus (Santen®), abatacept, sarilumab (Kevzara®), and daclizumab (Zenapax®)), cytotoxic drugs, surgical implant (e.g., fluocinolone insert), and vitrectomy.

Non-limiting examples of additional therapeutic agents and/or regimens for treating mucositis include AG013, SGX942 (dusquetide), amifostine (Ethyol®), cryotherapy, cepacol lozenges, capsaicin lozenges, mucoadhesives (e.g., MuGard®) oral diphenhydramine (e.g., Benadryl® elixir), oral bioadherents (e.g., polyvinylpyrrolidone-sodium hyaluronate gel (Gelclair®)), oral lubricants (e.g., Oral Balance®), caphosol, chamomilla recutita mouthwash, edible grape plant exosome, antiseptic mouthwash (e.g., chlorhexidine gluconate (e.g., Peridex® or Periogard®), topical pain relievers (e.g., lidocaine, benzocaine, dyclonine hydrochloride, xylocaine (e.g., viscous xylocaine 2%), and Ulcerease® (0.6% phenol)), corticosteroids (e.g., prednisone), pain killers (e.g., ibuprofen, naproxen, acetaminophen, and opioids), GC4419, palifermin (keratinocyte growth factor; Kepivance®), ATL-104, clonidine lauriad, IZN-6N4, SGX942, rebamipide, nepidermin, soluble β -1,3/1,6 glucan, P276, LP-0004-09, CR-3294, ALD-518, IZN-6N4, quercetin, granules comprising vaccinium myrtillus extract, macleaya cordata alkaloids and echinacea angustifolia extract (e.g., SAMITAL®), and gastrointestinal cocktail (an acid reducer such aluminum hydroxide and magnesium hydroxide (e.g., Maalox), an antifungal (e.g., nystatin), and an analgesic (e.g., hurricane liquid)). For example, non-limiting examples of treatments for oral mucositis include AG013, amifostine (Ethyol®), cryotherapy, cepacol lozenges, mucoadhesives (e.g., MuGard®) oral diphenhydramine (e.g., Benadryl® elixir), oral bioadherents (e.g., polyvinylpyrrolidone-sodium hyaluronate

gel (Gelclair®)), oral lubricants (e.g., Oral Balance®), caphosol, chamomilla recutita mouthwash, edible grape plant exosome, antiseptic mouthwash (e.g., chlorhexidine gluconate (e.g., Peridex® or Periogard®), topical pain relievers (e.g., lidocaine, benzocaine, dyclonine hydrochloride, xylocaine (e.g., viscous xylocaine 2%), and
5 Ulcerease® (0.6% phenol)), corticosteroids (e.g., prednisone), pain killers (e.g., ibuprofen, naproxen, acetaminophen, and opioids), GC4419, palifermin (keratinocyte growth factor; Kevivance®), ATL-104, clonidine lauriad, IZN-6N4, SGX942, rebamipide, nepidermin, soluble β -1,3/1,6 glucan, P276, LP-0004-09, CR-3294, ALD-518, IZN-6N4, quercetin, and
10 gastrointestinal cocktail (an acid reducer such aluminum hydroxide and magnesium hydroxide (e.g., Maalox), an antifungal (e.g., nystatin), and an analgesic (e.g., hurricane liquid)). As another example, non-limiting examples of treatments for esophageal mucositis include xylocaine (e.g., gel viscous Xylocaine 2%). As another example, treatments for intestinal mucositis, treatments to modify intestinal mucositis, and treatments for intestinal mucositis signs and symptoms include gastrointestinal cocktail (an
15 acid reducer such aluminum hydroxide and magnesium hydroxide (e.g., Maalox), an antifungal (e.g., nystatin), and an analgesic (e.g., hurricane liquid)).

In certain embodiments, the second therapeutic agent or regimen is administered to the subject prior to contacting with or administering the chemical entity (e.g., about one hour prior, or about 6 hours prior, or about 12 hours prior, or about 24 hours prior, or about
20 48 hours prior, or about 1 week prior, or about 1 month prior).

In other embodiments, the second therapeutic agent or regimen is administered to the subject at about the same time as contacting with or administering the chemical entity. By way of example, the second therapeutic agent or regimen and the chemical entity are provided to the subject simultaneously in the same dosage form. As another example, the
25 second therapeutic agent or regimen and the chemical entity are provided to the subject concurrently in separate dosage forms.

In still other embodiments, the second therapeutic agent or regimen is administered to the subject after contacting with or administering the chemical entity (e.g., about one hour after, or about 6 hours after, or about 12 hours after, or about 24 hours after, or about
30 48 hours after, or about 1 week after, or about 1 month after).

Patient Selection

In some embodiments, the methods described herein further include the step of identifying a subject (e.g., a patient) in need of such treatment (e.g., by way of biopsy, endoscopy, or other conventional method known in the art). In certain embodiments, the STING protein can serve as a biomarker for certain types of cancer, e.g., colon cancer and prostate cancer. In other embodiments, identifying a subject can include assaying the patient's tumor microenvironment for the absence of T-cells and/or presence of exhausted T-cells, e.g., patients having one or more cold tumors. Such patients can include those that are resistant to treatment with checkpoint inhibitors. In certain embodiments, such patients can be treated with a chemical entity herein, e.g., to recruit T-cells into the tumor, and in some cases, further treated with one or more checkpoint inhibitors, e.g., once the T-cells become exhausted.

In some embodiments, the chemical entities, methods, and compositions described herein can be administered to certain treatment-resistant patient populations (e.g., patients resistant to checkpoint inhibitors; e.g., patients having one or more cold tumors, e.g., tumors lacking T-cells or exhausted T-cells).

Compound Preparation

As can be appreciated by the skilled artisan, methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and RGM. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof. The starting materials used in preparing the compounds of the invention are known, made by known methods, or are commercially available. The skilled artisan will also recognize that conditions and reagents described herein that can be interchanged with alternative art-recognized equivalents. For example,

in many reactions, triethylamine can be interchanged with other bases, such as non-nucleophilic bases (e.g. diisopropylamine, 1,8-diazabicycloundec-7-ene, 2,6-di-*tert*-butylpyridine, or tetrabutylphosphazene).

5 The skilled artisan will recognize a variety of analytical methods that can be used to characterize the compounds described herein, including, for example, ¹H NMR, heteronuclear NMR, mass spectrometry, liquid chromatography, and infrared spectroscopy. The foregoing list is a subset of characterization methods available to a skilled artisan and is not intended to be limiting.

10 To further illustrate the foregoing, the following non-limiting, exemplary synthetic schemes are included. Variations of these examples within the scope of the claims are within the purview of one skilled in the art and are considered to fall within the scope of the invention as described, and claimed herein. The reader will recognize that the skilled artisan, provided with the present disclosure, and skill in the art is able to prepare and use the invention without exhaustive examples.

15

Examples

Abbreviation of chemical terms

Ac = acetyl

ADDP = 1,1'-(azodicarbonyl)-dipiperidine

20 ACN = acetonitrile

Boc₂O = di-*tert*-butyl pyrocarbonate

Bu = butyl

BOP = Benztiazol-1-yloxytris(dimethylamino)-phosphonium hexafluoro-phosphate

25 Bn = benzyl

Bz = benzoyl

CataCxiu A = Bis(adamant-1-yl)(butyl)phosphine

CMPB = (Cyanomethylene)tri-*n*-butylphosphorane

DAST = Diethylaminosulphur trifluoride

- DBAD = di-~~tert~~-butyl azodiformate
DCE = dichloroethane
DCM = dichloromethane
DEAD = diethyl azodiformate
5 DIBAL-H= Diisobutylaluminum hydride
DIAD = diisopropyl azodicarboxylate
DIEA = *N,N*-diisopropylethylamine
DMA = Dimethylacetamide
DMAP = 4-dimethylaminopyridine
10 DMF = *N,N*-dimethylformamide
DMF-DMA = *N,N*-dimethylformamide dimethyl acetal
DMSO = dimethyl sulfoxide
DPPA = diphenyl azidophosphate
Dppf = bis(diphenylphosphino)ferrocene
15 DtBPF = 1,1'-Bis[bis(1,1-dimethylethyl)phosphino]ferrocene
Grubbs 1st = Grubbs Catalyst 1st Generation
FA = Formic acid
HATU = 2-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium
hexafluorophosphateHMDS = 1,1,1,3,3,3-Hexamethyldisilazane
20 H₂O = Water
HPLC = high performance liquid chromatography
IBX = 2-iodoxybenzoic acid
LAH = Lithium aluminum hydride
LC-MS = liquid chromatography – mass spectrometry
25 Me = methyl
NMI = 1-methylimidazole
NMR = nuclear magnetic resonance
POT = tris(2-methylphenyl)phosphine
Pr = propyl
30 Py = pyridine

- RT = retention time
 TBDPS = t-butyl-diphenylsilyl
 TBS = tert-Butyldimethylsilyl
 TBUP = Tri-n-butylphosphine
 5 TCFH = N,N,N',N'-tetramethylchloroformamidinium-hexafluorophosphate
 TEA = trimethylamine
 Tf = trifluoromethanesulfonyl
 TFA = trifluoroacetic acid
 Tf₂O = trifluoromethanesulfonic anhydride
 10 THF = tetrahydrofuran
 TMS = Trimethylsilyl
 Tol = methylbenzene
 T₃P = 2,4,6-tripropyl-2,4,6-trioxo-1,3,5,2,4,6-trioxatriphosphorinane
 Ts = Tosyl
 15 t-AmOH = 2-methylbutan-2-ol
 XPhos = (2-(2,4,6-triisopropylphenethyl)phenyl)dicyclohexylphosphine
 Na₂SO₄ = Sodium sulfate
 Speedvac = Savant SC250EXP SpeedVac Concentrator
 DMSO = Dimethyl Sulfoxide
 20 Cs₂CO₃ = Cesium carbonate
 TCFH = N-(chloro(dimethylamino)methylene)-N-methylmethanaminium
 hexafluorophosphateN-
 HPLC-1 = high-performance liquid chromatography

25 **Materials and Methods**

For schemes 1-51 and examples 1-195 and, the LC-MS methods and prep-HPLC methods are one of the following methods.

LCMS Method A: Kinetex EVO C18 100A, 30*3mm, 0.5 µL injection, 1.2 mL/min flowrate, 90-900 amu scan range, 254 nm UV detection. Mobile Phase A (MPA):

Water/5mM NH_4HCO_3 and Mobile Phase B (MPB): Acetonitrile. Elution 10% MPB to 95% in 2.00 min, hold at 95% MPB for 0.30 min, 95% MPB to 10% in 0.10 min.

LCMS Method B: Xselect CSH C18, 50*3mm, 1.0 μL injection, 1.2 mL/min flowrate, 90-900 amu scan range, 254 nm UV detection. Mobile Phase A (MPA): Water/0.1% FA and
5 Mobile Phase B (MPB): Acetonitrile/0.1% FA. Elution 5% MPB to 100% in 2.00 min, hold at 100% MPB for 0.70 min, 100% MPB to 5% in 0.05 min, then equilibration to 5% MPB for 0.15 min.

LCMS Method C: XBridge Shield RP18, 50*4.6mm, 0.5 μL injection, 1.2 mL/min flowrate, 90-900 amu scan range, 254 nm UV detection. Mobile Phase A (MPA):
10 Water/0.04% $\text{NH}_3\cdot\text{H}_2\text{O}$ and Mobile Phase B (MPB): Acetonitrile. Elution 10% MPB to 95% in 2.00 min, hold at 95% MPB for 0.79 min, 95% MPB to 10% in 0.06 min, then equilibration to 10% MPB for 0.15 min.

LCMS Method D: kinetex 2.6 μm EVO, 50*3mm, 0.5 μL injection, 1.2 mL/min flowrate, 30-2000 amu scan range, 254 nm UV detection. Mobile Phase A (MPA): Water/5 mM
15 NH_4HCO_3 and Mobile Phase B (MPB): Acetonitrile. Elution 10% MPB to 95% in 2.00 min, hold at 95% MPB for 0.70 min, 95% MPB to 10% in 0.05 min, then equilibration to 10% MPB for 0.25 min.

LCMS Method E: HALOC18, 30*3mm, 0.5 μL injection, 1.5 mL/min flowrate, 30-2000 amu scan range, 254 nm UV detection. Mobile Phase A (MPA): Water/0.05% TFA and
20 Mobile Phase B (MPB): Acetonitrile/0.05% TFA. Elution 5% MPB to 100% in 1.20 min, hold at 100% MPB for 0.60 min, 100% MPB to 5% in 0.02 min, then equilibration to 5% MPB for 0.18 min.

LCMS Method F: Shim-pack Scepter C18-120, 33*3mm, 0.5 μL injection, 1.5 mL/min flowrate, 30-2000 amu scan range, 254 nm UV detection. Mobile Phase A (MPA): Water/5
25 mM NH_4HCO_3 and Mobile Phase B (MPB): Acetonitrile. Elution 50% MPB to 95% in 2.00 min, hold at 95% MPB for 0.60 min, 95% MPB to 10% in 0.05 min, then equilibration to 10% MPB for 0.25 min.

- LCMS Method G: Poroshell HPH C18, 50 *3mm, 0.5 µL injection, 1.2 mL/min flowrate, 30-2000 amu scan range, 254 nm UV detection. Mobile Phase A (MPA): Water/5 mM NH₄HCO₃+5 mM NH₄OH and Mobile Phase B (MPB): Acetonitrile. Elution 10% MPB to 95% in 2.00 min, hold at 95% MPB for 0.70 min, 95% MPB to 5% in 0.05 min, then
- 5 equilibration to 5% MPB for 0.25 min.

Method A

Instrument: Agilent LCMS system equipped with DAD and ELSD detector

Ion mode: Positive

Column: Waters X-Bridge C18, 50*2.1 mm*5 µm or equivalent

Mobile Phase: A: H₂O (0.04% TFA); B: CH₃CN (0.02% TFA)

Gradient: 4.5 min gradient method, actual method would depend on clogP of compound.

Flow Rate: 0.6 mL/min or 0.8 mL/min

Column Temp: 40 °C or 50 °C

UV: 220 nm

Method B

Instrument: Agilent LCMS system equipped with DAD and ELSD detector

Ion mode: Positive

Column: Waters X-Bridge ShieldRP18, 50*2.1 mm*5 µm or equivalent

Mobile Phase: A: H₂O (0.05% NH₃·H₂O) or 10 mM ammonia bicarbonate; B: CH₃CN

Gradient: 4.5 min gradient method; actual method would depend on the clogP of the compound.

Flow Rate: 0.6 mL/min or 0.8 mL/min

Column Temp: 40 °C

UV: 220 nm

Prep. HPLC condition**Instrument:**

1. GILSON 281 and Shimadzu LCMS 2010A
2. GILSON 215 and Shimadzu LC-20AP

3. GILSON 215

Mobile phase:

A: $\text{NH}_4\text{OH}/\text{H}_2\text{O} = 0.05\% \text{ v/v}$; B: ACN

A: $\text{FA}/\text{H}_2\text{O} = 0.225\% \text{ v/v}$; B: ACN

5 **Column**

Xtimate C18 150*25mm*5 μm

Flow rate: 25 mL/min or 30 mL/min

Monitor wavelength: 220&254 nm

Gradient: actual method would depend on $\log P$ of compound

10 **Detector: MS Trigger or UV**

NMR was recorded on BRUKER NMR 300.03 Mz, DUL-C-H, ULTRASHIELD™ 300, AVANCE II 300 B-ACS™ 120 or BRUKER NMR 400.13 Mz, BBFO, ULTRASHIELD™ 400, AVANCE III 400, B-ACS™ 120.

15 For scheme 52-75 and examples 196-289, the LC-MS, NMR, Prep-HPLC are conducted using one of the following methods.

LCMS Method A: Kinetex EVO C18 100A, 30*3mm, 0.5 μL injection, 1.2 mL/min flowrate, 90-900 amu scan range, 254 nm UV detection. Mobile Phase A (MPA): Water/5mM NH_4HCO_3 and Mobile Phase B (MPB): Acetonitrile. Elution 10% MPB to 95% in 2.00 min, hold at 95% MPB for 0.30 min, 95% MPB to 10% in 0.10 min.

LCMS Method B: Xselect CSH C18, 50*3mm, 1.0 μL injection, 1.2 mL/min flowrate, 90-900 amu scan range, 254 nm UV detection. Mobile Phase A (MPA): Water/0.1% FA and Mobile Phase B (MPB): Acetonitrile/0.1% FA. Elution 5% MPB to 100% in 2.00 min, hold at 100% MPB for 0.70 min, 100% MPB to 5% in 0.05 min, then equilibration to 5% MPB for 0.15 min.

LCMS Method C: XBridge Shield RP18, 50*4.6mm, 0.5 μL injection, 1.2 mL/min flowrate, 90-900 amu scan range, 254 nm UV detection. Mobile Phase A (MPA): Water/0.04% $\text{NH}_3 \cdot \text{H}_2\text{O}$ and Mobile Phase B (MPB): Acetonitrile. Elution 10% MPB to

95% in 2.00 min, hold at 95% MPB for 0.79 min, 95% MPB to 10% in 0.06 min, then equilibration to 10% MPB for 0.15 min.

LCMS Method D: kinetex 2.6µm EVO, 50*3mm, 0.5 µL injection, 1.2 mL/min flowrate, 30-2000 amu scan range, 254 nm UV detection. Mobile Phase A (MPA): Water/5 mM
5 NH₄HCO₃ and Mobile Phase B (MPB): Acetonitrile. Elution 10% MPB to 95% in 2.00 min, hold at 95% MPB for 0.70 min, 95% MPB to 10% in 0.05 min, then equilibration to 10% MPB for 0.25 min.

LCMS Method E: HALOC18, 30*3mm, 0.5 µL injection, 1.5 mL/min flowrate, 30-2000 amu scan range, 254 nm UV detection. Mobile Phase A (MPA): Water/0.05% TFA and
10 Mobile Phase B (MPB): Acetonitrile/0.05% TFA. Elution 5% MPB to 100% in 1.20 min, hold at 100% MPB for 0.60 min, 100% MPB to 5% in 0.02 min, then equilibration to 5% MPB for 0.18 min.

LCMS Method F: Shim-pack Scepter C18-120, 33*3mm, 0.5 µL injection, 1.5 mL/min flowrate, 30-2000 amu scan range, 254 nm UV detection. Mobile Phase A (MPA): Water/5
15 mM NH₄HCO₃ and Mobile Phase B (MPB): Acetonitrile. Elution 50% MPB to 95% in 2.00 min, hold at 95% MPB for 0.60 min, 95% MPB to 10% in 0.05 min, then equilibration to 10% MPB for 0.25 min.

Method A

Instrument: Agilent LCMS system equipped with DAD and ELSD detector

Ion mode: Positive

Column: Waters X-Bridge C18, 50*2.1 mm*5 µm or equivalent

Mobile Phase: A: H₂O (0.04% TFA); B: CH₃CN (0.02% TFA)

Gradient: 4.5 min gradient method, actual method would depend on clogP of compound.

Flow Rate: 0.6 mL/min or 0.8 mL/min

Column Temp: 40 °C or 50 °C

UV: 220 nm

Method B

Instrument: Agilent LCMS system equipped with DAD and ELSD detector

Ion mode: Positive

Column: Waters X-Bridge ShieldRP18, 50*2.1 mm*5 µm or equivalent

Mobile Phase: A: H₂O (0.05% NH₃·H₂O) or 10 mM ammonia bicarbonate; B:

CH₃CN

Gradient: 4.5 min gradient method; actual method would depend on the clogP of the compound.

Flow Rate: 0.6 mL/min or 0.8 mL/min

Column Temp: 40 °C

UV: 220 nm

Prep. HPLC-1 condition-1**Instrument:**

1. GILSON 281 and Shimadzu LCMS 2010A
2. GILSON 215 and Shimadzu LC-20AP
3. GILSON 215

Mobile phase:

5 A: NH₄OH/H₂O = 0.05% v/v; B: ACN

A: FA/H₂O = 0.225% v/v; B: ACN

Column

Xtimate C18 150*25mm*5µm

Flow rate: 25 mL/min or 30 mL/min

10 Monitor wavelength: 220&254 nm

Gradient: actual method would depend on clog P of compound

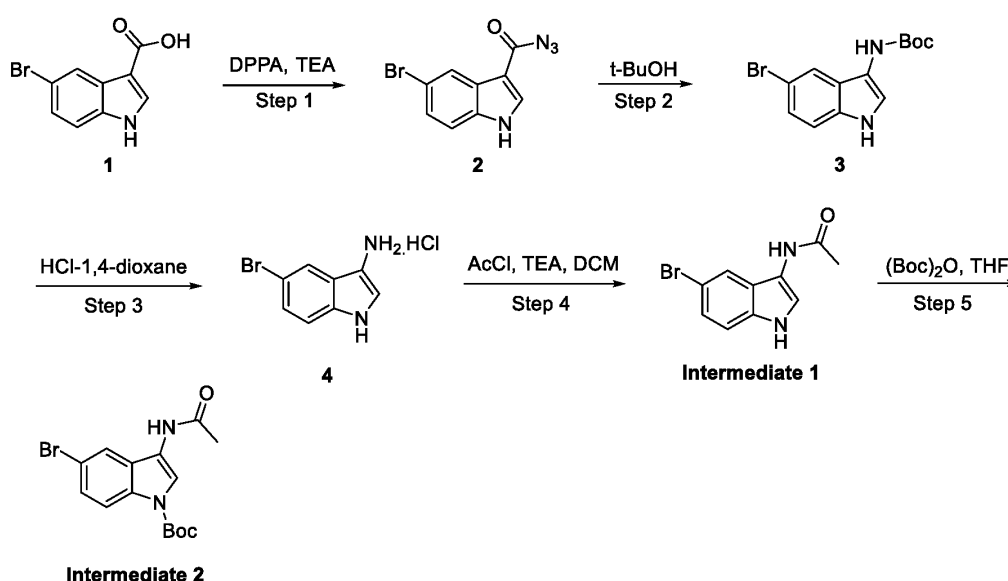
Detector: MS Trigger or UV

NMR was recorded on BRUKER NMR 300.03 Mz, DUL-C-H, ULTRASHIELD™ 300, AVANCE II 300 B-ACS™ 120 or BRUKER NMR 400.13 Mz, BBFO, 15 ULTRASHIELD™ 400, AVANCE III 400, B-ACS™ 120.

Preparative examples

Scheme for the preparation of Key Intermediates: Schemes below illustrate the preparation of key intermediates.

Scheme 1: Synthesis of intermediate 1 and intermediate 2 (*N*-(5-bromo-1*H*-indol-3-yl)acetamide and *tert*-butyl 3-acetamido-5-bromo-1*H*-indole-1-carboxylate)



Step 1: 5-bromo-1*H*-indole-3-carbonyl azide

5-Bromo-1*H*-indole-3-carboxylic acid (30.0 g, 124.9 mmol, 1.0 equiv.) was dissolved in THF (150 mL), then TEA (26.1 mL, 187.4 mmol, 1.5 equiv.) and DPPA (37.8 g, 137.4 mmol, 1.1 equiv.) were added. The reaction mixture was stirred for 12 hours at ambient temperature, then quenched by the addition of water and stirred for an additional 10 min. The precipitated solid was collected by filtration and dried to give 5-bromo-1*H*-indole-3-carbonyl azide (33.6 g) as an off-white solid. LCMS Method B: [M-H]⁺ = 263.

Step 2: *tert*-butyl (5-bromo-1*H*-indol-3-yl)carbamate

5-Bromo-1*H*-indole-3-carbonyl azide (33.6 g, 126.7 mmol, 1.0 equiv.) was dissolved in *t*-BuOH (300 mL). The reaction mixture was heated to 80 °C for 12 hours, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:10) to give *tert*-butyl (5-bromo-1*H*-indol-3-yl)carbamate (22.1 g) as a pale white solid. LCMS Method A: $[M+H]^+ = 311$.

Step 3: 5-bromo-1*H*-indol-3-amine hydrochloride

tert-Butyl (5-bromo-1*H*-indol-3-yl)carbamate (20.0 g, 64.2 mmol, 1.0 equiv.) was dissolved in HCl/1,4-dioxane (4 M, 150 mL). The reaction mixture was stirred for 2 hours at ambient temperature and then concentrated under vacuum to give 5-bromo-1*H*-indol-3-amine hydrochloride (18.7 g) as a brown solid. LCMS Method A: $[M+H]^+ = 211$.

Step 4: *N*-(5-bromo-1*H*-indol-3-yl)acetamide

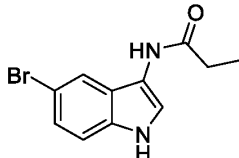
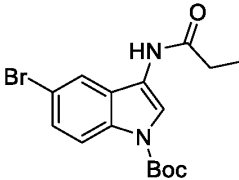
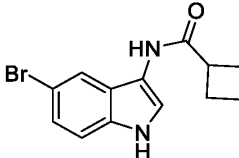
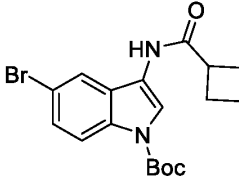
5-Bromo-1*H*-indol-3-amine (18.7 g, 88.6 mmol, 1.0 equiv.) and TEA (37.1 mL, 265.8 mmol, 3.0 equiv.) were dissolved in DCM (200 mL) and the solution was cooled to 0 °C. Then AcCl (6.9 mL, 97.4 mmol, 1.1 equiv.) was added dropwise, maintaining the solution at 0 °C. The reaction mixture was stirred for 3 hours at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with DCM, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:3) to give *N*-(5-bromo-1*H*-indol-3-yl)acetamide (15.0 g) as a brown solid. LCMS Method A: $[M+H]^+ = 253$.

Step 5: *tert*-butyl 5-bromo-3-acetamidoindole-1-carboxylate

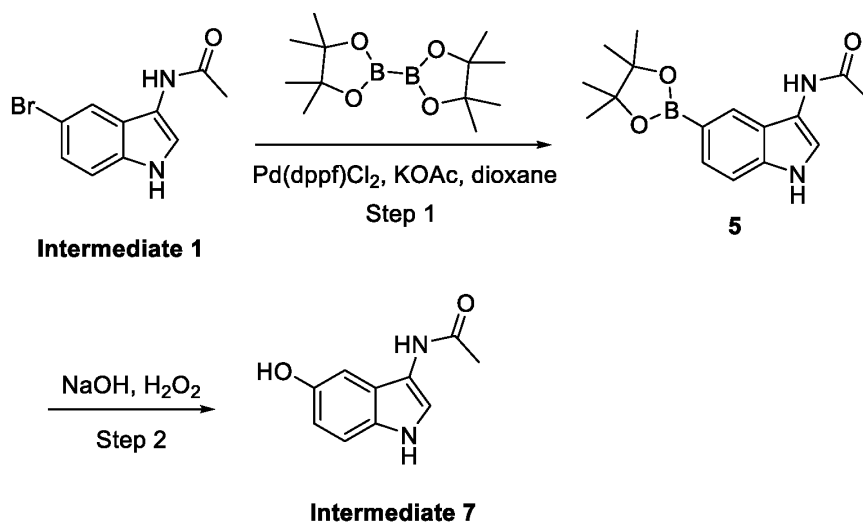
N-(5-bromo-1*H*-indol-3-yl)acetamide (1.0 g, 4.0 mmol, 1.0 equiv.) was dissolved in THF (30 mL), then TEA (1.1 mL, 7.9 mmol, 2 equiv.), Boc₂O (862.3 mg, 4.0 mmol, 1.0 equiv.) and DMAP (48.3 mg, 0.4 mmol, 0.1 equiv.) were added. The reaction mixture was stirred for 50 min at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over

anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give *tert*-butyl 5-bromo-3-acetamidoindole-1-carboxylate (800.0 mg) as a pale yellow solid. LCMS Method C: $[\text{M}+\text{H}]^+ = 353$.

- 5 The intermediates in the following table were prepared using the same method described for Intermediates 1 and 2.

Intermediate	Structure	LCMS data
Intermediate 3		Method A: MS-ESI: 267 $[\text{M}+\text{H}]^+$
Intermediate 4		Method A: MS-ESI: 367 $[\text{M}+\text{H}]^+$
Intermediate 5		Method A: MS-ESI: 293 $[\text{M}+\text{H}]^+$
Intermediate 6		Method A: MS-ESI: 393 $[\text{M}+\text{H}]^+$

Scheme 2: Synthesis of intermediate 7 (N-(5-hydroxy-1H-indol-3-yl)acetamide)



Step 1: *N*-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)acetamide

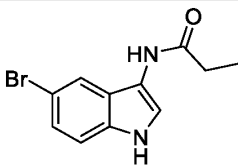
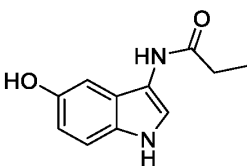
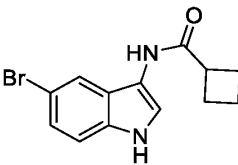
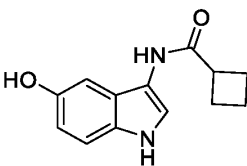
N-(5-bromo-1*H*-indol-3-yl)acetamide (10.0 g, 39.5 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (100 mL), then 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (20.1 g, 79.0 mmol, 2.0 equiv.), KOAc (7.7 g, 79.0 mmol, 2.0 equiv.) and Pd(dppf)Cl₂·CH₂Cl₂ (2.8 g, 3.9 mmol, 0.1 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 100 °C for 6 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (20:1) to give *N*-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)acetamide (9.1 g) as a brown solid. LCMS Method A: [M+H]⁺ = 301.

Step 2: *N*-(5-hydroxy-1*H*-indol-3-yl)acetamide

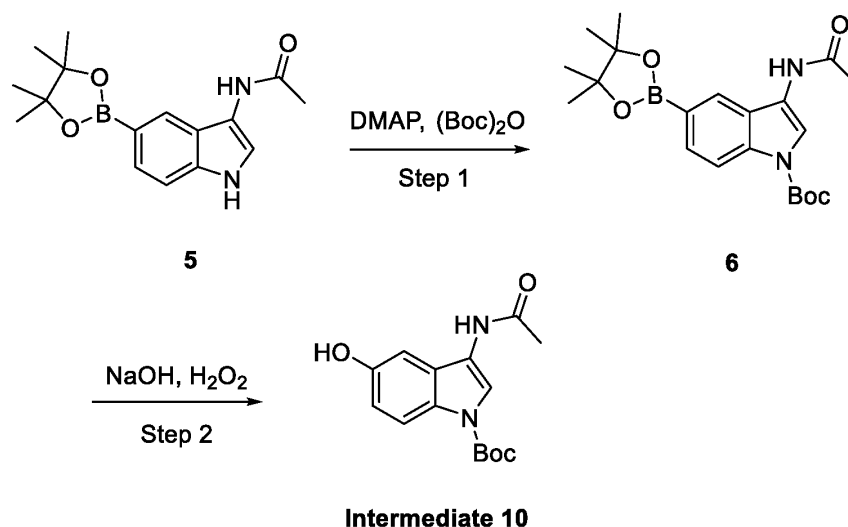
N-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)acetamide (6.5 g, 21.6 mmol, 1.0 equiv.) was dissolved in THF (50 mL) and water (50 mL), then NaOH (1.7 g, 42.5 mmol, 2.0 equiv.) was added. This was followed by the addition of H₂O₂ (30% wt. in water, 28.0 mL, 420.0 mmol, 20.0 equiv.) dropwise at 0 °C. The reaction mixture was stirred for 2 hours at ambient temperature, then quenched by the addition of saturated

aqueous NH_4Cl . The resulting solution was extracted with ethyl acetate, washed with brine and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (10:1) to give *N*-(5-hydroxy-1*H*-indol-3-yl)acetamide (2.5 g) as a grey solid. LCMS Method A: $[\text{M}+\text{H}]^+ = 191$.

- 5 The intermediates in the following table were prepared using the same method described for Intermediate 7.

Intermediate	Starting material	Structure	LCMS data
Intermediate 8	 Intermediate 3		Method A: MS-ESI: 205 $[\text{M}+\text{H}]^+$
Intermediate 9	 Intermediate 5		Method A: MS-ESI: 231 $[\text{M}+\text{H}]^+$

*Scheme 3: Synthesis of intermediate 10 (tert-butyl 3-acetamido-5-hydroxy-1*H*-indole-1-carboxylate)*



Step 1: *tert*-butyl 3-acetamido-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole-1-carboxylate

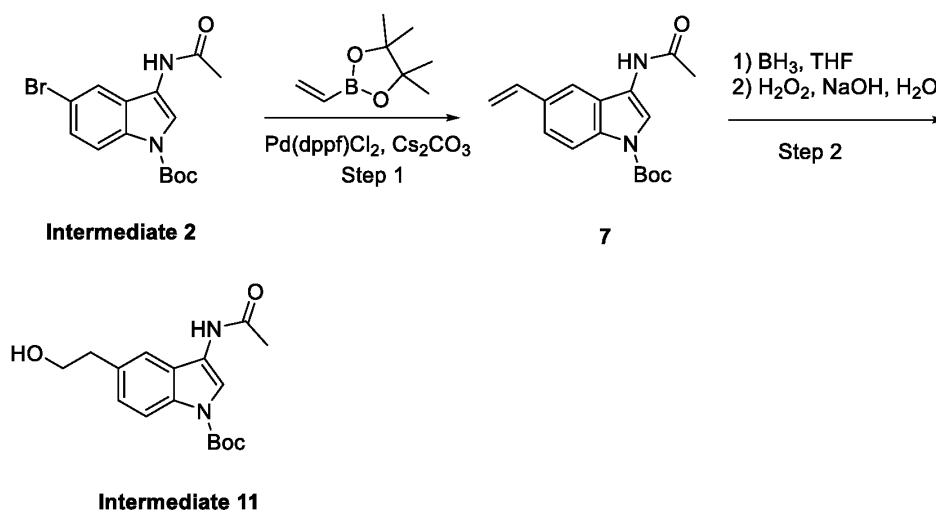
N-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl]acetamide (1.0 g, 3.3 mmol, 1.0 equiv.) and Boc_2O (872.5 mg, 4.0 mmol, 1.2 equiv.) were dissolved in THF, then TEA (0.9 mL, 6.7 mmol, 2.0 equiv.) and DMAP (40.7 mg, 0.3 mmol, 0.1 equiv.) were added. The reaction mixture was stirred overnight at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:7) to give *tert*-butyl 3-acetamido-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole-1-carboxylate (907.5 mg) as a yellow solid. LCMS Method B: $[\text{M}+\text{H}]^+ = 401$.

Step 2: *tert*-butyl 3-acetamido-5-hydroxyindole-1-carboxylate

tert-Butyl 3-acetamido-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole-1-carboxylate (1.0 g, 2.5 mmol, 1.0 equiv.) was dissolved in THF (10 mL), then aqueous NaOH (2% wt., 10 mL, 5.0 mmol, 2.0 equiv.) and H_2O_2 (30% wt., 2.6 mL, 25.0 mmol, 10.0 equiv.) were added. The reaction mixture was stirred for 2 hours at ambient temperature and then quenched by the addition of water. The resulting solution was

adjusted to pH 6 with saturated aqueous NH_4HCO_3 , then extracted with ethyl acetate and the combined organic layers were concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (20:1) to give *tert*-butyl 3-acetamido-5-hydroxyindole-1-carboxylate (690.0 mg) as a grey solid. LCMS Method B: $[\text{M}+\text{H}]^+ = 291$.

Scheme 4: Synthesis of intermediate 11 (*tert*-butyl 3-acetamido-5-(2-hydroxyethyl)-1H-indole-1-carboxylate)



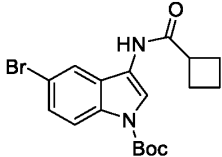
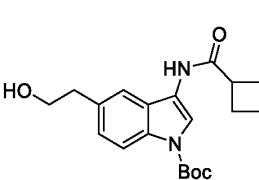
Step 1: *tert*-butyl 3-acetamido-5-ethenylindole-1-carboxylate

tert-Butyl 5-bromo-3-acetamidindole-1-carboxylate (660.0 mg, 1.9 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (4 mL) and water (1 mL), then 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (575.6 mg, 3.7 mmol, 2.0 equiv.), Cs_2CO_3 (1.2 g, 3.7 mmol, 2.0 equiv.) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (273.4 mg, 0.4 mmol, 0.2 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 85 °C for 4 hours, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:4) to give *tert*-butyl 3-acetamido-5-ethenylindole-1-carboxylate (400.0 mg%) as a pale yellow solid. LCMS Method C: $[\text{M}+\text{H}]^+ = 301$.

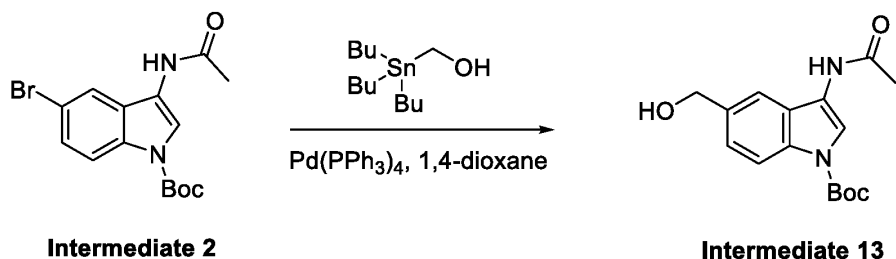
Step 2: *tert*-butyl 3-acetamido-5-(2-hydroxyethyl)-1H-indole-1-carboxylate

$tert$ -Butyl 3-acetamido-5-ethenylindole-1-carboxylate (500.0 mg, 1.7 mmol, 1.0 equiv.) was dissolved in THF (20 mL), then BH_3 -THF (1 M, 2.5 mL, 2.5 mmol, 1.5 equiv.) was added dropwise. The reaction mixture was stirred for 40 min at ambient temperature. Then a solution of aqueous NaOH (1 M, 3.3 mL, 3.3 mmol, 2.0 equiv.) was added and the reaction mixture was cooled to 0 °C. This was followed by the dropwise addition of H_2O_2 (30% wt. in water, 1.3 mL, 3.3 mmol, 2.0 equiv.), maintaining the reaction mixture at 0 °C. The reaction mixture was stirred for additional 30 min at 0 °C, then quenched by the addition of saturated aqueous NH_4Cl . The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (12:1) to give $tert$ -butyl 3-acetamido-5-(2-hydroxyethyl)indole-1-carboxylate (300.0 mg) as a pale yellow solid. LCMS Method A: $[M+H]^+ = 319$.

The intermediate in the following table was prepared using the same method described for **Intermediate 11**.

Intermediate	Starting material	Structure	LCMS data
Intermediate 12	 Intermediate 6		Method A: MS-ESI: 359 $[M+H]^+$

Scheme 5: Synthesis of intermediate 13 (tert-butyl 3-acetamido-5-(hydroxymethyl)-1H-indole-1-carboxylate)

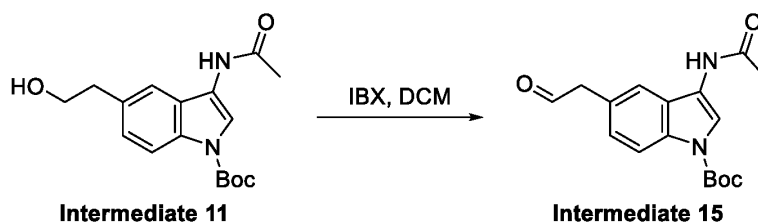


$tert$ -Butyl 5-bromo-3-acetamidoindole-1-carboxylate (500.0 mg, 1.4 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (5 mL), then (tributylstannyl)methanol (909.1 mg, 2.8 mmol, 2.0 equiv.) and $\text{Pd}(\text{PPh}_3)_4$ (327.2 mg, 0.3 mmol, 0.2 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 85 °C for 4 hours, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give $tert$ -butyl 3-acetamido-5-(hydroxymethyl)indole-1-carboxylate (262.5 mg) as a pale yellow solid. LCMS Method C: $[\text{M}+\text{H}]^+ = 305$.

The intermediate in the following table was prepared using the same method described for **Intermediate 13**.

Intermediate	Starting material	Structure	LCMS data
Intermediate 14	Intermediate 4		Method C: MS-ESI: 319 $[\text{M}+\text{H}]^+$

Scheme 6: Synthesis of intermediate 15 (tert-butyl 3-acetamido-5-(2-oxoethyl)-1H-indole-1-carboxylate)



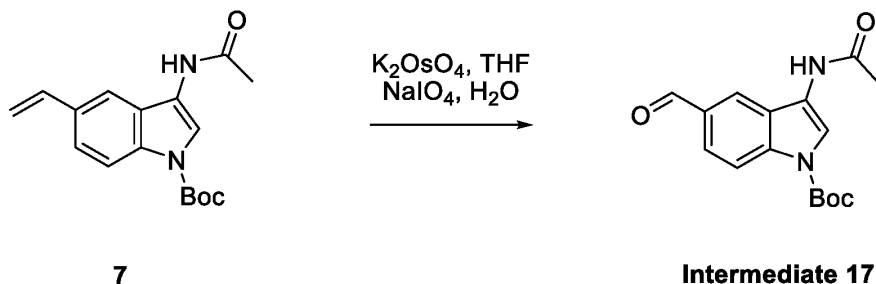
tert-Butyl 3-acetamido-5-(2-hydroxyethyl)indole-1-carboxylate (320.0 mg, 1.0 mmol, 1.0 equiv.) was dissolved in DCM (25 mL), then IBX (562.9 mg, 2.0 mmol, 2.0 equiv.) was added. The reaction mixture was heated to 50 °C for 3 hours, the cooled to ambient temperature and the solids were removed by filtration. The filtrate was concentrated under vacuum to give *tert*-butyl 3-acetamido-5-(2-oxoethyl)indole-1-carboxylate (311.2 mg) as a pale yellow solid. LCMS Method A: $[M+H]^+ = 317$.

The intermediate in the following table was prepared using the same method described for **Intermediate 15**.

Intermediate	Starting material	Structure	LCMS data
Intermediate 16	Intermediate 12		Method A: MS-ESI: 357 $[M+H]^+$

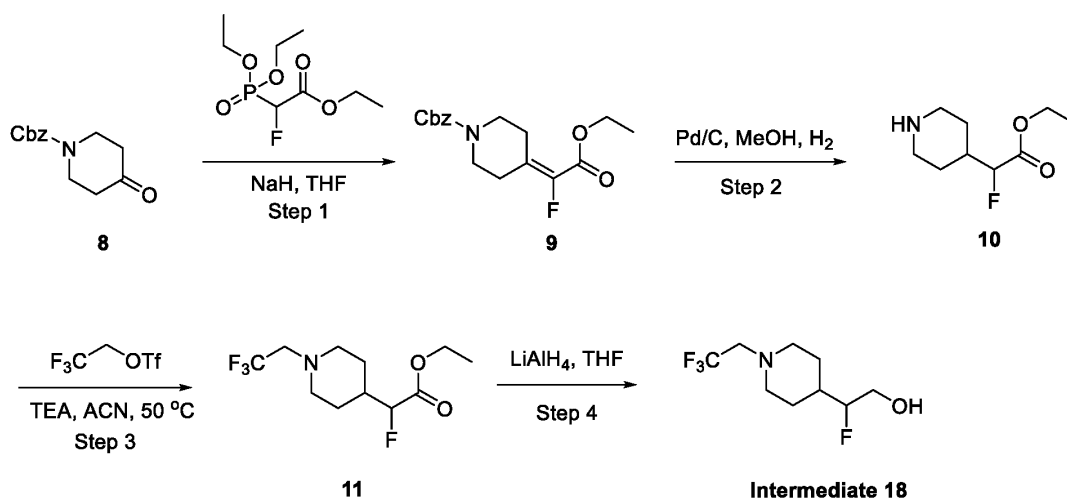
10

Scheme 7: Synthesis of intermediate 17 (tert-butyl 3-acetamido-5-formyl-1H-indole-1-carboxylate)



tert-Butyl 3-acetamido-5-ethenylindole-1-carboxylate (400.0 mg, 1.3 mmol, 1.0 equiv.) was dissolved in THF (15 mL) and water (15 mL), then K₂OsO₄•2H₂O (98.1 mg, 0.3 mmol, 0.2 equiv.) and NaIO₄ (1.1 g, 5.3 mmol, 4.0 equiv.) were added. The reaction mixture was stirred for 2 hours at ambient temperature and then diluted with water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give *tert*-butyl 3-acetamido-5-formylindole-1-carboxylate (350.0 mg) as a dark yellow solid. LCMS Method B: [M+H]⁺ = 303.

Scheme 8: Synthesis of intermediate 18 (2-fluoro-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethan-1-ol)



Step 1: benzyl 4-(2-ethoxy-1-fluoro-2-oxoethylidene)piperidine-1-carboxylate

Ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate (1.6 g, 6.4 mmol, 1.5 equiv.) was dissolved in THF (20 mL) and cooled to 0 °C, then NaH (60% wt., 342.9 mg, 8.6 mmol, 2.0 equiv.) was added, maintaining the reaction mixture at 0 °C. The reaction mixture was stirred for 30 min at ambient temperature. This was followed by the dropwise addition of benzyl 4-oxopiperidine-1-carboxylate (1.0 g, 4.3 mmol, 1.0 equiv.) at 0 °C. The resulting mixture was stirred for an additional 2 hours at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give benzyl 4-(2-ethoxy-1-fluoro-2-oxoethylidene)piperidine-1-carboxylate (1.2 g) as a colorless oil. LCMS Method A: [M+H]⁺ = 322.

Step 2: ethyl 2-fluoro-2-(piperidin-4-yl)acetate

Benzyl 4-(2-ethoxy-1-fluoro-2-oxoethylidene)piperidine-1-carboxylate (1.2 g, 3.7 mmol, 1.0 equiv.) was dissolved in MeOH (20 mL), then Pd/C (120.0 mg, 10% wt.) was added under an atmosphere of nitrogen. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 2 hours at ambient temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give ethyl 2-fluoro-2-(piperidin-4-yl)acetate (650.0 mg) as a colorless oil. LCMS Method A: [M+H]⁺ = 190.

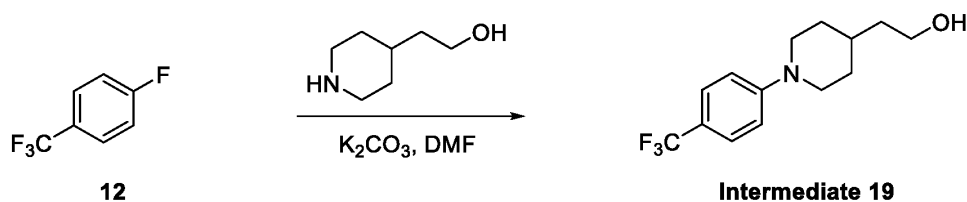
Step 3: ethyl 2-fluoro-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)acetate

Ethyl 2-fluoro-2-(piperidin-4-yl)acetate (1.0 g, 5.3 mmol, 1.0 equiv.) and TEA (1.5 mL, 10.6 mmol, 2.0 equiv.) were dissolved in ACN (20 mL), then 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.8 g, 7.9 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for 4 hours at ambient temperature and then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give ethyl 2-fluoro-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)acetate (820.0 mg) as a colorless oil. LCMS Method A: [M+H]⁺ = 272.

Step 4: 2-fluoro-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethan-1-ol

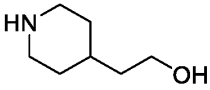
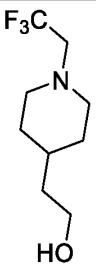
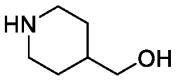
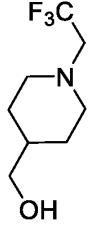
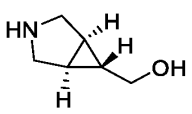
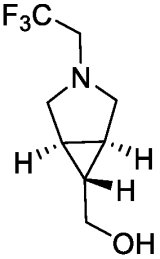
Ethyl 2-fluoro-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)acetate (400.0 mg, 1.5 mmol, 1.0 equiv.) was dissolved in THF (15 mL) and cooled to 0 °C, then LiAlH₄ (111.9 mg, 2.9 mmol, 2.0 equiv.) was added, maintaining the solution at 0 °C. The reaction mixture was stirred for 2 hours at ambient temperature and then quenched by the addition of Na₂SO₄•10H₂O. The solid was removed by filtration, then the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:2) to give 2-fluoro-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethan-1-ol (310.0 mg) as a colorless oil. LCMS Method A: [M+H]⁺ = 230.

Scheme 9: Synthesis of intermediate 19 (2-(1-(4-(trifluoromethyl)phenyl)piperidin-4-yl)ethan-1-ol)

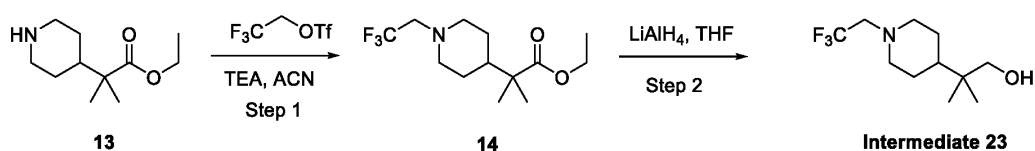


1-Fluoro-4-(trifluoromethyl)benzene (500.0 mg, 3.0 mmol, 1.0 equiv.) was dissolved in DMF (10 mL), then K₂CO₃ (842.1 mg, 6.0 mmol, 2.0 equiv.) and 4-piperidineethanol (393.6 mg, 3.0 mmol, 1.0 equiv.) were added. The reaction mixture was heated to 120 °C overnight, then cooled to ambient temperature and quenched by the addition of aqueous HCl (2N). The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give 2-[1-[4-(trifluoromethyl)phenyl]piperidin-4-yl]ethanol (280.0 mg) as a pale yellow solid. LCMS Method A: [M+H]⁺ = 274.

The intermediates in the following table were prepared using the same method described for **Intermediate 19**.

Intermediate	Starting material A	Starting material B	Structure	LCMS data
Intermediate 20		$\text{F}_3\text{C}-\text{CH}_2-\text{OTf}$		Method A: MS-ESI: 212 [M+H] ⁺
Intermediate 21		$\text{F}_3\text{C}-\text{CH}_2-\text{OTf}$		Method A: MS-ESI: 198 [M+H] ⁺
Intermediate 22		$\text{F}_3\text{C}-\text{CH}_2-\text{OTf}$		Method A: MS-ESI: 196 [M+H] ⁺

Scheme 10: Synthesis of intermediate 23 (2-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)propan-1-ol)



Step 1: ethyl 2-methyl-2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]propanoate

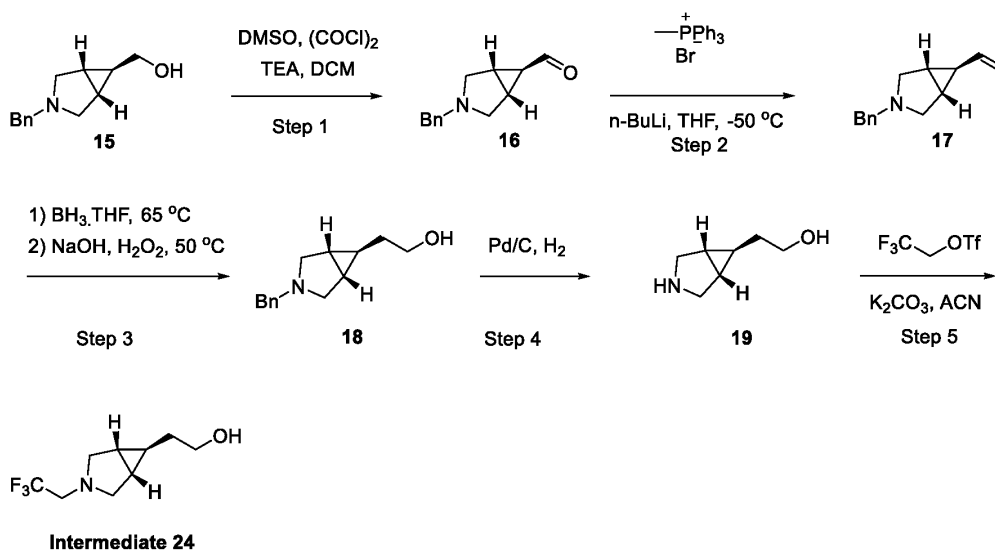
- 5 Ethyl 2-methyl-2-(piperidin-4-yl)propanoate (500.0 mg, 2.5 mmol, 1.0 equiv.) and TEA (0.5 mL, 3.8 mmol, 1.5 equiv.) were dissolved in ACN (25 mL), then 2,2,2-trifluoroethyl trifluoromethanesulfonate (873.5 mg, 3.8 mmol, 1.5 equiv.) was added. The reaction mixture was heated to 65 °C for 6 hours, then cooled to ambient temperature and

concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give ethyl 2-methyl-2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]propanoate (205.5 mg) as a yellow oil. LCMS Method C: $[M+H]^+ = 282$.

5 Step 2: 2-methyl-2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]propan-1-ol

Ethyl 2-methyl-2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]propanoate (200.0 mg, 0.7 mmol, 1.0 equiv.) was dissolved in THF (100 mL) and cooled to 0 °C. Then $LiAlH_4$ (40.5 mg, 1.1 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for 2 hours at ambient temperature and then quenched by the addition of water. The solid was removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give 2-methyl-2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]propan-1-ol (21.3 mg) as a yellow oil. LCMS Method C: $[M+H]^+ = 240$.

15 Scheme 11: Synthesis of intermediate 24 (2-((1R,5S,6S)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethan-1-ol)



Step 1: (1R,5S,6S)-3-benzyl-3-azabicyclo[3.1.0]hexane-6-carbaldehyde

Oxalyl chloride (1.0 mL, 12.3 mmol, 2.5 equiv.) was dissolved in DCM (30 mL) and cooled to -78 °C, then DMSO (1.7 mL, 24.6 mmol, 5.0 equiv.) was added dropwise. The reaction mixture was stirred for 1 hour at -78 °C under an atmosphere of nitrogen. This was followed by the dropwise addition of a solution of [(1R,5S,6S)-3-benzyl-3-azabicyclo[3.1.0]hexan-6-yl]methanol (1.0 g, 4.9 mmol, 1.0 equiv.) in DCM (20 mL), maintaining the solution at -78 °C. The reaction mixture was stirred for an additional 2 hours at -78 °C, then TEA (6.9 mL, 49.2 mmol, 10.0 equiv.) was added dropwise and the resulting solution was stirred for another 4 hours at ambient temperature. The reaction was quenched by the addition of water, extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give (1R,5S,6S)-3-benzyl-3-azabicyclo[3.1.0]hexane-6-carbaldehyde (980.0 mg) as a pale yellow liquid. LCMS Method A: [M+H]⁺ = 202.

Step 2: (1R,5S,6S)-3-benzyl-6-ethenyl-3-azabicyclo[3.1.0]hexane

Methyltriphenylphosphonium bromide (2.0 g, 5.7 mmol, 1.5 equiv.) was dissolved in THF (20 mL) and cooled to -50 °C, then n-BuLi (3M in THF, 1.9 mL, 5.7 mmol, 1.5 equiv.) was added dropwise under an atmosphere of nitrogen, maintaining the solution at -50 °C. After 30 min at -50 °C, a solution of (1R,5S,6S)-3-benzyl-3-azabicyclo[3.1.0]hexane-6-carbaldehyde (760.0 mg, 3.8 mmol, 1.0 equiv.) in THF (5 mL) was added dropwise. The resulting mixture was stirred for additional 4 hours at ambient temperature and then quenched by the addition of saturated aqueous NH₄Cl. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give (1R,5S,6S)-3-benzyl-6-ethenyl-3-azabicyclo[3.1.0]hexane (480.0 mg) as a pale yellow oil. LCMS Method A: [M+H]⁺ = 200.

Step 3: 2-[(1R,5S,6S)-3-benzyl-3-azabicyclo[3.1.0]hexan-6-yl]ethanol

(1R,5S,6S)-3-benzyl-6-ethenyl-3-azabicyclo[3.1.0]hexane (480.0 mg, 2.4 mmol, 1.0 equiv.) was dissolved in THF (20 mL), then BH₃-SMe₂ (0.80 mL, 2.4 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred for 1 hour at 65 °C, then cooled

down to 0 °C. Then a solution of NaOH (578.0 mg, 14.4 mmol, 6.0 equiv.) in H₂O (2 mL) was added, followed by the dropwise addition of H₂O₂ (30% aqueous, 1.5 mL, 14.4 mmol, 6.0 equiv.). The resulting mixture was heated to 50 °C overnight, then cooled to ambient temperature and quenched by the addition of saturated aqueous NH₄Cl. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give 2-[(1R,5S,6S)-3-benzyl-3-azabicyclo[3.1.0]hexan-6-yl]ethanol (510.0 mg) as a pale yellow oil. LCMS Method A: [M+H]⁺ = 218.

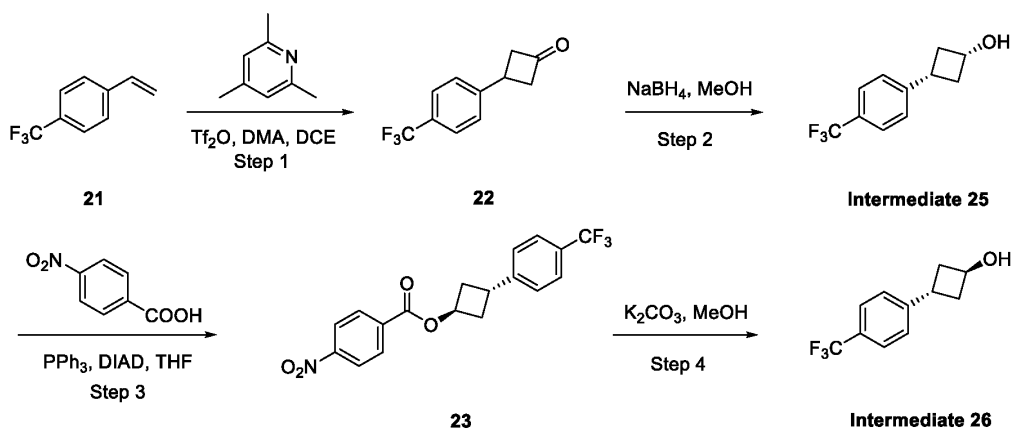
Step 4: 2-[(1R,5S,6S)-3-azabicyclo[3.1.0]hexan-6-yl]ethanol

2-[(1R,5S,6S)-3-benzyl-3-azabicyclo[3.1.0]hexan-6-yl]ethanol (450.0 mg, 2.1 mmol, 1.0 equiv.) was dissolved in MeOH (20 mL), then Pd/C (10% wt., 44.1 mg) was added. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 6 hours at 45 °C. The solids were removed by filtration and the filtrate was concentrated under vacuum to give 2-[(1R,5S,6S)-3-azabicyclo[3.1.0]hexan-6-yl]ethanol (250.0 mg) as a pale yellow oil. LCMS Method A: [M+H]⁺ = 128.

Step 5: 2-[(1R,5S,6S)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexan-6-yl]ethanol

2-[(1R,5S,6S)-3-azabicyclo[3.1.0]hexan-6-yl]ethanol (250.0 mg, 2.0 mmol, 1.0 equiv.) was dissolved in ACN (5 mL) and cooled to 0 °C, then K₂CO₃ (543.3 mg, 3.9 mmol, 2.0 equiv.) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (684.3 mg, 2.9 mmol, 1.5 equiv.) were added. The reaction mixture was heated to 80 °C for 50 min, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give 2-[(1R,5S,6S)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexan-6-yl]ethanol (260.0 mg) as a pale yellow oil. LCMS Method A: [M+H]⁺ = 210.

Scheme 12: Synthesis of intermediates 25/26 (cis-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol and trans-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol)



Step 1: 3-[4-(trifluoromethyl)phenyl]cyclobutan-1-one

DMA (1.3 mL, 13.9 mmol, 1.2 equiv.) was dissolved in DCE (30 mL) and cooled to 5 °C, then Ti_2O (2.7 mL, 16.3 mmol, 1.4 equiv.) was added dropwise, maintaining the solution at 5 °C. The reaction mixture was stirred for 30 min at 5 °C. This was followed by the addition of a solution of 1-ethenyl-4-(trifluoromethyl) benzene (840.0 mg, 4.9 mmol, 1.0 equiv.) and 2,4,6-collidine (2.0 g, 16.3 mmol, 1.4 equiv.) in DCE (10 mL) dropwise at 5 °C. The resulting mixture was heated to 80 °C overnight, then cooled to ambient temperature and concentrated under vacuum. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:7) to give 3-[4-(trifluoromethyl)phenyl]cyclobutan-1-one (450.0 mg) as a pale yellow oil. ^1H NMR (400 MHz, Chloroform- d) δ 7.64 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 3.79–3.75 (m, 1H), 3.63–3.50 (m, 2H), 3.34–3.23 (m, 2H).

Step 2: cis-3-[4-(trifluoromethyl)phenyl]cyclobutan-1-ol

3-[4-(Trifluoromethyl)phenyl]cyclobutan-1-one (300.0 mg, 1.4 mmol, 1.0 equiv.) was dissolved in MeOH (15 mL) and cooled to -10 °C, then NaBH₄ (106.0 mg, 2.8 mmol, 2.0 equiv.) was added, maintaining the solution at -10 °C. The reaction mixture was stirred for 50 min at -10 °C under an atmosphere of nitrogen and then quenched by the addition of ice-water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give cis-3-[4-(trifluoromethyl)phenyl]cyclobutan-1-ol (260.0 mg) as a pale yellow oil. LCMS Method A: [M+H]⁺ = 217.

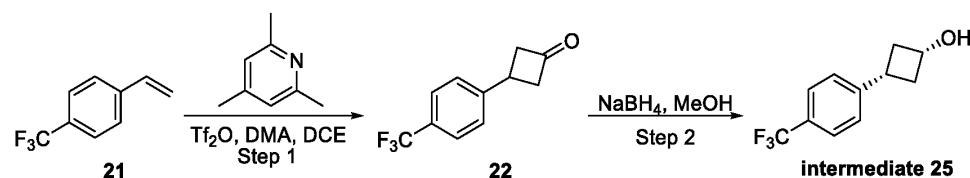
Step 3: trans-3-[4-(trifluoromethyl)phenyl]cyclobutyl 4-nitrobenzoate

Cis-3-[4-(trifluoromethyl)phenyl]cyclobutan-1-ol (130.0 mg, 0.6 mmol, 1.0 equiv.) was dissolved in THF (2 mL), then p-nitrobenzoic acid (100.5 mg, 0.6 mmol, 1.0 equiv.), PPh₃ (315.4 mg, 1.2 mmol, 2.0 equiv.) and DIAD (243.2 mg, 1.2 mmol, 2.0 equiv.) were added. The reaction mixture was stirred for 4 hours at ambient temperature, then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:6) to give trans-3-[4-(trifluoromethyl)phenyl]cyclobutyl 4-nitrobenzoate (160.0 mg) as a pale yellow solid. LCMS Method A: [M+H]⁺ = 366.

Step 4: trans-3-[4-(trifluoromethyl)phenyl]cyclobutan-1-ol

Trans-3-[4-(trifluoromethyl)phenyl]cyclobutyl 4-nitrobenzoate (300.0 mg, 0.8 mmol, 1.0 equiv.) was dissolved in MeOH (4 mL) and water (1 mL), then K₂CO₃ (227.0 mg, 1.6 mmol, 2.0 equiv.) was added. The reaction mixture was heated to 65 °C for 2 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give trans-3-[4-(trifluoromethyl)phenyl]cyclobutan-1-ol (155.2 mg) as a pale yellow oil. LCMS Method A: [M+H]⁺ = 217.

Scheme 12A: Synthesis of intermediate 25 (cis-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol)



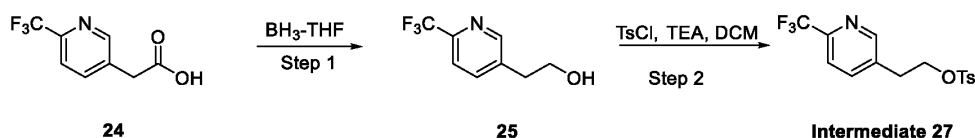
Step 1: 3-[4-(trifluoromethyl)phenyl]cyclobutan-1-one

DMA (12.1 g, 138.9 mmol, 1.2 equiv.) was dissolved in DCE (400 mL) and cooled to
 0 °C, then Ti_2O (46.0 g, 163.0 mmol, 1.4 equiv.) was added dropwise at 0-5 °C, over the
 course of 30 min. The resulting mixture was stirred for 1 hour at 5 °C, then 2,4,6-collidine
 (19.7 g, 162.5 mmol, 1.4 equiv.) and 1-ethenyl-4-(trifluoromethyl)benzene (20.0 g, 116.2
 mmol, 1.0 equiv.) were added at 5 °C. The resulting solution heated to 80 °C for 48 hours,
 then cooled to ambient temperature and concentrated under vacuum. The residue was
 diluted with 300 mL of water, extracted with ethyl acetate and concentrated under vacuum.
 The residue was purified by flash column chromatography on silica gel, eluting with ethyl
 acetate/petroleum ether (3:7) to give 3-(4-(trifluoromethyl)phenyl)cyclobutan-1-one (8.0
 g) as a yellow oil. ^1H NMR (400 MHz, Chloroform- d) δ 7.64 (d, J = 8.0 Hz, 2H), 7.45 (d,
 J = 8.0 Hz, 2H), 3.79–3.75 (m, 1H), 3.63–3.50 (m, 2H), 3.34–3.23 (m, 2H).

Step 2: cis-3-[4-(trifluoromethyl)phenyl]cyclobutan-1-ol

3-(4-(trifluoromethyl)phenyl)cyclobutan-1-one (7.9 g, 36.9 mmol, 1.0 equiv.) was
 dissolved in MeOH (50 mL) and cooled to 0 °C, then NaBH_4 (2.1 g, 55.3 mmol, 1.5 equiv.)
 was added in portions, while maintaining the reaction mixture at 0 °C. The resulting
 mixture was stirred for 1 hour at 0 °C, then quenched by the addition of ice-water. The
 resulting solution was extracted with ethyl acetate, dried over anhydrous Na_2SO_4 and
 concentrated under vacuum. The residue was purified by flash column chromatography on
 silica gel, eluting with DCM/MeOH (99:1) to afford cis-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol
 (60.5 g) as a yellow oil. ^1H NMR (400 MHz, DMSO- d_6) δ 7.65 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 5.14 (d, J = 7.2 Hz, 1H),
 4.11–4.01 (m, 1H), 3.02–2.93 (m, 1H), 2.66–2.60 (m, 2H), 1.95–1.86 (m, 2H).

Scheme 13: Synthesis of intermediates 27 (2-(6-(trifluoromethyl)pyridin-3-yl)ethyl 4-methylbenzenesulfonate)



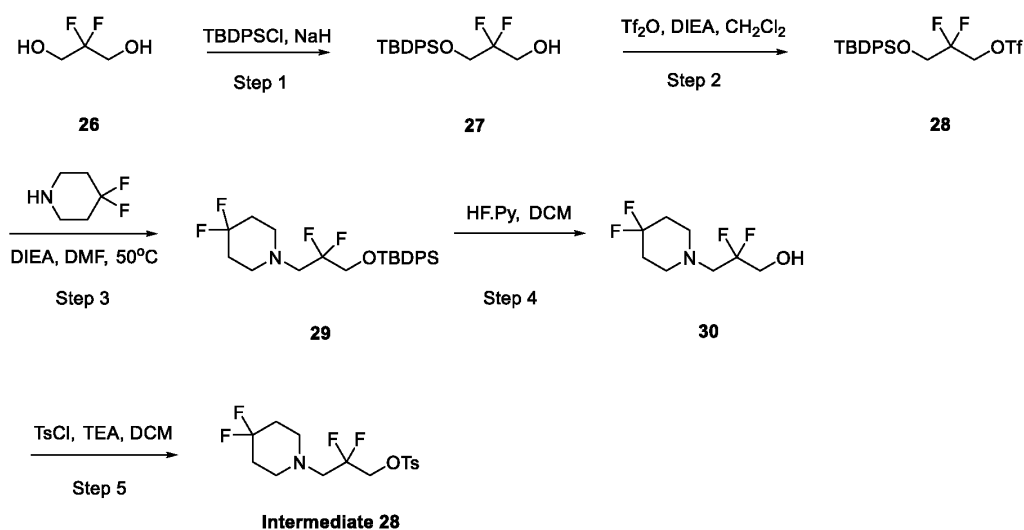
Step 1: 2-[6-(trifluoromethyl)pyridin-3-yl]ethanol

5 [6-(Trifluoromethyl)pyridin-3-yl]acetic acid (500.0 mg, 2.4 mmol, 1.0 equiv.) was dissolved in THF (30 mL) and cooled to 0 °C. Then BH₃•THF (1 M, 4.9 mL, 4.9 mmol, 1.5 equiv.) was added, maintaining the solution at 0 °C. The reaction mixture was stirred overnight at ambient temperature and the quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give 2-[6-(trifluoromethyl)pyridin-3-yl]ethanol (330.0 mg) as a yellow oil. LCMS Method A: [M+H]⁺ = 192.

Step 2: 2-[6-(trifluoromethyl)pyridin-3-yl]ethyl 4-methylbenzenesulfonate

15 2-[6-(Trifluoromethyl)pyridin-3-yl]ethanol (300.0 mg, 1.6 mmol, 1.0 equiv.) and TEA (1.1 mL, 7.8 mmol, 5.0 equiv.) were dissolved in DCM (3 mL), then TsCl (897.6 mg, 4.7 mmol, 3.0 equiv.) was added. The reaction mixture was stirred for 16 hours at ambient temperature and then quenched by the addition of water. The resulting solution was extracted with DCM, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give 2-[6-(trifluoromethyl)pyridin-3-yl]ethyl 4-methylbenzenesulfonate (500.0 mg) as a yellow solid. LCMS Method A: [M+H]⁺ = 346.

Scheme 14: Synthesis of intermediates 28 (3-(4,4-difluoropiperidin-1-yl)-2,2-difluoropropyl 4-methylbenzenesulfonate)



Step 1: 3-[(*tert*-butyldiphenylsilyl)oxy]-2,2-difluoropropan-1-ol

2,2-Difluoropropane-1,3-diol (2.0 g, 17.8 mmol, 1.0 equiv.) was dissolved in THF (20.0 mL) and cooled to 0 °C, then NaH (60% wt., 1.0 g, 26.7 mmol, 1.5 equiv.) was added, maintaining the solution at 0 °C. After 2 hours at 0 °C, TBDPSCl (9.8 g, 35.6 mmol, 2.0 equiv.) was added. The resulting mixture was stirred for an additional 2 hours at ambient temperature and then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give 3-[(*tert*-butyldiphenylsilyl)oxy]-2,2-difluoropropan-1-ol (5.1 g) as a yellow oil. LCMS Method C: [M+H]⁺ = 351.

Step 2: 3-[(*tert*-butyldiphenylsilyl)oxy]-2,2-difluoropropyl trifluoromethanesulfonate

3-[(*tert*-Butyldiphenylsilyl)oxy]-2,2-difluoropropan-1-ol (4.9 g, 14.0 mmol, 1.0 equiv.) was dissolved in DCE (20 mL) and cooled to -70 °C, then DIEA (9.7 mL, 55.9 mmol, 4.0 equiv.) and trifluoromethanesulfonic anhydride (4.7 mL, 27.9 mmol, 2.0 equiv.) were added dropwise at -70 °C under an atmosphere of nitrogen. The reaction mixture was stirred for 2 hours at -20 °C and then concentrated under vacuum. The residue was purified

by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:2) to give 3-[(*tert*-butyldiphenylsilyl)oxy]-2,2-difluoropropyl trifluoromethanesulfonate (5.2 g) as a yellow oil. LCMS Method A: $[M+H]^+ = 483$.

Step 3: 1-[3-[(*tert*-butyldiphenylsilyl)oxy]-2,2-difluoropropyl]-4,4-difluoropiperidine

3-[(*tert*-Butyldiphenylsilyl)oxy]-2,2-difluoropropyl trifluoromethanesulfonate (5.0 g, 10.3 mmol, 1.0 equiv.) was dissolved in DMF (20 mL), then 4,4-difluoropiperidine (1.5 g, 12.4 mmol, 1.2 equiv.) and DIEA (3.5 mL, 20.7 mmol, 2.0 equiv.) were added. The reaction mixture was heated to 50 °C, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give 1-[3-[(*tert*-butyldiphenylsilyl)oxy]-2,2-difluoropropyl]-4,4-difluoropiperidine (3.8 g) as a yellow oil. LCMS Method A: $[M+H]^+ = 454$.

Step 4: 3-(4,4-difluoropiperidin-1-yl)-2,2-difluoropropan-1-ol

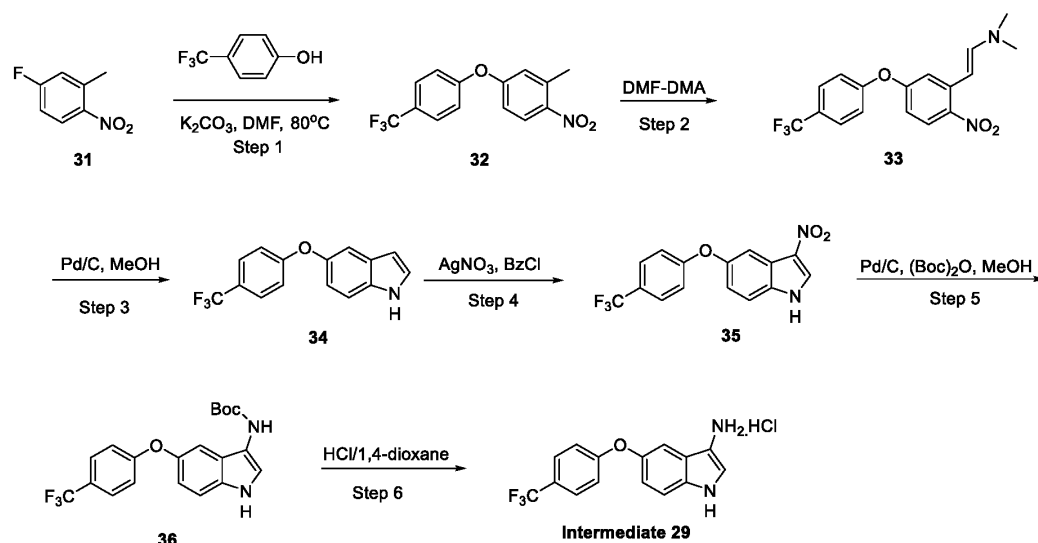
1-[3-[(*tert*-Butyldiphenylsilyl)oxy]-2,2-difluoropropyl]-4,4-difluoropiperidine (3.6 g, 7.9 mmol, 1.0 equiv.) was dissolved in DCM (10 mL), then $\text{HF}\cdot\text{Py}$ (70% wt., 1.1 mL, 31.7 mmol, 4.0 equiv.) was added. The reaction mixture was stirred for 12 hours at ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:4) to give 3-(4,4-difluoropiperidin-1-yl)-2,2-difluoropropan-1-ol (1.0 g) as a yellow oil. LCMS Method A: $[M+H]^+ = 216$.

Step 5: 3-(4,4-difluoropiperidin-1-yl)-2,2-difluoropropyl 4-methylbenzenesulfonate

3-(4,4-Difluoropiperidin-1-yl)-2,2-difluoropropan-1-ol (220.0 mg, 1.0 mmol, 1.0 equiv.) and TEA (0.3 mL, 2.0 mmol, 2.0 equiv.) were dissolved in DCM (10 mL), then TsCl (389.8 mg, 2.0 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 12 hours at ambient temperature and then concentrated under vacuum. The residue was

purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give 3-(4,4-difluoropiperidin-1-yl)-2,2-difluoropropyl 4-methylbenzenesulfonate (320.0 mg) as a white solid. LCMS Method A: $[M+H]^+ = 370$.

Scheme 15: Synthesis of intermediate 29 (5-(4-(trifluoromethyl)phenoxy)-1H-indol-3-amine hydrochloride)



Step 1: 2-methyl-1-nitro-4-(4-(trifluoromethyl)phenoxy)benzene

4-Fluoro-2-methyl-1-nitrobenzene (19.0 g, 122.5 mmol, 1.0 equiv.) was dissolved in DMF (100 mL), then K_2CO_3 (50.8 g, 367.4 mmol, 3.0 equiv.) and 4-(trifluoromethyl)phenol (23.8 g, 146.9 mmol, 1.2 equiv.) were added. The reaction mixture was heated to 80 °C for 2 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:9) to give 2-methyl-1-nitro-4-(4-(trifluoromethyl)phenoxy)benzene (30.0 g) as a yellow solid.

Step 2: (E)-N,N-dimethyl-2-(2-nitro-5-(4-(trifluoromethyl)phenoxy)phenyl)ethen-1-amine

2-Methyl-1-nitro-4-(4-(trifluoromethyl)phenoxy)benzene (20.0 g, 67.3, 1.0 equiv.) was dissolved in DMF (100 mL), then DMF-DMA (10.7 mL, 80.7 mmol, 1.2 equiv.) was added. The reaction mixture was heated to 140 °C for 2 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give (E)-*N,N*-dimethyl-2-(2-nitro-5-(4-(trifluoromethyl)phenoxy)phenyl)ethen-1-amine (24.0 g) as a red solid. LCMS Method A: [M+H]⁺ = 353.

Step 3: 5-(4-(trifluoromethyl)phenoxy)-1*H*-indole

(E)-*N,N*-dimethyl-2-(2-nitro-5-(4-(trifluoromethyl)phenoxy)phenyl)ethen-1-amine (24.0 g, 68.1 mmol, 1.0 equiv.) was dissolved in ethyl acetate (250 mL), then Pd/C (10% wt., 2.5 g) was added. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 36 hours at ambient temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:6) to give 5-(4-(trifluoromethyl)phenoxy)-1*H*-indole (11.5 g) as a green solid. LCMS Method A: [M+H]⁺ = 278.

Step 4: 3-nitro-5-(4-(trifluoromethyl)phenoxy)-1*H*-indole

A mixture of AgNO₃ (3.6 g, 21.6 mmol, 1.2 equiv.) and ACN (50 mL) was cooled to 0 °C, then benzoyl chloride (2.5 mL, 21.6 mmol, 1.2 equiv.) was added dropwise, maintaining the solution at 0 °C. The reaction mixture was stirred for 10 min at 0 °C, then a solution of 5-(4-(trifluoromethyl)phenoxy)-1*H*-indole (5.0 g, 18.0 mmol, 1.0 equiv.) in ACN (5 mL) was added dropwise. The resulting solution was stirred for 1 hour at ambient temperature and then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give 3-nitro-5-(4-

(trifluoromethyl)phenoxy)-1*H*-indole (3.1 g) as a black solid. LCMS Method B: $[M-H]^- = 321$.

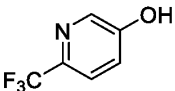
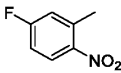
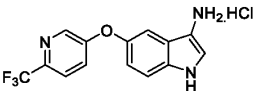
Step 5: *tert*-butyl (5-(4-(trifluoromethyl)phenoxy)-1*H*-indol-3-yl)carbamate

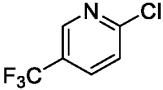
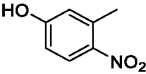
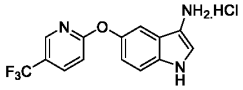
3-Nitro-5-(4-(trifluoromethyl)phenoxy)-1*H*-indole (3.1 g, 9.7 mmol, 1.0 equiv.) was dissolved in MeOH (50 mL), then (Boc)₂O (4.2g, 19.4 mmol, 2.0 equiv.) and Pd/C (10% wt., 0.4 g) were added. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 10 hours at ambient temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:4) to give *tert*-butyl (5-(4-(trifluoromethyl)phenoxy)-1*H*-indol-3-yl)carbamate (1.3 g) as a brown solid. LCMS Method A: $[M+H]^+ = 393$.

Step 6: 5-(4-(trifluoromethyl)phenoxy)-1*H*- indol-3-amine hydrochloride

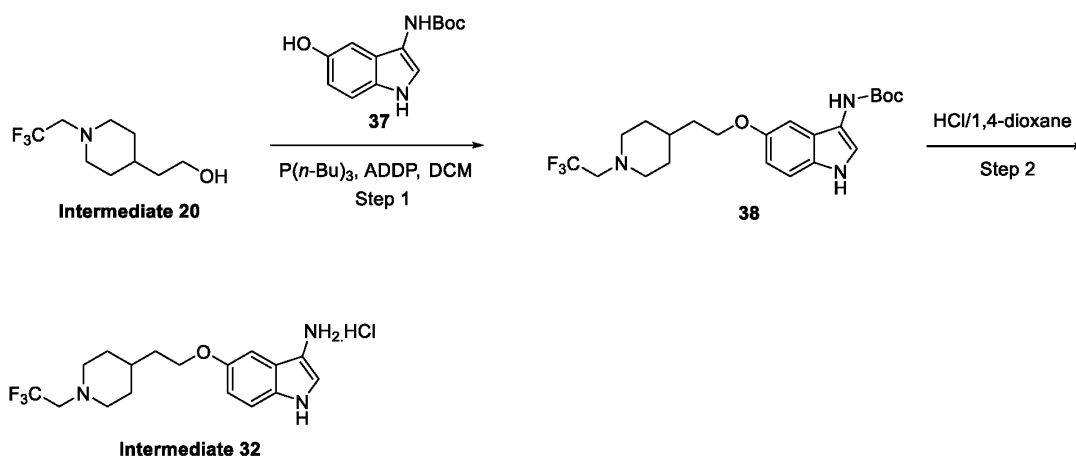
tert-Butyl (5-(4-(trifluoromethyl)phenoxy)-1*H*-indol-3-yl)carbamate (1.3 g, 3.3 mmol, 1.0 equiv.) was dissolved in HCl/1,4-dioxane (4N, 15 mL). The reaction mixture was stirred for 2 hours at ambient temperature and then concentrated under vacuum to give 5-(4-(trifluoromethyl)phenoxy)-1*H*- indol-3-amine hydrochloride (910.0 mg) as a green solid. LCMS Method A: $[M+H]^+ = 293$.

The intermediates in the following table were prepared using the same method described for **Intermediate 29**.

Intermediate	Starting material A	Starting material B	Structure	LCMS data
Intermediate 30				Method A: MS-ESI: 294 $[M+H]^+$

Intermediate 31				Method A: MS-ESI: 294 [M+H] ⁺
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Scheme 16: Synthesis of intermediate 32 (5-(2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethoxy)-1H-indol-3-amine hydrochloride)



Step 1: *tert*-butyl *N*-(5-[2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]ethoxy]-1H-indol-3-yl)carbamate

tert-Butyl *N*-(5-hydroxy-1H-indol-3-yl)carbamate (300.0 mg, 1.2 mmol, 1.0 equiv.) was dissolved in DCM (20 mL) and cooled to 0 °C, then 2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]ethanol (306.3 mg, 1.5 mmol, 1.2 equiv.) and P(*n*-Bu)₃ (733.4 mg, 3.6 mmol, 3.0 equiv.) were added under an atmosphere of nitrogen. This was followed by the dropwise addition of a solution of ADDP (609.8 mg, 2.4 mmol, 2.0 equiv.) in DCM (5 mL), maintaining the solution at 0 °C. The reaction mixture was stirred for 4 hours at ambient temperature and then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give *tert*-butyl *N*-(5-[2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]ethoxy]-1H-indol-3-yl)carbamate (285.0 mg) as a pale yellow solid. LCMS Method C: [M+H]⁺ = 442.

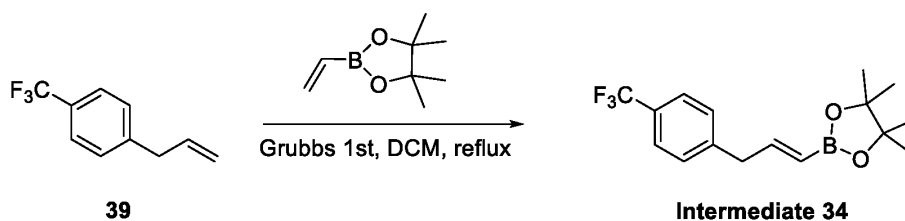
Step 2: 5-(2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethoxy)-1*H*-indol-3-amine hydrochloride

tert-Butyl *N*-(5-[2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]ethoxy]-1*H*-indol-3-yl)carbamate (1.0 g, 2.3 mmol, 1.0 equiv.) was dissolved in HCl/1,4-dioxane (4*N*, 10 mL). The reaction mixture was stirred for 40 min at ambient temperature and then concentrated under vacuum to give 5-(2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethoxy)-1*H*-indol-3-amine hydrochloride (910.0 mg) as a yellow solid. LCMS Method A: $[M+H]^+ = 342$.

The intermediate in the following table was prepared using the same method described for **Intermediate 32**.

Intermediate	Starting material	Structure	LCMS data
Intermediate 33			Method C: MS-ESI: 321 [M-H]⁻

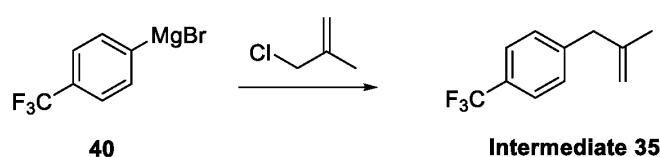
Scheme 17: Synthesis of intermediate 34 ((*E*)-4,4,5,5-tetramethyl-2-(3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-1,3,2-dioxaborolane)



1-Allyl-4-(trifluoromethyl)benzene (1.0 g, 5.4 mmol, 1.0 equiv.) was dissolved in DCM (10 mL), then 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.7 g, 10.7 mmol, 2.0 equiv.) and Grubbs 1st (224.8 mg, 0.3 mmol, 0.05 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 50 °C for 16 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was

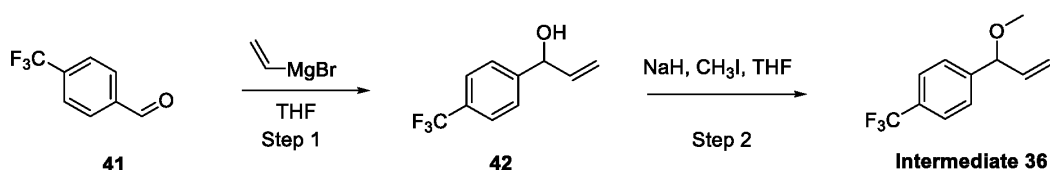
extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:4) to give (E)-4,4,5,5-tetramethyl-2-(3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-1,3,2-dioxaborolane (640 mg) as a brown liquid. LCMS Method A: $[\text{M}+\text{H}]^+ = 313$.

Scheme 18: Synthesis of intermediate 35 (1-(2-methylallyl)-4-(trifluoromethyl)benzene)



Bromo[4-(trifluoromethyl)phenyl]magnesium (8 mL, 0.5 mol/L, 4.0 mmol, 1.0 equiv.) was dissolved in THF (30 mL) and cooled to 0 °C. Then 3-chloro-2-methylpropene (0.4 g, 4.0 mmol, 1.0 equiv.) was added, maintaining the solution at 0 °C. The reaction mixture was stirred for 4 hours at 0 °C and then quenched by the addition of ice-water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether (100%) to give 1-(2-methylprop-2-en-1-yl)-4-(trifluoromethyl)benzene (410.0 mg) as a light yellow solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.57 (d, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.89–4.87 (m, 1H), 4.77–4.75 (m, 1H), 3.39 (s, 2H), 1.70 (s, 3H).

20 *Scheme 19: Synthesis of intermediate 36 (1-(2-methylallyl)-4-(trifluoromethyl)benzene)*



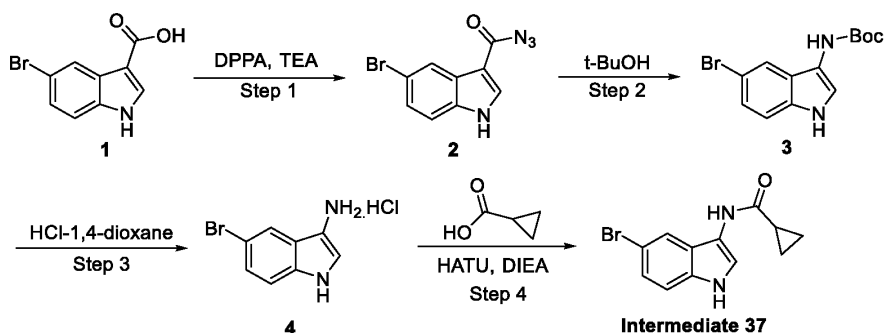
Step 1: 1-[4-(trifluoromethyl)phenyl]prop-2-en-1-ol

4-(Trifluoromethyl)benzaldehyde (2.0 g, 11.5 mmol, 1.0 equiv.) was dissolved in THF (30 mL) and cooled to 0 °C, then bromo(ethenyl)magnesium (1M in THF, 13.8 mL, 13.8 mmol, 1.2 equiv.) was added dropwise under an atmosphere of nitrogen, maintaining the solution at 0 °C. The reaction mixture was stirred for 2 hours at ambient temperature, then quenched by the addition of ice-water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:2) to give 1-[4-(trifluoromethyl)phenyl]prop-2-en-1-ol (1.0 g) as a pale yellow solid. LCMS Method A: [M+H]⁺ = 203.

Step 2: 1-(1-methoxyprop-2-en-1-yl)-4-(trifluoromethyl)benzene

1-[4-(Trifluoromethyl)phenyl]prop-2-en-1-ol (1.0 g, 4.9 mmol, 1.0 equiv.) was dissolved in THF (30 mL) and cooled to 0 °C, then NaH (60% wt., 0.4 g, 9.9 mmol, 2.0 equiv.) was added. This was followed by the dropwise addition of CH₃I (0.6 mL, 9.9 mmol, 2.0 equiv.) while maintaining the internal reaction temperature at 0 °C. The reaction mixture was allowed to warm to ambient temperature and for 2 hours, then quenched by the addition of ice water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give 1-(1-methoxyprop-2-en-1-yl)-4-(trifluoromethyl)benzene (0.9 g) as a pale yellow solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 5.97–5.82 (m, 1H), 5.37–5.23 (m, 2H), 4.70 (d, *J* = 6.8 Hz, 1H), 3.38 (s, 3H). LCMS Method A: [M+H]⁺ = 217.

Scheme 20: Synthesis of intermediate 37 (N-(5-bromo-1H-indol-3-yl)cyclopropanecarboxamide)



Step 1: 5-bromo-1*H*-indole-3-carbonyl azide

5-Bromo-1*H*-indole-3-carboxylic acid (30.0 g, 124.9 mmol, 1.0 equiv.) was dissolved in THF (150 mL), then TEA (26.1 mL, 187.4 mmol, 1.5 equiv.) and DPPA (37.8 g, 137.4 mmol, 1.1 equiv.) were added. The reaction mixture was stirred for 12 hours at ambient temperature, then quenched by the addition of water and stirred for an additional 10 min. The precipitated solid was collected by filtration and dried to give 5-bromo-1*H*-indole-3-carbonyl azide (33.6 g) as an off-white solid. LCMS Method B: $[M-H]^- = 263$.

Step 2: *tert*-butyl (5-bromo-1*H*-indol-3-yl)carbamate

5-Bromo-1*H*-indole-3-carbonyl azide (33.6 g, 126.7 mmol, 1.0 equiv.) was dissolved in *t*-BuOH (300 mL). The reaction mixture was heated to 80 °C for 12 hours, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:10) to give *tert*-butyl (5-bromo-1*H*-indol-3-yl)carbamate (22.1 g) as a pale white solid. LCMS Method A: $[M+H]^+ = 311$.

Step 3: 5-bromo-1*H*-indol-3-amine hydrochloride

tert-Butyl (5-bromo-1*H*-indol-3-yl)carbamate (20.0 g, 64.2 mmol, 1.0 equiv.) was dissolved in HCl/1,4-dioxane (4 M, 150 mL). The reaction mixture was stirred for 2 hours at ambient temperature and then concentrated under vacuum to give 5-bromo-1*H*-indol-3-amine hydrochloride (18.7 g) as a brown solid. LCMS Method A: $[M+H]^+ = 211$.

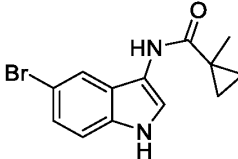
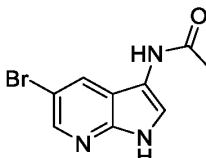
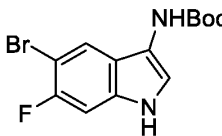
Step 4: *N*-(5-bromo-1*H*-indol-3-yl)cyclopropanecarboxamide

Cyclopropanecarboxylic acid (172.0 mg, 2.0 mmol, 1.0 equiv.) was dissolved in DCM (20 mL), then DIEA (1.0 mL, 6.0 mmol, 3.0 equiv.), HATU (1.1 g, 3.0 mmol, 1.5 equiv.) and 5-bromo-1*H*-indol-3-amine hydrogen chloride (500.0 mg, 2.0 mmol, 1.0 equiv.) were added. The reaction mixture was stirred for 2 hours at ambient temperature and then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl

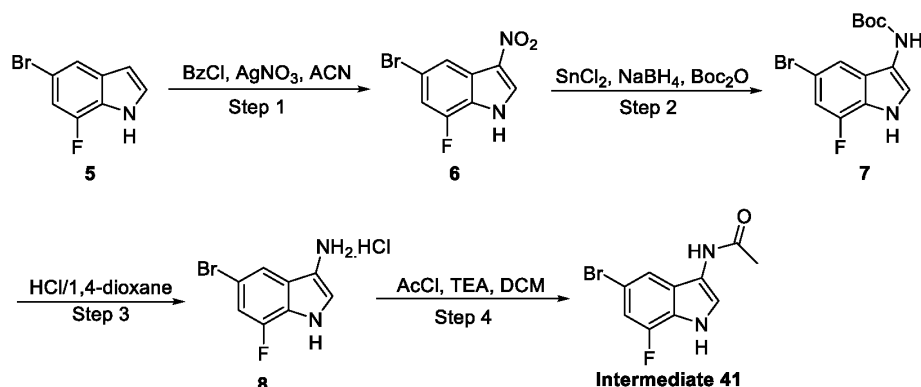
acetate/petroleum ether (1:1) to give *N*-(5-bromo-1*H*-indol-3-yl)cyclopropanecarboxamide (510.0 mg) as a white solid. LCMS Method A: $[M+H]^+ = 279$.

The intermediates in the following Table were prepared using the same method described for **Intermediate 37**.

5

Intermediate	Structure	LCMS data
Intermediate 38		Method A: MS-ESI: 293 $[M+H]^+$
Intermediate 39		Method A: MS-ESI: 254 $[M+H]^+$
Intermediate 40		Method A: MS-ESI: 329 $[M+H]^+$

*Scheme 21: Synthesis of intermediate 41 (N-(5-bromo-7-fluoro-1*H*-indol-3-yl)acetamide)*



Step 1: 5-bromo-7-fluoro-3-nitro-1H-indole

5-Bromo-7-fluoro-1H-indole (8.5 g, 39.7 mmol, 1.0 equiv.) was dissolved in in ACN (150 mL) and cooled to 0 °C, then AgNO₃ (10.1 g, 59.6 mmol, 1.5 equiv.) was added. The resulting mixture was stirred for 15 min, then benzoyl chloride (8.4 g, 59.6 mmol, 1.5 equiv.) was added batchwise, maintaining the reaction mixture at 0 °C. The reaction mixture was stirred for 3 hours at 0 °C, then quenched by the addition of ice-water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give 5-bromo-7-fluoro-3-nitro-1H-indole (7.4 g) as a black solid. LCMS Method A: [M+H]⁺ = 259.

Step 2: *tert*-butyl (5-bromo-7-fluoro-1H-indol-3-yl)carbamate

5-Bromo-7-fluoro-3-nitro-1H-indole (3.0 g, 11.6 mmol, 1.0 equiv.) was dissolved in MeOH (50 mL) then (Boc)₂O (3.0 g, 13.8 mmol, 1.2 equiv.) was added. This was followed by the portionwise addition of SnCl₂ (6.6 g, 34.7 mmol, 3.0 equiv.) and NaBH₄ (1.3 g, 34.7 mmol, 3.0 equiv.), while maintain the reaction mixture at 0 °C. The reaction mixture was stirred for 4 hours at 0 °C, then quenched by the addition of ice-water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:9) to give *tert*-butyl (5-bromo-

7-fluoro-1*H*-indol-3-yl)carbamate (1.3 g) as a yellow solid. LCMS Method A: $[M+H]^+ = 329$.

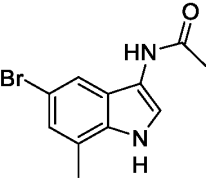
Step 3: 5-bromo-7-fluoro-1*H*-indol-3-amine hydrochloride

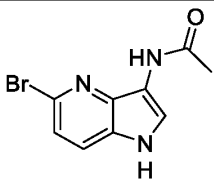
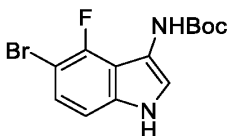
tert-Butyl (5-bromo-7-fluoro-1*H*-indol-3-yl)carbamate (1.3 g, 3.9 mmol, 1.0 equiv.) was dissolved in HCl/1,4-dioxane (4N, 15 mL). The reaction mixture was stirred for 2 hours at ambient temperature then concentrated under vacuum to give 5-bromo-7-fluoro-1*H*-indol-3-amine hydrochloride (980.0 mg) as a grey solid. LCMS Method A: $[M+H]^+ = 229$.

Step 4: *N*-(5-bromo-7-fluoro-1*H*-indol-3-yl)acetamide

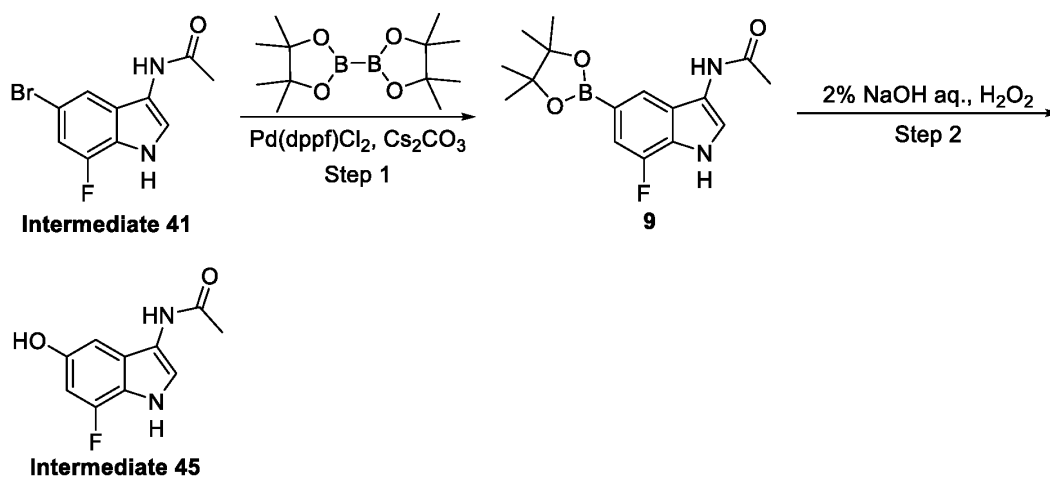
5-Bromo-7-fluoro-1*H*-indol-3-amine (980.0 mg, 4.3 mmol, 1.0 equiv.) and TEA (2.3 mL, 17.1 mmol, 4.0 equiv.) were dissolved in DCM (10 mL), then acetyl chloride (0.4 mL, 5.1 mmol, 1.2 equiv.) was added. The reaction mixture was stirred for 2 hours at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with dichloromethane, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (20:1) to give *N*-(5-bromo-7-fluoro-1*H*-indol-3-yl)acetamide (800.0 mg) as a brown solid. LCMS Method A: $[M+H]^+ = 271$.

The intermediates in the following table were prepared using the same method described for **Intermediate 41**.

Intermediate	Structure	LCMS data
Intermediate 42		Method A: MS-ESI: 267 $[M+H]^+$

Intermediate 43		Method A: MS-ESI: 254 [M+H] ⁺
Intermediate 44		Method A: MS-ESI: 329 [M+H] ⁺

Scheme 22: Synthesis of intermediate 45 (N-(7-fluoro-5-hydroxy-1H-indol-3-yl)acetamide)



Step 1: N-(7-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)acetamide

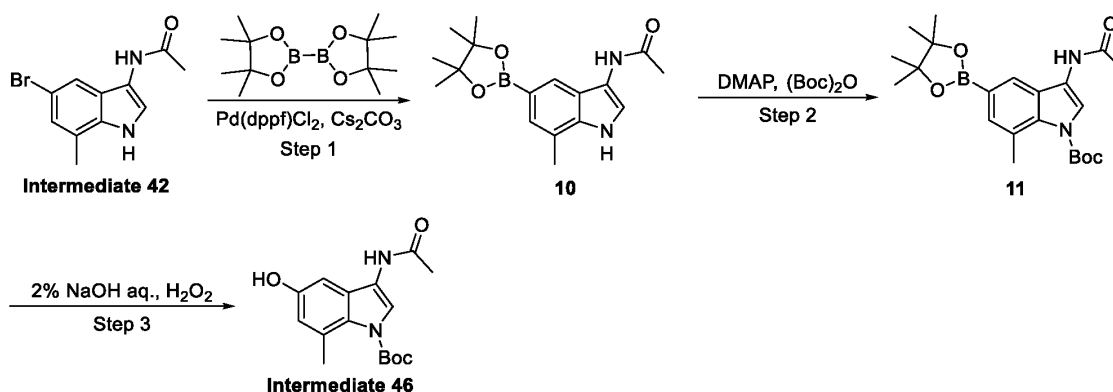
N-(5-Bromo-7-fluoro-1H-indol-3-yl)acetamide (1.0 g, 3.8 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (100 mL), then 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 g, 5.8 mmol, 1.5 equiv.), Cs₂CO₃ (2.5 g, 7.7 mmol, 2.0 equiv.) and Pd(dppf)Cl₂•CH₂Cl₂ (0.3 g, 0.4 mmol, 0.1 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 100 °C for 2 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted

with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:2) to give *N*-(7-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl) acetamide (880 mg) as a brown solid. LCMS Method A: $[\text{M}+\text{H}]^+ = 319$.

Step 2: *N*-(7-fluoro-5-hydroxy-1*H*-indol-3-yl)acetamide

N-(7-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)acetamide (830.0 mg, 2.6 mmol, 1.0 equiv.) was dissolved in THF (10 mL) and cooled to 0 °C, then a solution of NaOH in water (2% wt./wt., 11 mL, 5.5 mmol, 2.0 equiv.) was added. This was followed by the addition of H_2O_2 (30% wt./wt. in water, 2 mL, 19.2 mmol, 7.5 equiv.) dropwise at 0 °C. The reaction mixture was stirred for 2 hours at ambient temperature, then quenched by the addition of saturated aqueous NH_4Cl . The resulting solution was extracted with ethyl acetate, washed with brine and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (10:1) to give *N*-(7-fluoro-5-hydroxy-1*H*-indol-3-yl)acetamide (174.0 mg) as a black solid. LCMS Method A: $[\text{M}+\text{H}]^+ = 209$.

Scheme 23: Synthesis of intermediate 46 (*N*-(5-hydroxy-7-methyl-1*H*-indol-3-yl)acetamide)



Step 1: *N*-[7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl]acetamide

N-(5-Bromo-7-methyl-1*H*-indol-3-yl)acetamide (150.0 mg, 0.6 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (100 mL), then 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (213.9 mg, 0.8 mmol, 1.5 equiv.), KOAc (110.2 mg, 1.1 mmol, 2.0 equiv.) and Pd(dppf)Cl₂•CH₂Cl₂ (41.1 mg, 0.06 mmol, 0.1 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 85 °C for 6 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give *N*-[7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl]acetamide (100.0 mg) as a pale yellow solid. LCMS Method B: [M+H]⁺ = 315.

Step 2: *tert*-butyl 3-acetamido-7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole-1-carboxylate

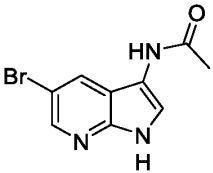
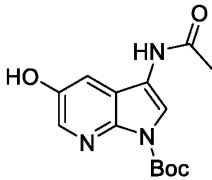
N-[7-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl]acetamide (50.0 mg, 0.2 mmol, 1.0 equiv.) and Boc₂O (41.7 mg, 0.2 mmol, 1.2 equiv.) were dissolved in THF (5 mL), then TEA (0.1 mL, 0.3 mmol, 2.0 equiv.) and DMAP (4.0 mg, 0.03 mmol, 0.2 equiv.) were added. The reaction mixture was stirred overnight at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:7) to give *tert*-butyl 3-acetamido-7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole-1-carboxylate (45.8 mg) as a pale yellow solid. LCMS Method B: [M+H]⁺ = 415.

Step 3: *tert*-butyl 3-acetamido-5-hydroxy-7-methylindole-1-carboxylate

tert-Butyl 3-acetamido-7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole-1-carboxylate (200.0 mg, 0.5 mmol, 1.0 equiv.) was dissolved in THF (10 mL) and cooled to 0 °C, then aqueous NaOH (2% wt./wt., 2 mL, 1.0 mmol, 1.0 equiv.) was added. This was followed by the addition of H₂O₂ (30% wt./wt. in water, 0.5 mL, 5.0 mmol,

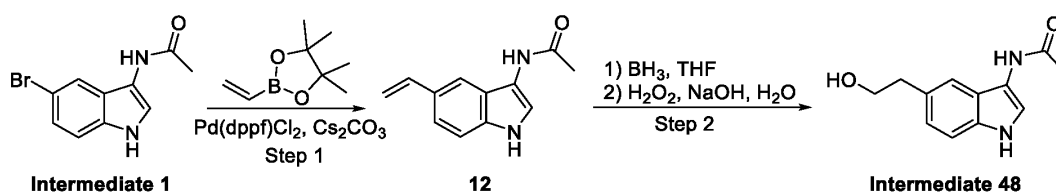
10.0 equiv.) dropwise at 0 °C. The reaction mixture was stirred for 2 hours at ambient temperature, then quenched by the addition of saturated aqueous NH₄Cl. The resulting solution was extracted with ethyl acetate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (20:1) to give *tert*-butyl 3-acetamido-5-hydroxy-7-methylindole-1-carboxylate (60.0 mg) as a light yellow solid. LCMS Method B: [M+H]⁺ = 305.

The intermediates in the following table were prepared using the same method described for **Intermediate 46**.

Intermediate	Starting material	Structure	LCMS data
Intermediate 47	 Intermediate 39	 Boc	Method A: MS-ESI: 292 [M+H] ⁺

10

Scheme 24: Synthesis of intermediate 48 (N-(5-(2-hydroxyethyl)-1H-indol-3-yl)acetamide)



Step 1: N-(5-vinyl-1H-indol-3-yl)acetamide

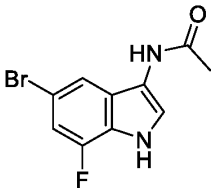
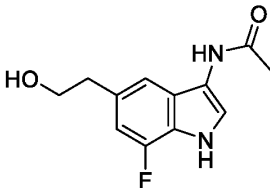
15 *N*-(5-bromo-1H-indol-3-yl)acetamide (3.0 g, 11.9 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (30 mL) and water (3 mL), then Pd(dppf)Cl₂·CH₂Cl₂ (1.9 g, 2.3 mmol, 0.2 equiv.), Cs₂CO₃ (7.7 g, 23.7 mmol, 2.0 equiv.) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (2.2 g, 14.2 mmol, 1.2 equiv.) were added under atmosphere of nitrogen.

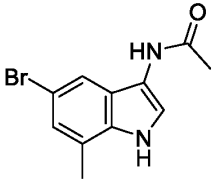
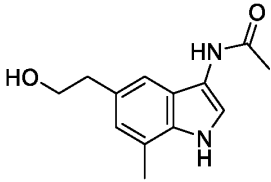
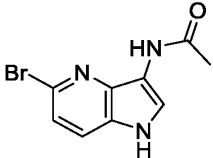
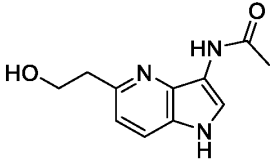
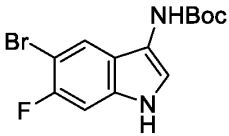
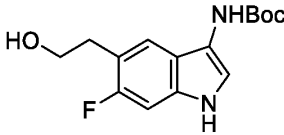
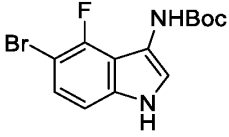
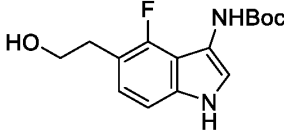
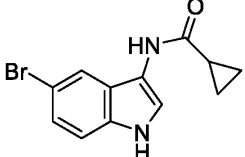
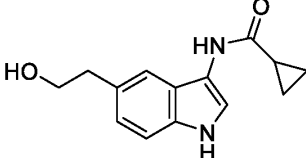
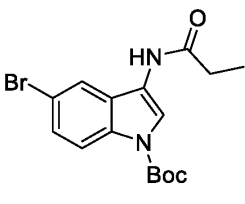
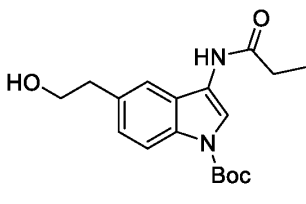
The reaction mixture was heated to 100 °C for 16 hours, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give *N*-(5-vinyl-1*H*-indol-3-yl)acetamide (1.5 g) as a brown solid. LCMS Method C: $[M+H]^+ = 201$.

Step 2: *N*-(5-(2-hydroxyethyl)-1*H*-indol-3-yl)acetamide

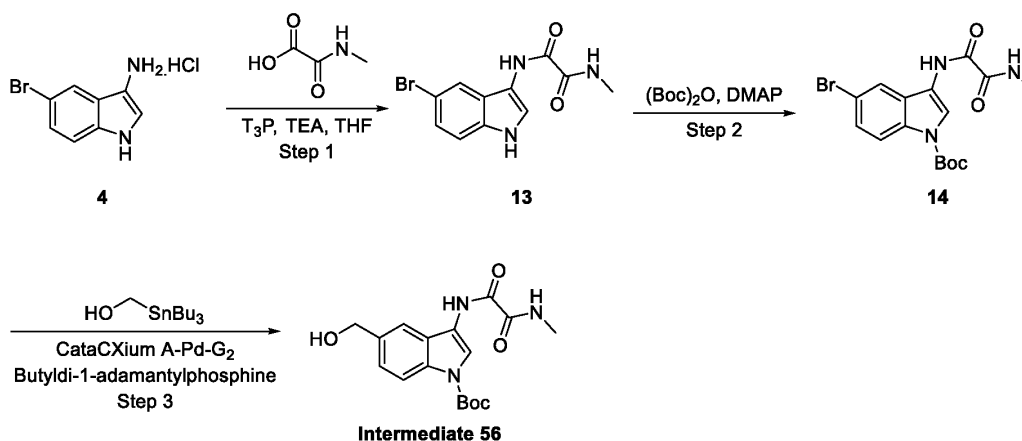
N-(5-vinyl-1*H*-indol-3-yl)acetamide (1.0 g, 5.0 mmol, 1.0 equiv.) was dissolved in THF (30 mL) and cooled to 0 °C, then BH₃-THF (1 M, 20 mL, 20.0 mmol, 4.0 equiv.) was added dropwise. After 2 hours at ambient temperature, a solution of aqueous NaOH (1 M, 10 mL, 10.0 mmol, 2.0 equiv.) was added. This was followed by the addition of H₂O₂ (30% wt./wt. in water, 1.3 mL, 38.2 mmol, 7.6 equiv.), maintaining the reaction mixture at 0 °C. The reaction mixture was stirred for an additional 30 min at 0 °C, then quenched by the addition of saturated aqueous NH₄Cl. The resulting solution was adjusted to pH 6-7 with aqueous HCl (6M), extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (3:2) to give *N*-(5-(2-hydroxyethyl)-1*H*-indol-3-yl)acetamide (294.0 mg) as a pale brown solid. LCMS Method A: $[M+H]^+ = 219$.

The intermediates in the following table were prepared using the same method described for **Intermediate 48**.

Intermediate	Starting material	Structure	LCMS data
Intermediate 49	 Intermediate 41		Method A: MS-ESI: 237 $[M+H]^+$

Intermediate 50	 Intermediate 42		Method A: MS-ESI: 233 [M+H]⁺
Intermediate 51	 Intermediate 43		Method A: MS-ESI: 220 [M+H]⁺
Intermediate 52	 Intermediate 40		Method A: MS-ESI: 295 [M+H]⁺
Intermediate 53	 Intermediate 44		Method A: MS-ESI: 295 [M+H]⁺
Intermediate 54	 Intermediate 37		Method A: MS-ESI: 245 [M+H]⁺
Intermediate 55	 Intermediate 4		Method A: MS-ESI: 333 [M+H]⁺

Scheme 25: Synthesis of intermediate 56 (tert-butyl 5-(hydroxymethyl)-3-(2-(methylamino)-2-oxoacetamido)-1H-indole-1-carboxylate)



Step 1: *N*1-(5-bromo-1*H*-indol-3-yl)-*N*2-methyloxalamide

5 5-Bromo-1*H*-indol-3-amine (1.7 g, 8.0 mmol, 1.0 equiv.) was dissolved in THF (20 mL), then TEA (3.3 mL, 24.1 mmol, 3.0 equiv.), 2-(methylamino)-2-oxoacetic acid (830.2 mg, 8.0 mmol, 1.0 equiv.) and T₃P (50% wt., 3.84 g, 12.0 mmol, 1.5 equiv.) were added. The reaction mixture was stirred for 30 min at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with
10 brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give *N*1-(5-bromo-1*H*-indol-3-yl)-*N*2-methyloxalamide (1.2 g) as a brown solid. LCMS Method A: [M+H]⁺ = 296.

Step 2: tert-butyl 5-bromo-3-(2-(methylamino)-2-oxoacetamido)-1*H*-indole-1-carboxylate

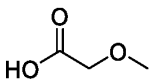
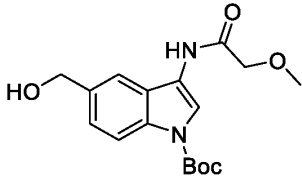
15 *N*1-(5-Bromo-1*H*-indol-3-yl)-*N*2-methyloxalamide (1.2 g, 4.0 mmol, 1.0 equiv.) was dissolved in DCM (12 mL), then DMAP (50.0 mg, 0.4 mmol, 0.1 equiv.) and (Boc)₂O (1.0 g, 4.8 mmol, 1.2 equiv.) were added. The reaction mixture was stirred for 1 hour at ambient temperature, then quenched by the addition of water. The resulting solution was
20 extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and

concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:2) to give *tert*-butyl 5-bromo-3-(2-(methylamino)-2-oxoacetamido)-1*H*-indole-1-carboxylate (950.0 mg) as a white solid. LCMS Method A: $[M+H]^+ = 396$

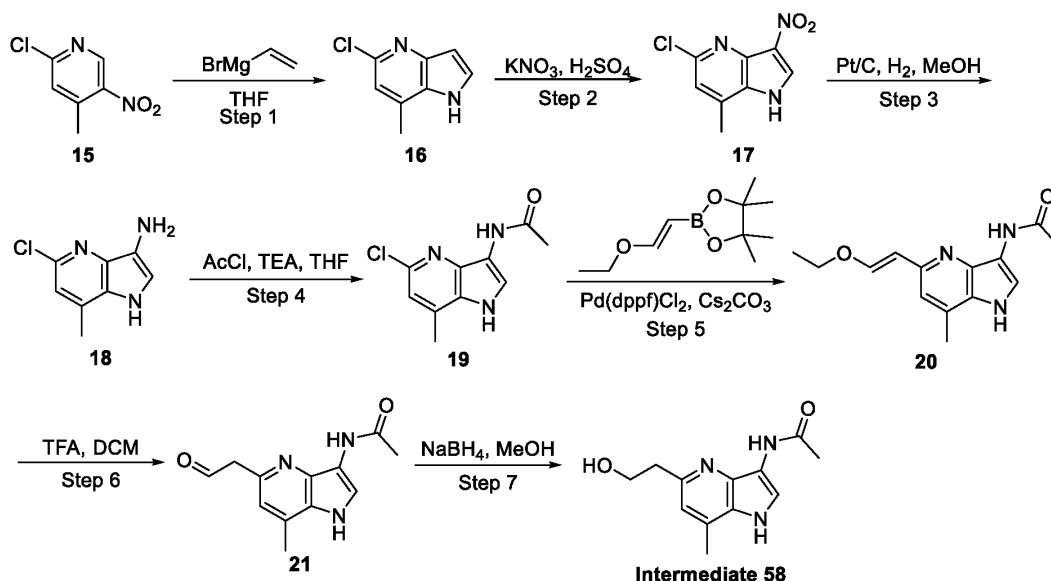
5 Step 3: *tert*-butyl 5-(hydroxymethyl)-3-(2-(methylamino)-2-oxoacetamido)-1*H*-indole-1-carboxylate

tert-Butyl 5-bromo-3-(2-(methylamino)-2-oxoacetamido)-1*H*-indole-1-carboxylate (900.0 mg, 2.2 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (10 mL), then (tributylstannyl)methanol (1823.2 mg, 5.6 mmol, 2.5 equiv.), butyl di-1-adamantylphosphine (162.8 mg, 0.4 mmol, 0.20 equiv.) and CataCXium A-Pd-G2 (151.8 mg, 0.2 mmol, 0.1 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 100 °C for 6 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (2:1) to give *tert*-butyl 5-(hydroxymethyl)-3-(2-(methylamino)-2-oxoacetamido)-1*H*-indole-1-carboxylate (750.0 mg) as an off-white solid. LCMS Method C: $[M+H]^+ = 348$.

The intermediates in the following table were prepared using the same method described for **Intermediate 56**.

Intermediate	Starting material	Structure	LCMS data
Intermediate 57			Method C: MS-ESI: 335 $[M+H]^+$

Scheme 26: Synthesis of intermediate 58 (*N*-(5-(2-hydroxyethyl)-7-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)acetamide)



Step 1: 5-chloro-7-methyl-1H-pyrrolo[3,2-b]pyridine

2-Chloro-4-methyl-5-nitropyridine (10 g, 57.9 mmol, 1.0 equiv.) was dissolved in THF (50 mL) and cooled to -60 °C, then bromo(ethenyl)magnesium (1M in THF, 173.8 mL, 173.8 mmol, 3.0 equiv.) was added dropwise under an atmosphere of nitrogen, maintaining the solution at -60 °C. The reaction mixture was stirred overnight at ambient temperature, then quenched by the addition of saturated NH₄Cl aqueous at 0 °C. The reaction mixture was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give 5-chloro-7-methyl-1H-pyrrolo[3,2-b]pyridine (1.6 g) as a light yellow solid. LCMS Method A: [M+H]⁺ = 167.

Step 2: 5-chloro-7-methyl-3-nitro-1H-pyrrolo[3,2-b]pyridine

5-Chloro-7-methyl-1H-pyrrolo[3,2-b]pyridine (1.0 g, 6.0 mmol, 1.0 equiv.) was dissolved in H₂SO₄ (15 mL) and cooled to 0 °C, then KNO₃ (900.0 mg, 9.0 mmol, 1.5 equiv.) was added in portions, maintaining the solution at 0 °C. The reaction mixture was stirred for 40 min at ambient temperature, then cooled to 0 °C and quenched by the addition

of ice-water. The precipitated solids were collected by filtration, washed with ethyl acetate and dried under vacuum to give 5-chloro-7-methyl-3-nitro-1*H*-pyrrolo[3,2-*b*]pyridine (890.0 mg) as a pale yellow solid. LCMS Method A: $[M+H]^+ = 212$.

Step 3: 5-chloro-7-methyl-1*H*-pyrrolo[3,2-*b*] pyridin-3-amine

5 5-Chloro-7-methyl-3-nitro-1*H*-pyrrolo[3,2-*b*]pyridine (800.0 mg, 3.8 mmol, 1.0 equiv.) was dissolved in MeOH (20 mL), then Pt/C (147.5 mg, 0.8 mmol, 0.2 equiv.) was added. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred overnight at ambient temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum. This gave 5-chloro-7-methyl-10 1*H*-pyrrolo[3,2-*b*] pyridin-3-amine (550.0 mg) as a yellow solid. LCMS Method A: $[M+H]^+ = 182$.

Step 4: *N*-{5-chloro-7-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl}acetamide

5-Chloro-7-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-amine (550.0 mg, 3.0 mmol, 1.0 equiv.) and TEA (0.8 mL, 6.1 mmol, 2.0 equiv.) were dissolved in THF (20 mL) and cooled 15 to 0 °C, then acetyl chloride (0.3 mL, 3.6 mmol, 1.2 equiv.) was added, maintaining the solution at 0 °C. The reaction mixture was stirred for 4 hours at ambient temperature, then quenched by the addition of MeOH. The resulting solution was concentrated under vacuum and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give *N*-{5-chloro-7-methyl-1*H*-pyrrolo[3,2-20 *b*]pyridin-3-yl}acetamide (600.0 mg) as a yellow solid. LCMS Method A: $[M+H]^+ = 224$.

Step 5: *N*-{5-[(*E*)-2-ethoxyethenyl]-7-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl}acetamide

N-{5-Chloro-7-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl}acetamide (300.0 mg, 1.3 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (3 mL) and water (0.5 mL), then 2-[(*E*)-25 2-ethoxyethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (398.5 mg, 2.0 mmol, 1.5 equiv.), Cs₂CO₃ (874.1 mg, 2.7 mmol, 2.0 equiv.), and Pd(dppf)Cl₂ (196.3 mg, 0.3 mmol, 0.2 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated

to 90 °C overnight, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:2) to give *N*-{5-[(*E*)-2-ethoxyethenyl]-7-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl}acetamide (200.0 mg) as a yellow solid. LCMS Method A: [M+H]⁺ = 260.

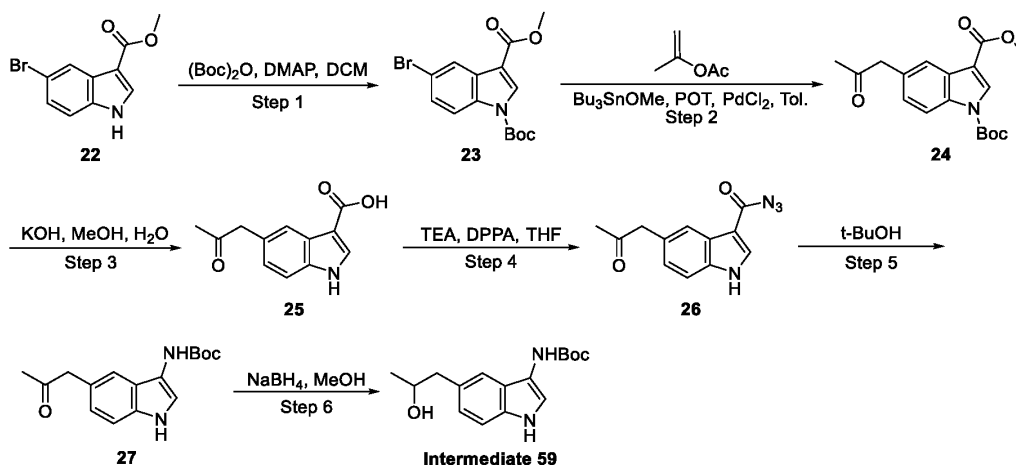
Step 6: *N*-[7-methyl-5-(2-oxoethyl)-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl]acetamide

N-{5-[(*E*)-2-ethoxyethenyl]-7-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl}acetamide (200.0 mg, 0.8 mmol, 1.0 equiv.) was dissolved in DCM (10 mL) and TFA (1 mL). The reaction mixture was stirred for 2 hours at 60 °C, then cooled to ambient temperature and concentrated under vacuum to give *N*-[7-methyl-5-(2-oxoethyl)-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl]acetamide (175.0 mg) as a brown solid, which was used in next step directly without further purification. LCMS Method A: [M+H]⁺ = 232.

Step 7: *N*-[5-(2-hydroxyethyl)-7-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl]acetamide

N-[7-methyl-5-(2-oxoethyl)-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl]acetamide (175.0 mg, 0.8 mmol, 1.0 equiv.) was dissolved in MeOH (10 mL) and cooled to 0 °C, then NaBH₄ (114.5 mg, 3.0 mmol, 3.8 equiv.) was added. The reaction mixture was stirred for 1 hour at ambient temperature, then concentrated under vacuum. The residue was purified by reverse flash chromatography using the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 5% to 100% gradient in 10 min; detector, UV 254 nm. This gave in *N*-[5-(2-hydroxyethyl)-7-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl]acetamide (85.0 mg) as a pale yellow solid. LCMS Method A: [M+H]⁺ = 234.

*Scheme 27: Synthesis of intermediate 59 (tert-butyl (5-(2-hydroxypropyl)-1*H*-indol-3-yl)carbamate)*



Step 1: 1-*tert*-butyl 3-methyl 5-bromoindole-1,3-dicarboxylate

Methyl 5-bromo-1*H*-indole-3-carboxylate (5.0 g, 19.6 mmol, 1.0 equiv.) was dissolved in DCM (100 mL), then Boc_2O (8.6 g, 39.3 mmol, 2.0 equiv.) and DMAP (480.8 mg, 3.9 mmol, 0.2 equiv.) were added. The reaction mixture was stirred for 3 hours at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give 1-*tert*-butyl 3-methyl 5-bromoindole-1,3-dicarboxylate (6.5 g) as a white solid. LCMS Method A: $[\text{M}+\text{H}]^+ = 354$.

Step 2: 1-*tert*-butyl 3-methyl 5-(2-oxopropyl)indole-1,3-dicarboxylate

1-*tert*-Butyl 3-methyl 5-bromoindole-1,3-dicarboxylate (3.0 g, 8.4 mmol, 1.0 equiv.) and 1-propen-2-ol acetate (1.7 g, 16.9 mmol, 2.0 equiv.) were dissolved in toluene (60 mL), then Bu_3SnOMe (3.2 g, 10.1 mmol, 1.2 equiv.), PdCl_2 (0.3 g, 1.6 mmol, 0.2 equiv.) and POT (0.6 g, 2.1 mmol, 0.2 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 100 °C for 3 hours, then cooled to ambient temperature and concentrated under vacuum. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl

acetate/petroleum ether (1:5) to give 1-*tert*-butyl 3-methyl 5-(2-oxopropyl)indole-1,3-dicarboxylate (2.5 g) as a white solid. LCMS Method A: $[M+H]^+ = 332$.

Step 3: 5-(2-oxopropyl)-1*H*-indole-3-carboxylic acid

1-*tert*-Butyl 3-methyl 5-(2-oxopropyl)indole-1,3-dicarboxylate (2.5 g, 7.5 mmol, 1.0 equiv.) was dissolved in MeOH (20 mL) and water (4 mL), then KOH (0.8 g, 15.0 mmol, 2.0 equiv.) was added. The reaction mixture was heated to 80 °C overnight, then cooled to ambient temperature and concentrated under vacuum. The residue was diluted with water and adjusted to pH 2 with aqueous HCl (2 N). The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give 5-(2-oxopropyl)-1*H*-indole-3-carboxylic acid (1.5 g) as a white solid. LCMS Method B: $[M-H]^- = 216$.

Step 4: 5-(2-oxopropyl)-1*H*-indole-3-carbonyl azide

5-(2-Oxopropyl)-1*H*-indole-3-carboxylic acid (1.5 g, 6.9 mmol, 1.0 equiv.) was dissolved in THF (20 mL), then TEA (2.9 mL, 20.7 mmol, 3.0 equiv.) and DPPA (2.8 g, 10.3 mmol, 1.5 equiv.) were added. The reaction mixture was stirred overnight at ambient temperature, then concentrated under vacuum to give 5-(2-oxopropyl)-1*H*-indole-3-carbonyl azide (1.1 g) as a white solid, which was used in the next step directly without further purification. LCMS Method A: $[M+H]^+ = 243$.

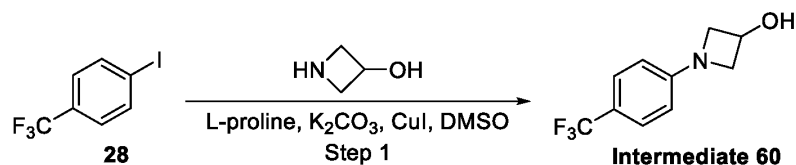
Step 5: *tert*-butyl *N*-[5-(2-oxopropyl)-1*H*-indol-3-yl]carbamate

5-(2-Oxopropyl)-1*H*-indole-3-carbonyl azide (1.0 g, 4.1 mmol, 1.0 equiv.) was dissolved in 2-methyl-2-propanol (30 mL). The reaction mixture was heated to 90 °C overnight, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18; mobile phase, ACN in water (0.5% NH₄HCO₃), 0% ACN to 100% gradient in 15 min; detector, UV 254 nm. This gave *tert*-butyl *N*-[5-(2-oxopropyl)-1*H*-indol-3-yl]carbamate (600.0 mg) as a white solid. LCMS Method A: $[M+H]^+ = 289$.

Step 6: *tert*-butyl *N*-[5-(2-hydroxypropyl)-1*H*-indol-3-yl]carbamate

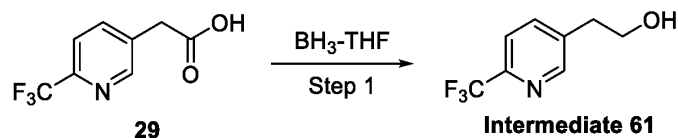
tert-Butyl *N*-[5-(2-oxopropyl)-1*H*-indol-3-yl]carbamate (550.0 mg, 1.9 mmol, 1.0 equiv.) was dissolved in MeOH (15 mL), then NaBH₄ (144.3 mg, 3.8 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 4 hours at ambient temperature, then concentrated under vacuum. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give *tert*-butyl *N*-[5-(2-hydroxypropyl)-1*H*-indol-3-yl]carbamate (550.0 mg) as a white solid. LCMS Method A: [M+H]⁺ = 291.

Scheme 28: Synthesis of intermediate 60 (1-[4-(trifluoromethyl)phenyl]azetidin-3-ol)



1-Iodo-4-(trifluoromethyl)benzene (1.0 g, 3.7 mmol, 1.0 equiv.) and azetidin-3-ol (0.5 g, 7.4 mmol, 2.0 equiv.) were dissolved in DMSO (5 mL), then L-proline (0.4 g, 3.7 mmol, 1.0 equiv.), K₂CO₃ (1.0 g, 7.4 mmol, 2.0 equiv.) and CuI (0.4 g, 1.8 mmol, 0.5 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred overnight at 90 °C, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give 1-[4-(trifluoromethyl)phenyl]azetidin-3-ol (600.0 mg) as an off-white solid. LCMS Method B: [M+H]⁺ = 218.

Scheme 29: Synthesis of intermediate 61 (2-(6-(trifluoromethyl)pyridin-3-yl)ethan-1-ol)

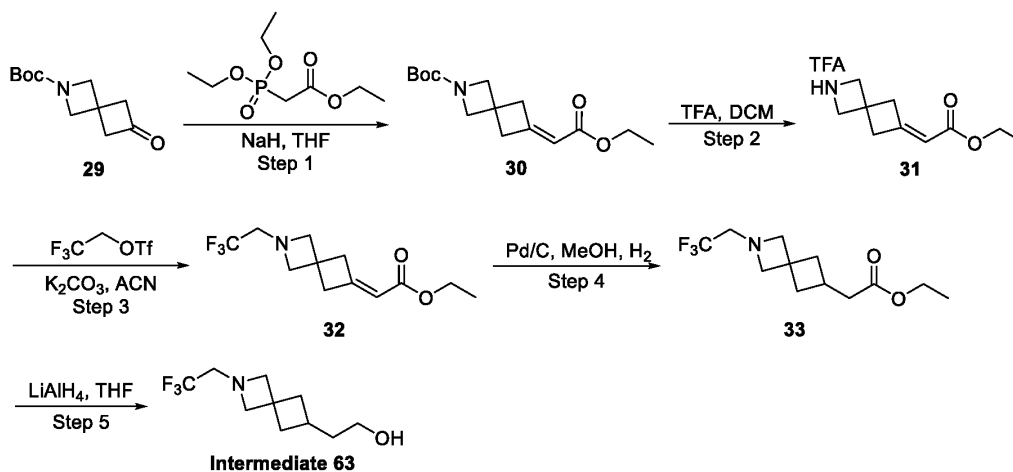


[6-(Trifluoromethyl)pyridin-3-yl]acetic acid (4.8 g, 23.2 mmol, 1.0 equiv.) was dissolved in THF (100 mL) and cooled to 0 °C, then BH₃-THF (1M, 69.5 mL, 69.5 mmol, 3.0 equiv.) was added dropwise, maintaining the solution at 0 °C. The reaction mixture was stirred for 1 hour at ambient temperature, then quenched by the addition of ice-water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (95:5) to give 2-[6-(trifluoromethyl)pyridin-3-yl]ethanol (4.3 g) as a yellow oil. LCMS Method A: [M+H]⁺ = 192.

The intermediates in the following table were prepared using the same method described for **Intermediate 61**.

Intermediate	Starting material	Structure	LCMS data
Intermediate 62			Method C: MS-ESI: 249 [M+H]⁺

Scheme 30: Synthesis of intermediate 63 (2-(2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl)ethan-1-ol)



Step 1: tert-butyl 6-(2-ethoxy-2-oxoethylidene)-2-azaspiro[3.3]heptane-2-carboxylate

Triethyl phosphonoacetate (1.3 g, 5.7 mmol, 1.2 equiv.) was dissolved in THF (50 mL) and cooled to 0 °C, then NaH (60% wt. in mineral oil, 0.3 g, 7.1 mmol, 1.5 equiv.). After 30 min at 0 °C, tert-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (1.0 g, 4.7 mmol, 1.0 equiv.) was added. The reaction mixture was stirred for an additional 2 hours at ambient temperature, then quenched by the addition of ice-water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give tert-butyl 6-(2-ethoxy-2-oxoethylidene)-2-azaspiro[3.3]heptane-2-carboxylate (1.3 g) as a yellow oil. LCMS Method A: [M+H]⁺ = 282.

Step 2: ethyl 2-{2-azaspiro[3.3]heptan-6-ylidene}acetate TFA salt

tert-Butyl 6-(2-ethoxy-2-oxoethylidene)-2-azaspiro[3.3]heptane-2-carboxylate (1.3 g, 4.6 mmol, 1.0 equiv.) was dissolved in DCM (40 mL) and TFA (2 mL). The reaction mixture was stirred for 40 min at ambient temperature, then concentrated under vacuum to give in ethyl 2-{2-azaspiro[3.3]heptan-6-ylidene}acetate TFA salt (1.0 g) as a yellow oil. LCMS Method A: [M+H]⁺ = 182.

Step 3: ethyl 2-[2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-ylidene]acetate

Ethyl 2-{2-azaspiro[3.3]heptan-6-ylidene}acetate TFA salt (1.0 g, 5.5 mmol, 1.0 equiv.) was dissolved in ACN (40 mL), then K₂CO₃ (1.5 g, 11.0 mmol, 2.0 equiv.) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.4 g, 6.1 mmol, 1.1 equiv.) were added. The reaction mixture was heated to 80 °C for 2 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give *ethyl* 2-[2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-ylidene]acetate (1.4 g) as a light yellow oil. LCMS Method A: [M+H]⁺ = 264.

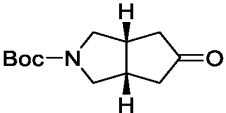
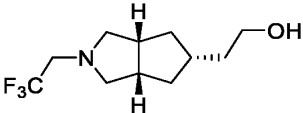
Step 4: ethyl 2-[2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl]acetate

Ethyl 2-[2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-ylidene]acetate (1.2 g, 4.6 mmol, 1.0 equiv.) was dissolved in MeOH (40 mL), then Pd/C (120.0 mg, 10% wt.) was added under an atmosphere of nitrogen. The reaction mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 2 hours at ambient temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:3) to give ethyl 2-[2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl]acetate (260.0 mg) as a light yellow oil. LCMS Method A: [M+H]⁺ = 266.

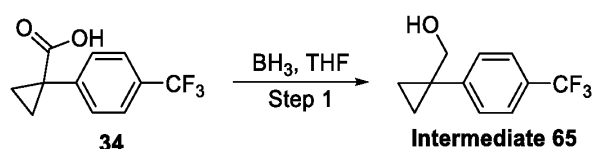
Step 5: 2-[2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl]ethanol

Ethyl 2-[2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl]acetate (260.0 mg, 1.0 mmol, 1.0 equiv.) was dissolved in THF (15 mL) and cooled to 0 °C, then LiAlH₄ (74.4 mg, 2.0 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 60 min at ambient temperature, then cooled to 0 °C and quenched by the addition of ice-water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give 2-[2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl]ethanol (210.0 mg) as a light yellow oil. LCMS Method A: [M+H]⁺ = 224.

The intermediates in the following table were prepared using the same method described for **Intermediate 63**.

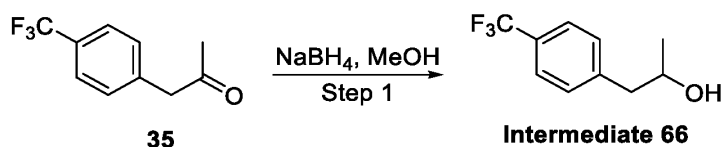
Intermediate	Starting material	Structure	LCMS data
Intermediate 64			Method C: MS-ESI: 238 [M+H]⁺

Scheme 31: Synthesis of intermediate 65 ((1-(4-(trifluoromethyl)phenyl)cyclopropyl)methanol)



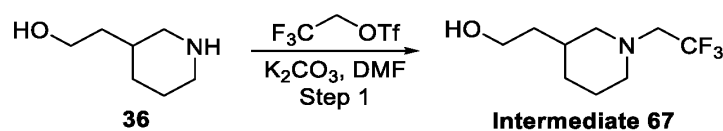
1-[4-(Trifluoromethyl)phenyl]cyclopropane-1-carboxylic acid (200.0 mg, 0.8 mmol, 1.0 equiv.) was dissolved in THF (5 mL) and cooled to 0 °C, then BH₃-THF (1M, 4.3 mL, 4.3 mmol, 5.0 equiv.) was added dropwise, maintaining the solution at 0 °C. The reaction mixture was stirred for 1 hour at ambient temperature then concentrated under vacuum. The residue was diluted with of water, extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give [1-[4-(trifluoromethyl)phenyl]cyclopropyl]methanol (150.0 mg) as a yellow oil. LCMS Method A: [M+H]⁺ = 217.

Scheme 32: Synthesis of intermediate 66 (1-(4-(trifluoromethyl)phenyl)propan-2-ol)



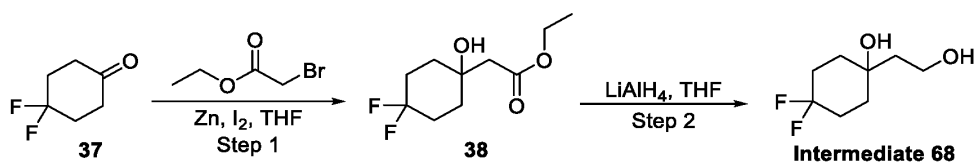
1-[4-(Trifluoromethyl)phenyl]propan-2-one (1.0 g, 4.9 mmol, 1.0 equiv.) was dissolved in MeOH (30 mL), then NaBH₄ (0.2 g, 5.8 mmol, 1.2 equiv.) was added. The reaction mixture was stirred for 2 hours at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with
 5 brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give 1-[4-(trifluoromethyl)phenyl]propan-2-ol (0.9 g) as a light yellow oil.

Scheme 33: Synthesis of intermediate 67 (2-(1-(2,2,2-trifluoroethyl)piperidin-3-yl)ethan-1-ol)



2-(Piperidin-3-yl)ethanol hydrochloride (2.0 g, 12.1 mmol, 1.0 equiv.) was dissolved in DMF (30 mL), then 2,2,2-trifluoroethyl trifluoromethanesulfonate (5.6 g, 24.2 mmol, 2.0 equiv.) and K₂CO₃ (3.3 g, 24.2 mmol, 2.0 equiv.) were added. The reaction mixture was heated to 80 °C for 2 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with
 15 brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18; mobile phase, MeOH in water, 10% to 50% gradient in 10 min; detector, UV 254 nm. This gave 2-[1-(2,2,2-trifluoroethyl)piperidin-3-yl]ethanol (1.4 g) as a yellow oil. LCMS Method A: [M+H]⁺ = 212.

Scheme 34: Synthesis of intermediate 68 (4,4-difluoro-1-(2-hydroxyethyl)cyclohexan-1-ol)



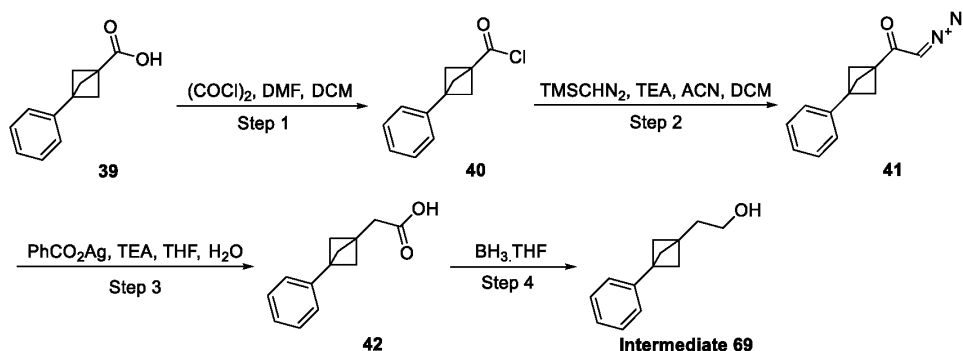
Step 1: Ethyl 2-(4,4-difluoro-1-hydroxycyclohexyl)acetate

Zinc powder (2.4 g, 37.3 mmol, 5.0 equiv.) was suspended in THF (25 mL) and cooled to 0 °C, then I₂ (1.9 g, 7.5 mmol, 1.0 equiv.) was added. After 10 min at 0 °C, 4,4-difluorocyclohexan-1-one (1.0 g, 7.5 mmol, 1.0 equiv.) and ethyl 2-bromoacetate (1.5 g, 8.9 mmol, 1.2 equiv.) were added dropwise, maintaining the reaction mixture at 0 °C. The reaction mixture was heated to 65 °C for 2 hours, then cooled to ambient temperature and quenched by the addition of saturated aqueous NaHCO₃. The mixture was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give ethyl 2-(4,4-difluoro-1-hydroxycyclohexyl)acetate (380.0 mg) as a colorless oil. LCMS Method A: [M+H]⁺ = 223.

Step 2: 4,4-difluoro-1-(2-hydroxyethyl)cyclohexan-1-ol

Ethyl 2-(4,4-difluoro-1-hydroxycyclohexyl)acetate (380.0 mg, 1.7 mmol, 1.0 equiv.) was dissolved in THF (10 mL) and cooled to 0 °C, then LiAlH₄ (97.4 mg, 2.6 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for 2 hours at ambient temperature, then quenched by the addition of solid Na₂SO₄·10·H₂O. The solids were filtered out and the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (10:1) to give 4,4-difluoro-1-(2-hydroxyethyl)cyclohexan-1-ol (120.0 mg) as colorless oil. LCMS Method A: [M+H]⁺ = 181.

Scheme 35: Synthesis of intermediate 69 (2-(3-phenylbicyclo[1.1.1]pentan-1-yl)ethan-1-ol)



Step 1: 3-phenylbicyclo[1.1.1]pentane-1-carbonyl chloride

3-Phenylbicyclo[1.1.1]pentane-1-carboxylic acid (500.0 mg, 2.7 mmol, 1.0 equiv.) was dissolved in DCM (20 mL) and cooled to 0 °C, then (COCl)₂ (0.35 mL, 4.0 mmol, 1.5 equiv.) was added dropwise, maintaining the solution at 0 °C. This was followed by the addition of DMF (0.03 mL, 0.3 mmol, 0.1 equiv.). The reaction mixture was stirred for 2.5 hours at ambient temperature, then concentrated under vacuum to give 3-phenylbicyclo[1.1.1]pentane-1-carbonyl chloride (620 mg) as a yellow solid.

Step 2: 2-diazo-1-{3-phenylbicyclo[1.1.1]pentan-1-yl}ethanone

3-Phenylbicyclo[1.1.1]pentane-1-carbonyl chloride (600.0 mg, 2.9 mmol, 1.0 equiv.) was dissolved in DCM (10 mL) and ACN (10 mL) and cooled to 0° C. Then TEA (1.2 mL, 8.7 mmol, 3.0 equiv.) and TMSCHN₂ (1.3 mg, 11.6 mmol, 4.0 equiv.) were added. The reaction mixture was stirred for 4 hours at ambient temperature and then quenched by the addition of saturated aqueous citric acid. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give 2-diazo-1-{3-phenylbicyclo[1.1.1]pentan-1-yl}ethanone (610.0 mg) as a pale yellow solid.

Step 3: {3-phenylbicyclo[1.1.1]pentan-1-yl}acetic acid

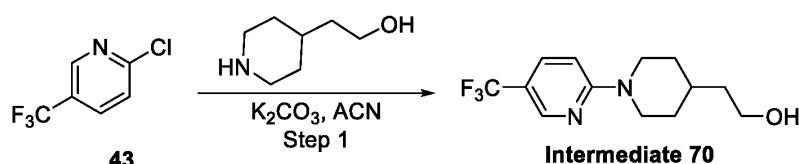
2-Diazo-1-{3-phenylbicyclo[1.1.1]pentan-1-yl}ethanone (600.0 mg, 2.8 mmol, 1.0 equiv.) was dissolved in THF (15 mL) and H₂O (5 mL), then TEA (1.6 mL, 11.3 mmol, 4.0 equiv.) and PhCO₂Ag (129.5 mg, 0.6 mmol, 0.2 equiv.) were added. The reaction

mixture was heated to 70 °C for 2 hours. The solid was removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 100% gradient in 20 min; detector, UV 254 nm. This gave {3-phenylbicyclo[1.1.1]pentan-1-yl}acetic acid (330.0 mg) as a yellow solid. LCMS Method B: $[M-H]^- = 201$.

Step 4: 2-{3-phenylbicyclo[1.1.1]pentan-1-yl}ethanol

{3-Phenylbicyclo[1.1.1]pentan-1-yl}acetic acid (300.0 mg, 1.5 mmol, 1.0 equiv.) was dissolved in THF (10 mL) and cooled to 0 °C, then $BH_3 \cdot THF$ (1M, 1.5 mL, 1.5 mmol, 3.0 equiv.) was added dropwise. The reaction mixture was stirred for 2 hours at ambient temperature, then concentrated under vacuum. The residue was diluted with of water, extracted with ethyl acetate and concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 100% gradient in 20 min; detector, UV 254 nm. This gave 2-{3-phenylbicyclo[1.1.1]pentan-1-yl}ethanol (130.0 mg) as a pale yellow solid. LCMS Method A: $[M+H]^+ = 189$.

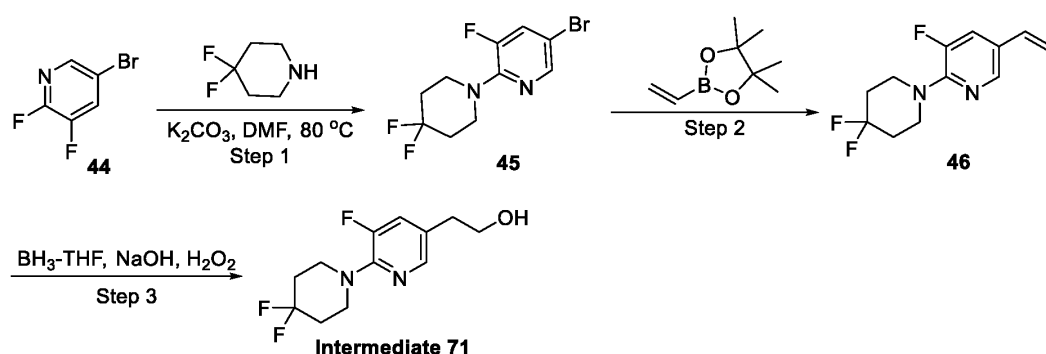
Scheme 36: Synthesis of intermediate 70 (2-(1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)ethan-1-ol)



2-Chloro-5-(trifluoromethyl)pyridine (1.0 g, 5.5 mmol, 1.0 equiv.) was dissolved in ACN (10 mL), then 2-(piperidin-4-yl)ethan-1-ol (850 mg, 6.6 mmol, 1.2 equiv.) and K_2CO_3 (1.5 g, 11.0 mmol, 2.0 equiv.) were added. The reaction mixture was heated to 70 °C for 2 hours, then cooled to ambient temperature and quenched by the addition of water. Then resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by

flash column chromatography on silica gel, eluting with dichloromethane/MeOH (10:1) to give 2-(1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)ethan-1-ol (980 mg) as a white solid. LCMS Method A: $[M+H]^+ = 275$.

5 **Scheme 37: Synthesis of intermediate 71 (2-(6-(4,4-difluoropiperidin-1-yl)-5-fluoropyridin-3-yl)ethan-1-ol)**



Step 1: 5-bromo-2-(4,4-difluoropiperidin-1-yl)-3-fluoropyridine

5-Bromo-2,3-difluoropyridine (4.0 g, 20.6 mmol, 1.0 equiv.) and 4,4-difluoropiperidine (2.7 g, 22.7 mmol, 1.1 equiv.) were dissolved in DMF (20 mL), then K_2CO_3 (5.7 g, 41.2 mmol, 2.0 equiv.) was added. The reaction mixture was heated to 80 °C for 2 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:9) to give 5-bromo-2-(4,4-difluoropiperidin-1-yl)-3-fluoropyridine (4.5 g) as a yellow solid. LCMS Method A: $[M+H]^+ = 295$.

Step 2: 2-(4,4-difluoropiperidin-1-yl)-3-fluoro-5-vinylpyridine

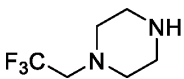
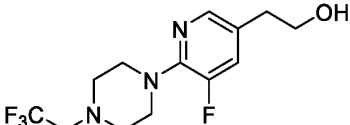
5-Bromo-2-(4,4-difluoropiperidin-1-yl)-3-fluoropyridine (3.0 g, 10.2 mmol, 1.0 equiv.) and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.9 g, 12.2 mmol, 1.2 equiv.) were dissolved in 1,4-dioxane (30 mL), then $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.4 g, 0.5 mmol, 0.05 equiv.) and Cs_2CO_3 (6.6 g, 20.3 mmol, 2.0 equiv.) were added under an atmosphere

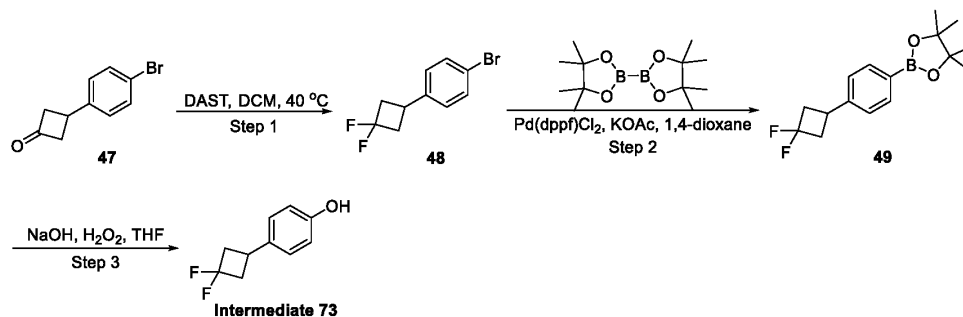
of nitrogen. The reaction mixture was heated to 80 °C for 4 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:7) to give 2-(4,4-difluoropiperidin-1-yl)-3-fluoro-5-vinylpyridine (1.1 g) as a yellow oil. LCMS Method A: $[M+H]^+ = 243$.

Step 3: 2-(6-(4,4-difluoropiperidin-1-yl)-5-fluoropyridin-3-yl)ethan-1-ol

2-(4,4-Difluoropiperidin-1-yl)-3-fluoro-5-vinylpyridine (1.0 g, 4.1 mmol, 1.0 equiv.) was dissolved in THF and cooled to 0 °C, then BH_3 -THF (1M, 16.5 mL, 16.5 mmol, 4.0 equiv.) was added dropwise, maintaining the solution at 0 °C. The reaction mixture was stirred for 1 hour at ambient temperature. Then a solution of aqueous NaOH (1 M, 2.9 mL, 2.9 mmol, 0.7 equiv.) was added and the reaction mixture was cooled to 0 °C. This was followed by the dropwise addition of H_2O_2 (30% wt./wt. in water, 4.8 mL, 7.2 mmol, 1.8 equiv.), maintaining the reaction mixture at 0 °C. The reaction mixture was stirred for additional 1 hour at ambient temperature, then quenched by the addition of saturated aqueous NH_4Cl . The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/MeOH (10:1) to give 2-(6-(4,4-difluoropiperidin-1-yl)-5-fluoropyridin-3-yl)ethan-1-ol (880.0 mg) as a white solid. LCMS Method A: $[M+H]^+ = 261$.

The intermediates in the following table were prepared using the same method described for **Intermediate 71**.

Intermediate	Starting material	Structure	LCMS data
Intermediate 72			Method A: MS-ESI: 308 $[M+H]^+$

Scheme 38: Synthesis of intermediate 73 (4-(3,3-difluorocyclobutyl)phenol)**Step 1: 1-bromo-4-(3,3-difluorocyclobutyl)benzene**

3-(4-Bromophenyl)cyclobutan-1-one (1.0 g, 4.4 mmol, 1.0 equiv.) was dissolved in DCM (20 mL) and cooled to 0 °C, then DAST (2.2 g, 13.3 mmol, 3.0 equiv.) was added dropwise, maintaining the solution at 0 °C. The reaction mixture was stirred for 4 hours at 40 °C, then cooled to 0 °C and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give 1-bromo-4-(3,3-difluorocyclobutyl)benzene (870.0 mg) as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 3.47–3.35 (m, 1H), 3.08–2.90 (m, 2H), 2.74–2.57 (m, 2H).

Step 2: 2-(4-(3,3-difluorocyclobutyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

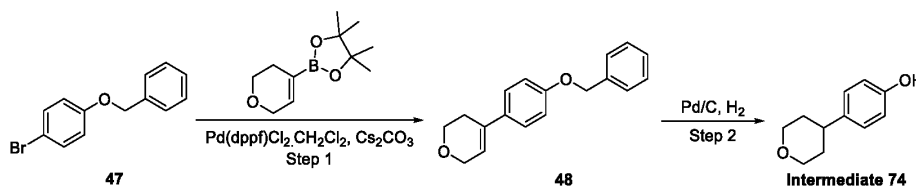
1-Bromo-4-(3,3-difluorocyclobutyl)benzene (800.0 mg, 3.2 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (150 mL), then 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.2 g, 4.9 mmol, 1.5 equiv.), Pd(dppf)Cl₂ (236.9 mg, 0.3 mmol, 0.1 equiv.) and KOAc (635.5 mg, 6.5 mmol, 2.0 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 90 °C for 4 hours, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give 2-(4-(3,3-

difluorocyclobutyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (805.0 mg) as a colorless oil. LCMS Method A: $[M+H]^+ = 295$.

Step 3: 4-(3,3-difluorocyclobutyl)phenol

2-(4-(3,3-Difluorocyclobutyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (800.0 mg, 2.7 mmol, 1.0 equiv.) was dissolved in THF (20 mL) and cooled to 0°C, then aqueous NaOH (2% wt./wt., 10 mL, 5.0 mmol, 2.0 equiv.) and H₂O₂ (30% wt./wt., 1.0 mL, 8.8 mmol, 3.0 equiv.) were added dropwise. The reaction mixture was stirred for additional 2 hours at ambient temperature, then quenched by the addition of saturated NH₄Cl aqueous. The mixture was extracted with ethyl acetate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give 4-(3,3-difluorocyclobutyl)phenol (320.0 mg) as a colorless oil. LCMS Method B: $[M-H]^- = 183$.

Scheme 39: Synthesis of intermediate 74 (4-(tetrahydro-2H-pyran-4-yl)phenol)



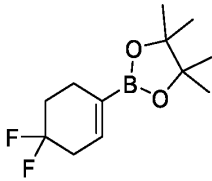
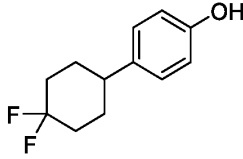
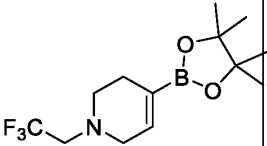
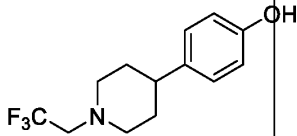
Step 1: 4-[4-(benzyloxy)phenyl]-3,6-dihydro-2H-pyran

1-(Benzyloxy)-4-bromobenzene (1.0 g, 3.8 mmol, 1.0 equiv) was dissolved in 1,4-dioxane (10 mL), then 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.2 g, 5.7 mmol, 1.5 equiv.), Cs₂CO₃ (2.5 g, 7.6 mmol, 2.0 equiv.) and Pd(dppf)Cl₂CH₂Cl₂ (309.0 mg, 0.4 mmol, 0.1 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 90 °C for 6 hours, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:8) to give 4-[4-(benzyloxy)phenyl]-3,6-dihydro-2H-pyran (712.0 mg) as a yellow solid. LCMS Method A: $[M+H]^+ = 267$.

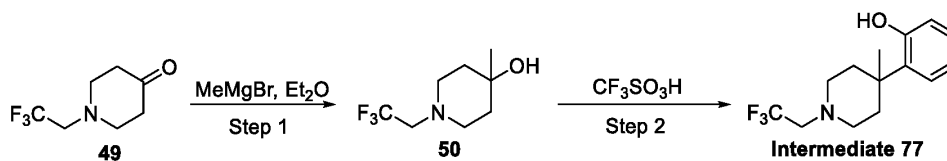
Step 2: 4-(oxan-4-yl)phenol

4-[4-(Benzyloxy)phenyl]-3,6-dihydro-2H-pyran (500.0 mg, 1.9 mmol, 1.0 equiv.) was dissolved in EtOH (10 mL), then Pd/C (10% wt., 50.0 mg) was added under an atmosphere of nitrogen. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 5 hours at ambient temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give 4-(oxan-4-yl)phenol (150.0 mg) as a pale yellow solid. LCMS Method B: $[M-H]^- = 177$.

The intermediates in the following table were prepared using the same method described for **Intermediate 74**.

Intermediate	Starting material	Structure	LCMS data
Intermediate 75			Method C: MS-ESI: 213 $[M+H]^+$
Intermediate 76			Method C: MS-ESI: 260 $[M+H]^+$

Scheme 40: Synthesis of intermediate 77 (2-(4-methyl-1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenol)



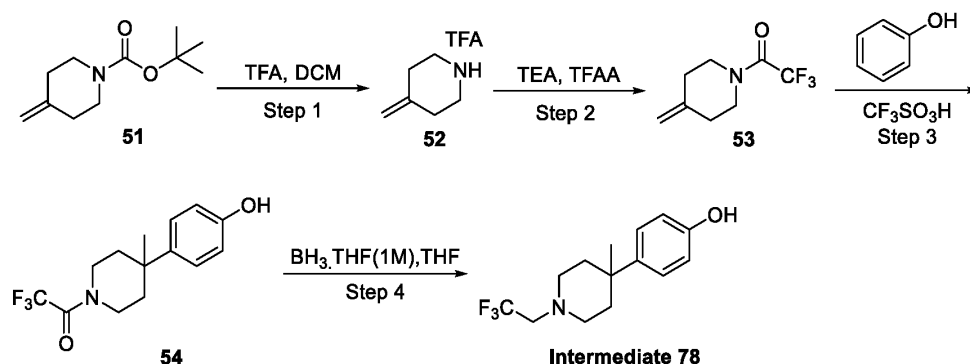
Step 1: 4-methyl-1-(2,2,2-trifluoroethyl)piperidin-4-ol

1-(2,2,2-Trifluoroethyl)piperidin-4-one (1.0 g, 5.5 mmol, 1.0 equiv.) was dissolved in Et₂O (40 mL) and cooled to -55 °C, then MeMgBr (1M in THF, 11.0 mL, 11.0 mmol, 2.0 equiv.) was added dropwise, maintaining the solution at -5 °C. The reaction mixture was stirred for 4 hours at ambient temperature, then quenched by the addition of saturated aqueous NH₄Cl at 0 °C. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give 4-methyl-1-(2,2,2-trifluoroethyl)piperidin-4-ol (1.0 g) as a pale yellow oil. LCMS Method A: [M+H]⁺ = 198.

Step 2: 2-[4-methyl-1-(2,2,2-trifluoroethyl)piperidin-4-yl]phenol

4-Methyl-1-(2,2,2-trifluoroethyl)piperidin-4-ol (600.0 mg, 3.0 mmol, 1.0 equiv.) was dissolved in CF₃SO₃H (5 mL), then phenol (859.0 mg, 9.1 mmol, 3.0 equiv.) was added. The reaction mixture was stirred overnight at ambient temperature and then quenched by the addition of ice-water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, ACN in water, 10% to 100% gradient in 15 min; Detector, UV 254 nm. This gave 2-[4-methyl-1-(2,2,2-trifluoroethyl)piperidin-4-yl]phenol (170.0 mg) as a pale yellow oil. LCMS Method A: [M+H]⁺ = 274.

Scheme 41: Synthesis of intermediate 78 (4-(4-methyl-1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenol)



Step 1: 4-methylidenepiperidine TFA salt

tert-Butyl 4-methylidenepiperidine-1-carboxylate (2.0 g, 10.1 mmol, 1.0 equiv.) was dissolved in DCM (40 mL), then TFA (3.1 mL, 40.6 mmol, 4.0 equiv.) was added. The reaction mixture was stirred for 1 hour at ambient temperature, then concentrated under vacuum to give 4-methylidenepiperidine TFA as a yellow solid, which was used in the next step directly without further purification. LCMS Method A: $[M+H]^+ = 98$.

Step 2: 2,2,2-trifluoro-1-(4-methylenepiperidin-1-yl)ethan-1-one

4-Methylidenepiperidine (1.0 g, 10.3 mmol, 1.0 equiv.) and TEA (2.9 mL, 20.6 mmol, 2.0 equiv.) were dissolved in ACN (10 mL), then TFAA (2.9 mL, 20.6 mmol, 2.0 equiv.) was added dropwise. The reaction mixture was heated to 80 °C for 2 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to give 2,2,2-trifluoro-1-(4-methylenepiperidin-1-yl)ethanone (710.0 mg) as a colorless oil. LCMS Method A: $[M+H]^+ = 194$.

Step 3: 2,2,2-trifluoro-1-[4-(4-hydroxyphenyl)-4-methylpiperidin-1-yl]ethanone

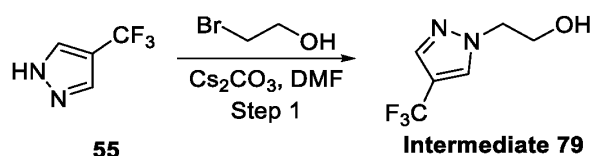
2,2,2-Trifluoro-1-(4-methylidenepiperidin-1-yl)ethanone (700.0 mg, 3.6 mmol, 1.0 equiv.) was dissolved in $\text{CF}_3\text{SO}_3\text{H}$ (10 mL), then phenol (1.0 g, 10.9 mmol, 3.0 equiv.) was added. The reaction mixture was stirred overnight at ambient temperature, then quenched by the addition of ice-water. The resulting solution was adjusted to pH 6 with aqueous NaOH (20% wt./wt), extracted with ethyl acetate, washed with brine, dried over

anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 5% to 100% gradient in 25 min; detector, UV 254 nm. This gave 2,2,2-trifluoro-1-[4-(4-hydroxyphenyl)-4-methylpiperidin-1-yl]ethanone (180.0 mg) as a yellow oil. LCMS Method B: [M-H]⁻ = 286.

Step 4: 4-[4-methyl-1-(2,2,2-trifluoroethyl)piperidin-4-yl]phenol

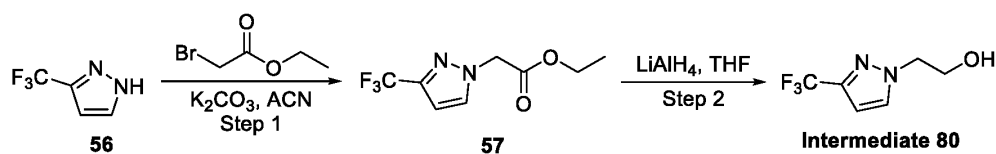
2,2,2-Trifluoro-1-[4-(4-hydroxyphenyl)-4-methylpiperidin-1-yl]ethanone (180.0 mg, 0.6 mmol, 1.0 equiv.) was dissolved in THF (15 mL) and cooled to 0 °C, then BH₃•THF (1M, 2.5 mL, 2.5 mmol, 4.0 equiv.) was added dropwise. The reaction mixture was heated to 70 °C for 1 hour, then cooled to 0 °C and quenched by the addition of MeOH. The resulting solution was concentrated under vacuum and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:8) to give 4-[4-methyl-1-(2,2,2-trifluoroethyl)piperidin-4-yl]phenol (150.0 mg) as a light yellow oil. LCMS Method B: [M-H]⁻ = 272.

Scheme 42: Synthesis of intermediate 79 (2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-ol)



4-(Trifluoromethyl)-1H-pyrazole (500.0 mg, 3.7 mmol, 1.0 equiv.) and 2-bromoethanol (918.3 mg, 7.3 mmol, 2.0 equiv.) were dissolved in DMF (5 mL), then Cs₂CO₃ (2.4 g, 7.3 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 2 hours at ambient temperature, then concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in Water (10 mM NH₄HCO₃), 10% ACN to 50% gradient in 10 min; detector, UV 254 nm. This gave 2-[4-(trifluoromethyl)pyrazol-1-yl]ethanol (310.0 mg) as a pale yellow oil. LCMS Method A: [M+H]⁺ = 181.

Scheme 43: Synthesis of intermediate 80 (2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-ol)



Step 1: ethyl 2-[3-(trifluoromethyl)pyrazol-1-yl]acetate

5 3-(Trifluoromethyl)-1H-pyrazole (2.0 g, 14.7 mmol, 1.0 equiv.) was dissolved in ACN (20 mL), then K₂CO₃ (4.1 g, 29.4 mmol, 2.0 equiv.) and ethyl bromoacetate (2.5 g, 14.7 mmol, 1.0 equiv.) were added. The reaction mixture was heated to 60 °C for 6 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄

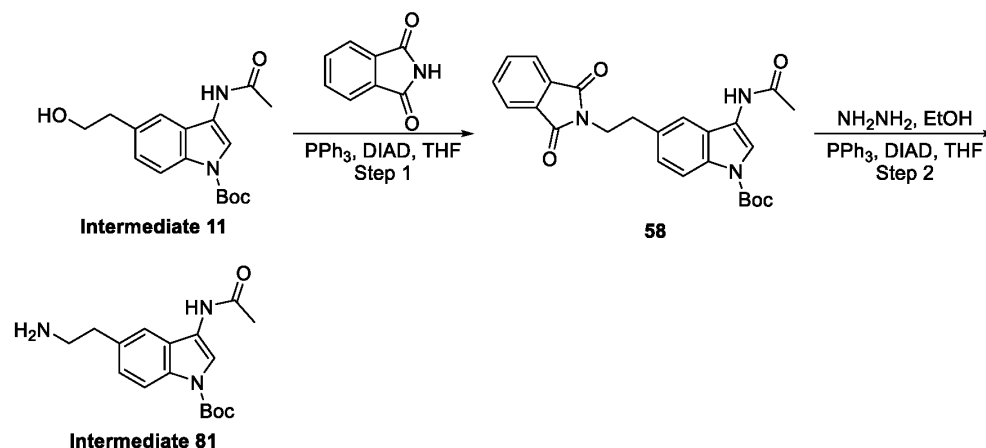
10 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give ethyl 2-[3-(trifluoromethyl)pyrazol-1-yl]acetate (1.8 g) as a yellow solid. LCMS Method A: [M+H]⁺ = 223.

Step 2: 2-[3-(trifluoromethyl)pyrazol-1-yl]ethanol

15 Ethyl 2-[3-(trifluoromethyl)pyrazol-1-yl]acetate (800.0 mg, 3.6 mmol, 1.0 equiv.) was dissolved in THF (10 mL) and cooled to 0 °C, then LiAlH₄ (164.0 mg, 4.3 mmol, 1.2 equiv.) was added. The reaction mixture was stirred for 2 hours at 0 °C and then quenched by the addition of saturated aqueous sodium hyposulfite. The solid was removed by filtration, and the filtrate was concentrated under vacuum to give 2-[3-

20 (trifluoromethyl)pyrazol-1-yl]ethanol (560.0 mg) as a yellow oil, which was used in the next step directly without further purification. LCMS Method A: [M+H]⁺ = 181.

Scheme 44: Synthesis of intermediate 81 (tert-butyl 3-acetamido-5-(2-aminoethyl)-1H-indole-1-carboxylate)



Step 1: *tert*-butyl 5-(hydroxymethyl)-3-(2-(methylamino)-2-oxoacetamido)-1*H*-indole-1-carboxylate

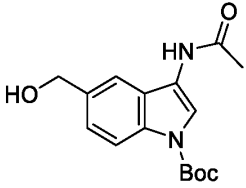
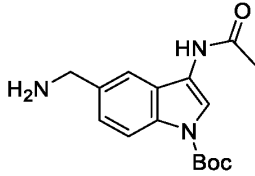
tert-Butyl 3-acetamido-5-(2-hydroxyethyl)indole-1-carboxylate (300.0 mg, 0.9 mmol, 1.0 equiv.) was dissolved in THF (3 mL), then phthalimide (277.3 mg, 1.9 mmol, 2.0 equiv.) and PPh₃ (494.3 mg, 1.9 mmol, 2.0 equiv.) were added. The reaction mixture was cooled to 0 °C, then DIAD (381.1 mg, 1.9 mmol, 2.0 equiv.) was added dropwise, maintaining the solution at 0 °C. The reaction mixture was stirred for 6 hours at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give *tert*-butyl 5-[2-(1,3-dioxoisindol-2-yl)ethyl]-3-acetamidindole-1-carboxylate (340.0 mg) as a brown solid. LCMS Method A: [M+H]⁺ = 448.

Step 2: *tert*-butyl 5-(2-aminoethyl)-3-acetamidindole-1-carboxylate

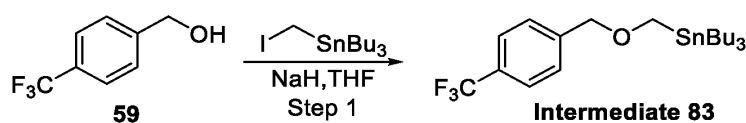
tert-Butyl 5-[2-(1,3-dioxoisindol-2-yl)ethyl]-3-acetamidindole-1-carboxylate (310.0 mg, 0.7 mmol, 1.0 equiv.) was dissolved in EtOH (3.5 mL), then hydrazine (44.4 mg, 1.4 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 5 hours at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and

concentrated under vacuum to give crude *tert*-butyl 5-(2-aminoethyl)-3-acetamidindole-1-carboxylate (280.0 mg) as brown solid. LCMS Method A: $[M+H]^+ = 318$.

The intermediate in the following table were prepared using the same method described for **Intermediate 81**.

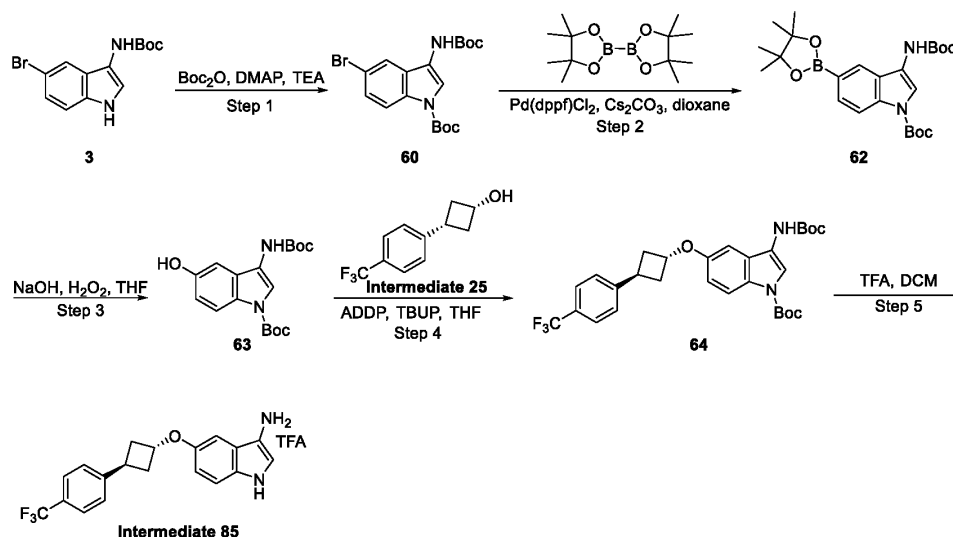
Intermediate	Starting material	Structure	LCMS data
Intermediate 82	 Intermediate 13		Method A: MS-ESI: 304 $[M+H]^+$

Scheme 45: Synthesis of intermediate 83 (tributyl({[4-(trifluoromethyl) phenyl] methoxy} methyl)stannane)



[4-(Trifluoromethyl)phenyl]methanol (5.0 g, 28.4 mmol, 1.0 equiv.) was dissolved in THF (50 mL) and cooled to 0 °C, then NaH (60% wt., 1.4 g, 34.1 mmol, 1.2 equiv.) was added. After 30 min at 0 °C, tributyl(iodomethyl)stannane (13.4 g, 31.2 mmol, 1.1 equiv.) was added. The reaction mixture was stirred for an additional 4 hours at ambient temperature, then cooled to 0 °C and quenched by the addition of MeOH. The resulting solution was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/petroleum ether (5:1) to give tributyl({[4-(trifluoromethyl)phenyl]methoxy} methyl)stannane (9.5 g) as a colorless oil. LCMS Method A: $[M+H]^+ = 481$.

Scheme 46: Synthesis of intermediate 85 (5-((trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-amine TFA salt)



Step 1: *tert*-butyl 5-bromo-3-((*tert*-butoxycarbonyl)amino)-1*H*-indole-1-carboxylate

tert-Butyl (5-bromo-1*H*-indol-3-yl)carbamate (5.0 g, 16.1 mmol, 1.0 equiv.) was dissolved in THF (80.0 mL), then (Boc)₂O (4.2 g, 19.3 mmol, 1.2 equiv.), DMAP (0.2 g, 1.6 mmol, 0.1 equiv.) and TEA (4.6 mL, 32.1 mmol, 2.0 equiv.) were added. The reaction mixture was stirred for 4 hours at ambient temperature, then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give *tert*-butyl 5-bromo-3-((*tert*-butoxycarbonyl)amino)-1*H*-indole-1-carboxylate (6.5 g) as a white solid.

Step 2: *tert*-butyl 3-((*tert*-butoxycarbonyl)amino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-1-carboxylate

tert-Butyl 5-bromo-3-((*tert*-butoxycarbonyl)amino)-1*H*-indole-1-carboxylate (6.0 g, 14.6 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (100.0 mL), then 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (5.6 g, 21.9 mmol, 1.5 equiv.), Pd(dppf)Cl₂ (1.1 g, 1.5 mmol, 0.1 equiv.) and Cs₂CO₃ (9.5 g, 29.2 mmol, 2.0 equiv.)

were added under an atmosphere of nitrogen. The reaction mixture was stirred overnight at 90 °C under nitrogen, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:4) to give *tert*-butyl 3-((*tert*-butoxycarbonyl)amino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-1-carboxylate (6.0 g) as a white solid.

Step 3: *tert*-butyl 3-((*tert*-butoxycarbonyl)amino)-5-hydroxy-1*H*-indole-1-carboxylate

tert-Butyl 3-((*tert*-butoxycarbonyl)amino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-1-carboxylate (6.0 g, 13.1 mmol, 1.0 equiv.) was dissolved in THF (80.0 mL) and cooled to 0 °C. Then NaOH (1.6 g, 39.3 mmol, 3.0 equiv.) was added at 0 °C, followed by the dropwise addition of H₂O₂ (30% w.t/wt, 3.0 g, 26.2 mmol, 2.0 equiv), maintaining the reaction mixture at 0 °C. The reaction mixture was stirred for 2 hours at ambient temperature, then quenched by the addition of brine. The resulting resolution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give *tert*-butyl 3-((*tert*-butoxycarbonyl)amino)-5-hydroxy-1*H*-indole-1-carboxylate (2.2 g) as a grey solid.

Step 4: *tert*-butyl 3-((*tert*-butoxycarbonyl)amino)-5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indole-1-carboxylate

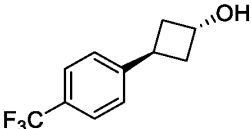
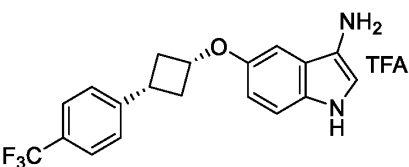
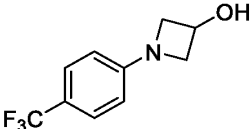
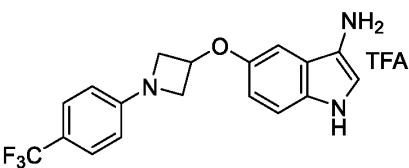
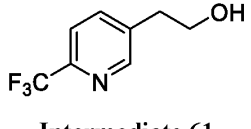
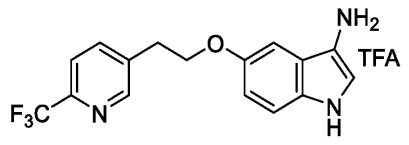
tert-Butyl 3-((*tert*-butoxycarbonyl)amino)-5-hydroxy-1*H*-indole-1-carboxylate (1.0 g, 2.9 mmol, 1.0 equiv.) and cis-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol (1.2 g, 5.7 mmol, 2.0 equiv.) were dissolved in THF (20.0 mL) and cooled to 0 °C, then TBUP (1.7 g, 8.6 mmol, 3.0 equiv.) was added at 0 °C under an atmosphere of nitrogen. This was followed by the dropwise addition of ADDP (2.2 g, 8.6 mmol, 3.0 equiv.), maintaining the solution at 0 °C. The reaction mixture was heated to 50 °C for 2 hours, then cooled to ambient temperature and concentrated under vacuum. The residue was

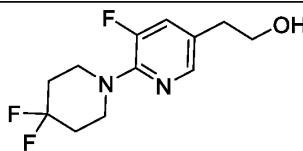
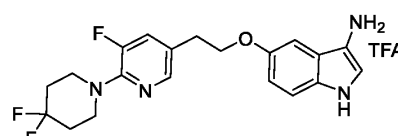
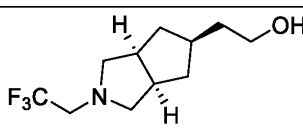
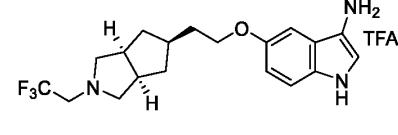
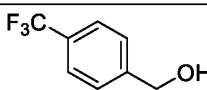
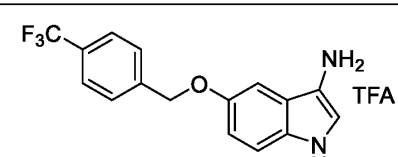
purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase A: 0.05% NH_4HCO_3 in water; mobile phase B: Acetonitrile, 45% phase B to 70% gradient in 20 min; detector, UV 254 nm. This gave *tert*-butyl 3-((*tert*-butoxycarbonyl)amino)-5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indole-1-carboxylate (1.2 g) as an off-white solid.

Step 5: 5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-amine TFA salt

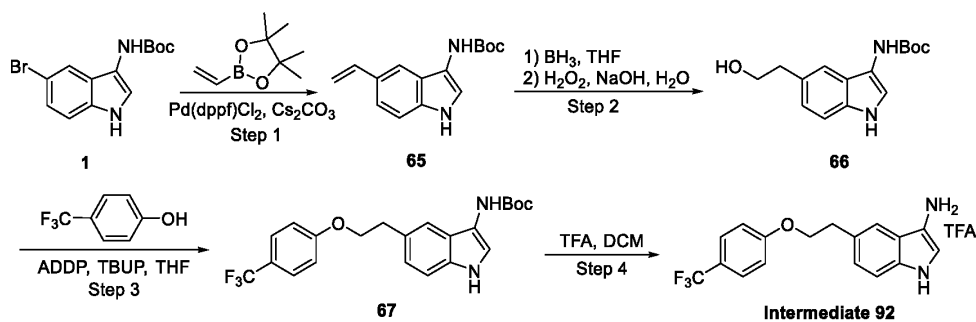
tert-Butyl 3-((*tert*-butoxycarbonyl)amino)-5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indole-1-carboxylate (190.0 mg, 0.3 mmol, 1.0 equiv.) was dissolved in DCM (2.0 mL), then TFA (2.0 mL) was added. The resulting mixture was stirred for 1 hour at ambient temperature and then concentrated under vacuum to give 5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-amine TFA salt (120.0 mg) as a white solid. LCMS Method A: $[\text{M}+\text{H}]^+ = 347$.

The intermediates in the following table were prepared using the same method described for **Intermediate 85**.

Intermediate	Starting material	Structure	LCMS data
Intermediate 86	 Intermediate 26		Method A: MS-ESI: 347 $[\text{M}+\text{H}]^+$
Intermediate 87	 Intermediate 60		Method A: MS-ESI: 348 $[\text{M}+\text{H}]^+$
Intermediate 88	 Intermediate 61		Method C: MS-ESI:

			322 [M+H] ⁺
Intermediate 89	 Intermediate 71	 Method C: MS-ESI: 391 [M+H]⁺	
Intermediate 90	 Intermediate 64	 Method C: MS-ESI: 368 [M+H]⁺	
Intermediate 91		 Method C: MS-ESI: 307 [M+H]⁺	

Scheme 47: Synthesis of intermediate 92 (5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-amine TFA salt)



Steps 1-2: *tert*-butyl (5-(2-hydroxyethyl)-1H-indol-3-yl)carbamate

5 The title compound was prepared using the same methods described for **Intermediate 48 (Step 1 to 2)**. LCMS Method A: [M+H]⁺ = 277.

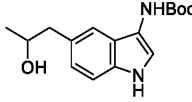
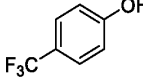
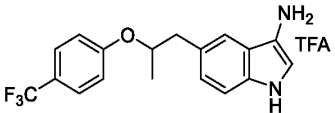
Step 3: *tert*-butyl *N*-(5-[2-[4-(trifluoromethyl)phenoxy]ethyl]-1*H*-indol-3-yl)carbamate

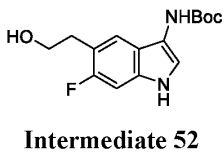
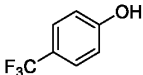
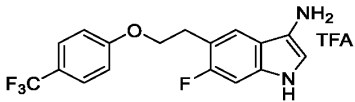
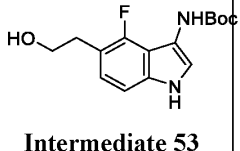
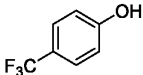
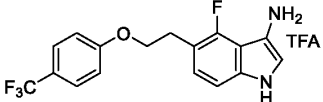
tert-Butyl *N*-[5-(2-hydroxyethyl)-1*H*-indol-3-yl]carbamate (338.0 mg, 1.2 mmol, 1.0 equiv.) and 4-(trifluoromethyl)phenol (198.2 mg, 1.2 mmol, 1.0 equiv.) were dissolved in THF (10 mL), then ADDP (612.4 mg, 2.4 mmol, 2.0 equiv.) and TBUP (494.9 mg, 2.4 mmol, 2.0 equiv.) were added. The reaction mixture was heated to 70 ° C for 5 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give *tert*-butyl *N*-(5-[2-[4-(trifluoromethyl)phenoxy]ethyl]-1*H*-indol-3-yl)carbamate (260.0 mg) as a brown solid. LCMS Method A: $[M+H]^+ = 421$.

Step 4: 5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1*H*-indol-3-amine TFA salt

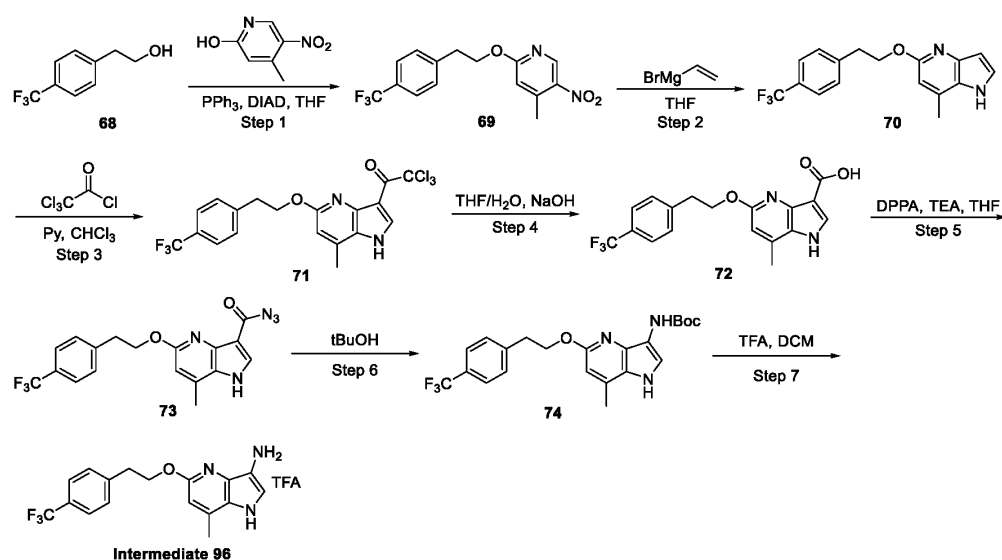
tert-Butyl *N*-(5-{2-[4-(trifluoromethyl)phenoxy]ethyl}-1*H*-indol-3-yl)carbamate (260.0 mg, 0.6 mmol, 1.0 equiv.) was dissolved in DCM (2 mL) and TFA (2 mL). The reaction mixture was stirred for 30 min at ambient temperature then concentrated under vacuum to give 5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1*H*-indol-3-amine TFA salt (350.0 mg) as a yellow solid. LCMS Method A: $[M+H]^+ = 321$.

The intermediates in the following table were prepared using the same method described for **Intermediate 92**.

Intermediate	Starting material A	Starting material B	Structure	LCMS data
Intermediate 93	 Intermediate 59			Method A: MS-ESI: 335 $[M+H]^+$

Intermediate 94	 Intermediate 52	 		Method C: MS-ESI: 339 [M+H] ⁺
Intermediate 95	 Intermediate 53	 		Method C: MS-ESI: 339 [M+H] ⁺

Scheme 48: Synthesis of intermediate 96 (7-methyl-5-(4-(trifluoromethyl)phenoxy)-1H-pyrrolo[3,2-b]pyridin-3-amine TFA salt)



5 Step 1: 4-methyl-5-nitro-2-{2-[4-(trifluoromethyl)phenyl]ethoxy}pyridine

2-[4-(Trifluoromethyl)phenyl]ethanol (5.0 g, 26.3 mmol, 1.0 equiv.) was dissolved in THF (30 mL) and cooled to 0 °C, then 4-methyl-5-nitropyridin-2-ol (4.1 g, 26.3 mmol, 1.0 equiv.) and DIAD (10.6 g, 52.6 mmol, 2.0 equiv.) were added. The reaction mixture was stirred for 6 hours at ambient temperature under an atmosphere of nitrogen, then concentrated under vacuum. The residue was purified by flash column chromatography

on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give 4-methyl-5-nitro-2-{2-[4-(trifluoromethyl)phenyl]ethoxy}pyridine (6.2 g) as a pale yellow solid. LCMS Method A: $[M+H]^+ = 327$.

Step 2: 7-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-b]pyridine

4-Methyl-5-nitro-2-{2-[4-(trifluoromethyl)phenyl]ethoxy}pyridine (1.0 g, 3.15 mmol, 1.0 equiv.) was dissolved in THF (20 mL) and cooled to -60 °C, then bromo(ethenyl)magnesium (1M in THF, 70.0 mL, 70.0 mmol, 22 equiv.) was added dropwise, maintaining the solution at -60 °C under an atmosphere of nitrogen. The reaction mixture was stirred for 8 hours at ambient temperature and then quenched by the addition of saturated aqueous NH_4Cl . The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:2) to give 7-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-b]pyridine (380.0 mg) as a yellow solid. LCMS Method A: $[M+H]^+ = 321$.

Step 3: 2,2,2-trichloro-1-(7-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-b]pyridin-3-yl)ethanone

7-Methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-b]pyridine (500.0 mg, 1.6 mmol, 1 equiv.) and Pyridine (246.9 mg, 3.1 mmol, 2.0 equiv.) were dissolved in CHCl_3 (20 mL), then trichloroacetyl chloride (851.4 mg, 4.7 mmol, 3.0 equiv.) was added dropwise. The reaction mixture was heated to 65 °C for 2 days, then concentrated vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 5% to 100% gradient in 10 min; detector, UV 254 nm. This gave 2,2,2-trichloro-1-(7-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-b]pyridin-3-yl)ethanone (130.0 mg) as a yellow solid. LCMS Method A: $[M+H]^+ = 465$.

Step 4: 7-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-b]pyridine-3-carboxylic acid

2,2,2-Trichloro-1-(7-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-b]pyridin-3-yl)ethanone (220.0 mg, 0.5 mmol, 1.0 equiv.) was dissolved in THF (15 mL) and water (3 mL), then NaOH (37.8 mg, 0.9 mmol, 2.0 equiv.) was added. The reaction mixture was heated to 65 °C for 1 hour, then cooled to ambient temperature and concentrated under vacuum. The residue was diluted with water and then adjusted to pH 5 with aqueous HCl (4M). The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give 7-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-b]pyridine-3-carboxylic acid (150.0 mg) as a yellow solid. LCMS Method B: [M-H]⁻ = 363.

Step 5: 7-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-b]pyridine-3-carbonyl azide

7-Methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-b]pyridine-3-carboxylic acid (150.0 mg, 0.4 mmol, 1.0 equiv.) was dissolved in THF (15 mL), then TEA (0.1 mL, 0.8 mmol, 2.0 equiv.) and DPPA (226.6 mg, 0.8 mmol, 2.0 equiv.) were added. The reaction mixture was stirred for 6 hours at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give 7-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-b]pyridine-3-carbonyl azide (150.0 mg) as a yellow solid. LCMS Method A: [M+H]⁺ = 390.

Step 6: *tert*-butyl *N*-(7-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-b]pyridin-3-yl)carbamate

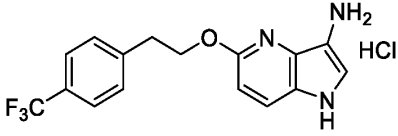
7-Methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-b]pyridine-3-carbonyl azide (150.0 mg, 0.4 mmol, 1.0 equiv.) was dissolved in toluene (3 mL), then *t*-BuOH (142.8 mg, 1.9 mmol, 5 equiv.) was added. The reaction mixture was heated to 100 °C overnight, then cooled to ambient temperature and concentrated under vacuum.

The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 5% to 100% gradient in 10 min; detector, UV 254 nm. This gave *tert*-butyl *N*-(7-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)carbamate (50.0 mg) as a yellow solid. LCMS Method A: $[M+H]^+ = 436$.

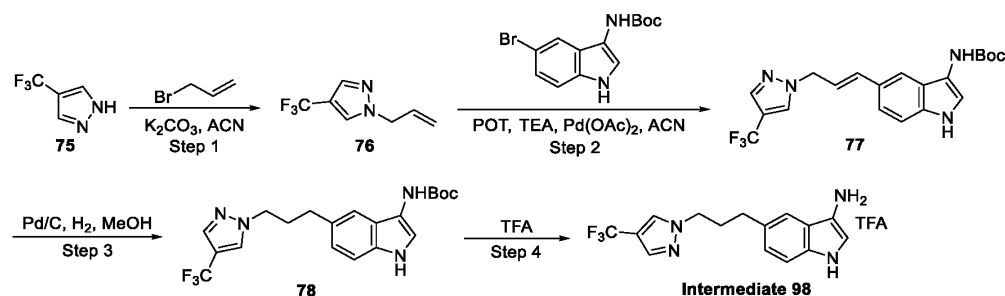
Step 7: 7-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-*b*]pyridin-3-amine TFA salt

tert-Butyl *N*-(7-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl) carbamate (50.0 mg, 0.1 mmol, 1.0 equiv.) was dissolved in DCM (2 mL) and TFA (0.5 mL). The reaction mixture was stirred for 50 min at ambient temperature and then concentrated under vacuum to give crude 7-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1*H*-pyrrolo[3,2-*b*]pyridin-3-amine TFA salt (35.0 mg) as a light yellow solid. LCMS Method A: $[M+H]^+ = 336$.

The intermediates in the following table were prepared using the same method described for **Intermediate 96**.

Intermediate	Structure	LCMS data
Intermediate 97		Method A: MS-ESI: 322 $[M+H]^+$

Scheme 49: Synthesis of intermediate 98 (5-(3-(4-(trifluoromethyl)-1*H*-pyrazol-1-yl)propyl)-1*H*-indol-3-amine TFA salt)



Step 1: 1-(prop-2-en-1-yl)-4-(trifluoromethyl)pyrazole

4-(Trifluoromethyl)-1H-pyrazole (500.0 mg, 3.6 mmol, 1.0 equiv.) and K₂CO₃ (1.0 g, 7.3 mmol, 2.0 equiv.) was dissolved in ACN (10 mL), then allyl bromide (666.7 mg, 5.5 mmol, 1.5 equiv.) was added. The reaction mixture was heated to 100 °C for 2 hours and then cooled to ambient temperature. After removing the solid by filtration, the filtrate was used in the next step directly without further manipulation. LCMS Method A: [M+H]⁺ = 165.

Step 2: *tert*-butyl *N*-{5-[(1E)-3-[4-(trifluoromethyl)pyrazol-1-yl]prop-1-en-1-yl]-1H-indol-3-yl}carbamate

To the above solution of 1-(prop-2-en-1-yl)-4-(trifluoromethyl)pyrazole in ACN (10 mL), *tert*-butyl *N*-(5-bromo-1H-indol-3-yl)carbamate (1.3 g, 4.2 mmol, 1.5 equiv.), TEA (0.8 mL, 5.6 mmol, 2.0 equiv.), POT (172.8 mg, 0.5 mmol, 0.2 equiv.) and Pd(OAc)₂ (127.4 mg, 0.5 mmol, 0.2 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 100 °C for 5 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give *tert*-butyl *N*-{5-[(1E)-3-[4-(trifluoromethyl)pyrazol-1-yl]prop-1-en-1-yl]-1H-indol-3-yl}carbamate (370.0 mg) as a brown oil. LCMS Method A: [M+H]⁺ = 407.

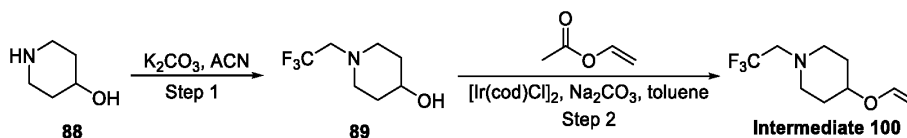
Step 3: *tert*-butyl *N*-(5-{3-[4-(trifluoromethyl)pyrazol-1-yl]propyl}-1H-indol-3-yl)carbamate

tert-Butyl *N*-{5-[(1*E*)-3-[4-(trifluoromethyl)pyrazol-1-yl]prop-1-en-1-yl]-1*H*-indol-3-yl}carbamate (300 mg, 0.7 mmol, 1.0 equiv.) was dissolved in MeOH (10 mL), placed under an atmosphere of nitrogen, then Pd/C (10% wt., 60.0 mg) was added. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 2 hours at ambient temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum to give *tert*-butyl *N*-(5-{3-[4-(trifluoromethyl)pyrazol-1-yl]propyl}-1*H*-indol-3-yl)carbamate (250.0 mg) as a yellow solid. LCMS Method A: $[M+H]^+ = 409$.

Step 4: 5-{3-[4-(trifluoromethyl)pyrazol-1-yl]propyl}-1*H*-indol-3-amine TFA salt

tert-Butyl *N*-(5-{3-[4-(trifluoromethyl)pyrazol-1-yl]propyl}-1*H*-indol-3-yl)carbamate (210.0 mg, 0.5 mmol, 1 equiv.) was dissolved in DCM (15 mL) and TFA (5 mL). The reaction mixture was stirred for 1 hour at ambient temperature and then concentrated under vacuum. This gave 5-{3-[4-(trifluoromethyl)pyrazol-1-yl]propyl}-1*H*-indol-3-amine TFA salt (150.0 mg) as a brown solid. LCMS Method A: $[M+H]^+ = 309$.

Scheme 50: Synthesis of intermediate 100 (1-(2,2,2-trifluoroethyl)-4-(vinylloxy)piperidine)



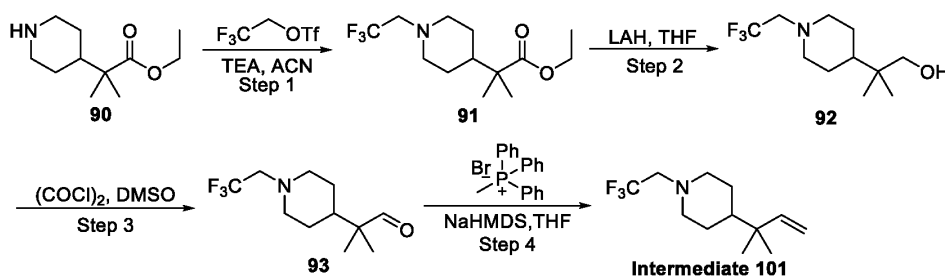
Step 1: 1-(2,2,2-trifluoroethyl)piperidin-4-ol

Piperidin-4-ol (1.0 g, 9.9 mmol, 1.0 equiv.) was dissolved in ACN (6 mL), then K_2CO_3 (2.7 g, 19.8 mmol, 2.0 equiv.) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (2.8 g, 11.9 mmol, 1.2 equiv.) were added. The reaction mixture was heated to 70 °C for 4 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to give 1-(2,2,2-trifluoroethyl)piperidin-4-ol (1.5 g) as a colorless oil. LCMS Method A: $[M+H]^+ = 184$.

Step 2: 4-(ethenyloxy)-1-(2,2,2-trifluoroethyl)piperidine

1-(2,2,2-Trifluoroethyl)piperidin-4-ol (1.0 g, 5. mmol, 1.0 equiv.) was dissolved in toluene (5 mL), then vinyl acetate (0.9 g, 10.9 mmol, 2.0 equiv.), Na₂CO₃ (1.2 g, 10.9 mmol, 2.0 equiv.) and [Ir(cod)Cl]₂ (0.4 g, 0.5 mmol, 0.1 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 100 °C overnight, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:6) to give 4-(ethenyloxy)-1-(2,2,2-trifluoroethyl)piperidine (500.0 mg) as a pale yello oil. LCMS Method A: [M+H]⁺ = 210.

Scheme 51: Synthesis of intermediate 101 (4-(2-methylbut-3-en-2-yl)-1-(2,2,2-trifluoroethyl)piperidine)

**Step 1: ethyl 2-methyl-2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]propanoate**

Ethyl 2-methyl-2-(piperidin-4-yl)propanoate (2.0 g, 10.0 mmol, 1.0 equiv.) was dissolved in ACN (30 mL), then TEA (2.8 mL, 20.1 mmol, 2.0 equiv.) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (2.8 g, 12.0 mmol, 1.2 equiv.) were added. The reaction mixture was heated to 80 °C for 4 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give ethyl 2-methyl-2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]propanoate (2.3 g) as a colorless oil. LCMS Method A: [M+H]⁺ = 282.

Step 2: 2-methyl-2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]propan-1-ol

Ethyl 2-methyl-2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]propanoate (2.3 g, 8.2 mmol, 1.0 equiv.) was dissolved in THF (30 mL) and cooled to 0 °C, then LiAlH₄ (0.9 g, 24.5 mmol, 3.0 equiv.) was added, maintaining the solution at 0 °C. The reaction mixture was stirred for 6 hours at ambient temperature and then quenched by the addition of MeOH. The resulting mixture was concentrated under vacuum and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:4) to give 2-methyl-2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]propan-1-ol (1.1 g) as a yellow oil. LCMS Method A: [M+H]⁺ = 240.

Step 3: 2-methyl-2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]propanal

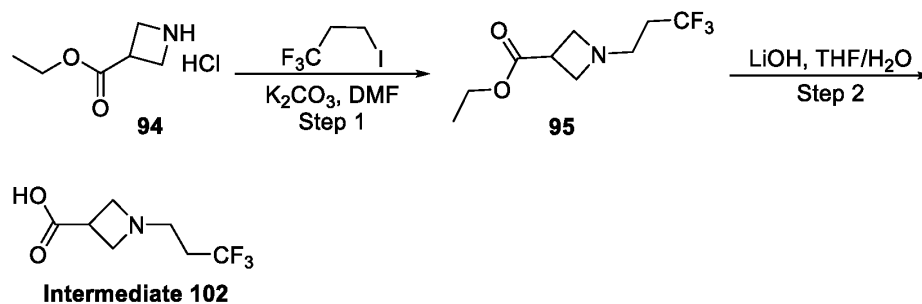
Oxalyl chloride (1.0 mL, 11.5 mmol, 2.5 equiv.) was dissolved in DCM (30 mL) and cooled to -70 °C, then DMSO (1.6 mL, 23.0 mmol, 5.0 equiv.) was added dropwise, maintaining the solution at -70 °C. After 30 min at -70 °C, a solution of 2-methyl-2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]propan-1-ol (1.1 g, 4.6 mmol, 1.0 equiv.) in DCM (10 mL) was added dropwise. The reaction mixture was stirred for an additional 4 hours at -70 °C. This was followed by the addition of TEA (6.4 mL, 46.0 mmol, 10.0 equiv.). The reaction mixture was allowed to warm to ambient temperature and stir for 1 hour, then concentrated under vacuum. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give 2-methyl-2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]propanal (510.0 mg) as a pale yellow oil. LCMS Method A: [M+H]⁺ = 238.

Step 4: 4-(2-methylbut-3-en-2-yl)-1-(2,2,2-trifluoroethyl)piperidine

Methyltriphenylphosphonium bromide (2.3 g, 6.4 mmol, 3.0 equiv.) was dissolved in THF (25 mL), then NaHMDS (1.2 g, 6.4 mmol, 3.0 equiv.) was added. After 30 min, 2-methyl-2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]propanal (510.0 mg, 2.1 mmol, 1.0 equiv.) was added. The reaction mixture was stirred for 4 hours at ambient temperature, then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give 4-(2-methylbut-3-en-2-

yl)-1-(2,2,2-trifluoroethyl)piperidine (310.0 mg) as a colorless oil. LCMS Method A: $[M+H]^+ = 236$.

Scheme 52: Synthesis of intermediate 102 (1-(3,3,3-trifluoropropyl)azetidine-3-carboxylic acid)



Step 1: ethyl 1-(3,3,3-trifluoropropyl)azetidine-3-carboxylate

Ethyl azetidine-3-carboxylate hydrochloride (2.6 g, 15.5 mmol, 1.0 equiv.) and 1,1,1-trifluoro-3-iodopropane (2.9 g, 13.3 mmol, 0.9 equiv.) were dissolved in ACN (10 mL), then K_2CO_3 (5.0 g, 36.4 mmol, 2.3 equiv.) was added. The reaction mixture was heated to 80 °C for 4 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to give ethyl 1-(3,3,3-trifluoropropyl)azetidine-3-carboxylate (1.8 g) as a yellow oil. LCMS Method A: $[M+H]^+ = 226$.

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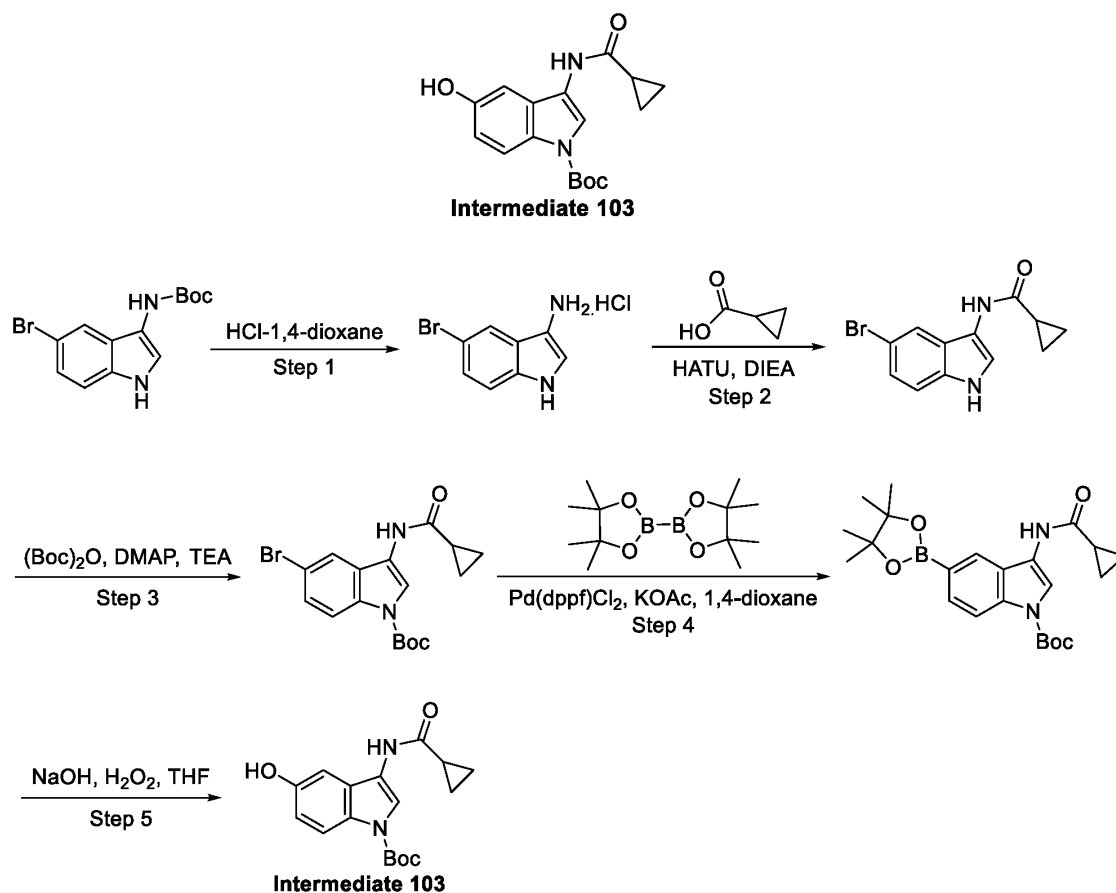
Step 2: 1-(3,3,3-trifluoropropyl)azetidine-3-carboxylic acid

Ethyl 1-(3,3,3-trifluoropropyl)azetidine-3-carboxylate (1.0 g, 4.4 mmol, 1.0 equiv.) was dissolved in THF/ H_2O (10/1 mL), LiOH (0.3 g, 13.4 mmol, 3.0 equiv.) was added. The reaction mixture was stirred for 6 hours at ambient temperature and concentrated under vacuum. The residue was diluted with water, then adjusted to pH 4 with aqueous HCl (6M). The resulting solution was extracted with DCM and concentrated under vacuum to give crude 1-(3,3,3-trifluoropropyl)azetidine-3-carboxylic acid (1.2 g) as a yellow oil. LCMS Method A: $[M-H]^- = 196$.

15

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Scheme 53: Synthesis of intermediate 103 (tert-butyl 3-(cyclopropane carboxamido)-5-hydroxy-1H-indole-1-carboxylate)



Step 1: 5-bromo-1H-indol-3-amine hydrochloride

tert-Butyl (5-bromo-1H-indol-3-yl)carbamate (20.0 g, 64.2 mmol, 1.0 equiv.) was dissolved in HCl/1,4-dioxane (4 M, 150 mL). The reaction mixture was stirred for 2 hours at rt and then concentrated under vacuum to give 5-bromo-1H-indol-3-amine hydrochloride (18.7 g) as a brown solid. LCMS Method A: $[M+H]^+ = 211.2$.

Step 2: N-(5-bromo-1H-indol-3-yl)cyclopropanecarboxamide

Cyclopropanecarboxylic acid (172.0 mg, 2.0 mmol, 1.0 equiv.) was dissolved in DCM (20 mL), then DIEA (1.0 mL, 6.0 mmol, 3.0 equiv.), HATU (1.1 g, 3.0 mmol, 1.5 equiv.) and 5-bromo-1*H*-indol-3-amine hydrogen chloride (500.0 mg, 2.0 mmol, 1.0 equiv.) were added. The reaction mixture was stirred for 2 hours at rt and then quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/petroleum ether (1:1) to give *N*-(5-bromo-1*H*-indol-3-yl)cyclopropanecarboxamide (510.0 mg) as a white solid. LCMS Method A: [M+H]⁺ = 279.2.

Step 3: *tert*-butyl 5-bromo-3-(cyclopropanecarboxamido)-1*H*-indole-1-carboxylate

N-(5-bromo-1*H*-indol-3-yl)cyclopropanecarboxamide (200.0 mg, 0.7 mmol, 1.0 equiv.) and (Boc)₂O (156.3 mg, 0.7 mmol, 1.0 equiv.) were dissolved in THF (10 mL), then DMAP (8.7 mg, 0.07 mmol, 0.1 equiv.) and TEA (0.2 mL, 1.4 mmol, 2.0 equiv.) were added. The reaction mixture was stirred overnight at rt and then concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in Water (10mmol/L NH₄HCO₃), 30% to 90% gradient in 30 min; detector, UV 254 nm. This resulted in *tert*-butyl 5-bromo-3-(cyclopropanecarboxamido)-1*H*-indole-1-carboxylate (106.0 mg) as a brown yellow oil. LCMS Method A: [M+H]⁺ = 379.2.

Step 4: *tert*-butyl 3-(cyclopropanecarboxamido)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-1-carboxylate

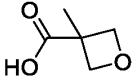
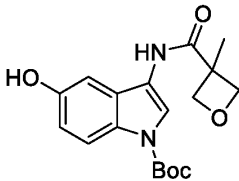
tert-Butyl 5-bromo-3-cyclopropaneamidoindole-1-carboxylate (200.0 mg, 0.5 mmol, 1.0 equiv.) and bis(pinacolato)diboron (200.9 mg, 0.8 mmol, 1.5 equiv.) were dissolved in 1,4-dioxane (10 mL), then Pd(dppf)Cl₂ (38.6 mg, 0.05 mmol, 0.1 equiv.) and KOAc (103.5 mg, 1.05 mmol, 2.0 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred overnight at 90 °C, then cooled to rt and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/petroleum ether (1:7) to give *tert*-butyl 3-(cyclopropanecarboxamido)-5-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-1-carboxylate (186.0 mg) as a brown solid. LCMS Method A: $[M+H]^+ = 427.2$.

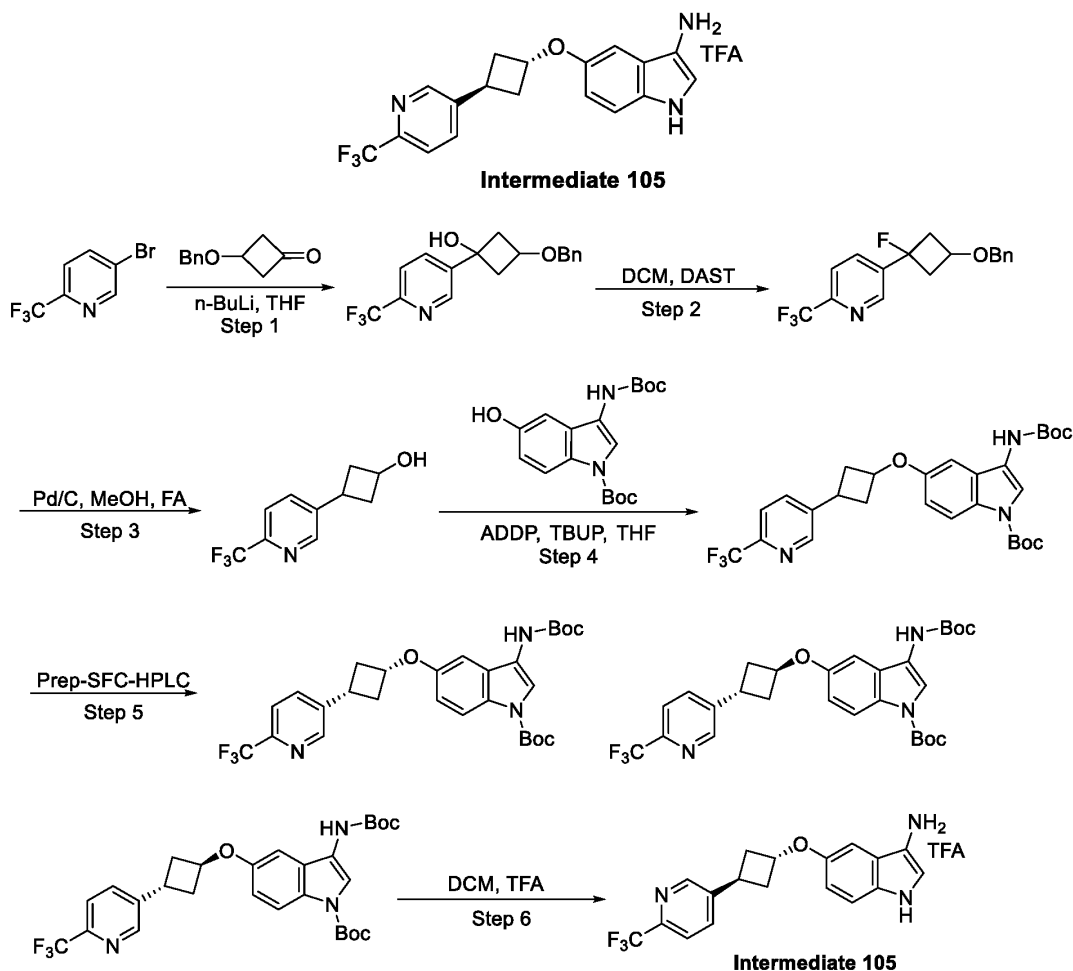
Step 5: *tert*-butyl 3-(cyclopropanecarboxamido)-5-hydroxy-1*H*-indole-1-carboxylate

5 *tert*-Butyl 3-(cyclopropanecarboxamido)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-1-carboxylate (500.0 mg, 1.2 mmol, 1.0 equiv.) was dissolved in THF (15 mL) and cooled to 0 ° C, then a solution of NaOH in water (30% wt./wt., 4.0 mL, 3.5 mmol, 2.0 equiv.) was added. This was followed by the addition of H₂O₂ (30% wt./wt. in water, 0.3 mL, 2.4 mmol, 2.0 equiv.) dropwise at 0 °C. The reaction mixture was stirred
10 overnight at rt and then concentrated under vacuum. The residue was diluted with water, extracted with EtOAc, washed with brine and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (20:1) to give *tert*-butyl 3-(cyclopropanecarboxamido)-5-hydroxy-1*H*-indole-1-carboxylate (161.0 mg) as a yellow solid. LCMS Method A: $[M+H]^+$
15 = 317.2.

The intermediates in the following table were prepared using the same method described for Intermediates 103.

Intermediate	Starting material	Structure	LCMS data
Intermediate 104			Method A: MS-ESI: 292.0 $[M+H]^+$

20 **Scheme 54: Synthesis of intermediate 105 (5-(*trans*-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1*H*-indol-3-amine TFA salt)**



Step 1: 3-(benzyloxy)-1-(6-(trifluoromethyl)pyridin-3-yl)cyclobutan-1-ol

5-Bromo-2-(trifluoromethyl)pyridine (4.0 g, 17.6 mmol, 1.0 equiv.) was dissolved in THF (40 mL) and cooled to -70 °C, then n-BuLi (2.5M in hexane, 8.5 mL, 21.3 mmol, 1.2 equiv.) added dropwise, maintaining the solution at -70 °C under an atmosphere of nitrogen. After stirred for 30 min at -70 °C, 3-(benzyloxy)cyclobutan-1-one (3.7 g, 21.2 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred for additional 2 hours at rt and then quenched by the addition of saturated aqueous NH₄Cl. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by reverse flash column with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.5%

NH₄HCO₃), 10% to 100% gradient in 25 min; detector, UV 254 nm. This resulted in 3-(benzyloxy)-1-(6-(trifluoromethyl)pyridin-3-yl)cyclobutan-1-ol (2.7 g) as a pale yellow solid. LCMS Method A: [M+H]⁺ = 324.2.

Step 2: 5-(3-(benzyloxy)-1-fluorocyclobutyl)-2-(trifluoromethyl)pyridine

5 3-(Benzyloxy)-1-(6-(trifluoromethyl)pyridin-3-yl)cyclobutan-1-ol (2.7 g, 8.3 mmol, 1.0 equiv.) was dissolved in DCM (10 mL) and cooled to -70 °C, then DAST (2.6 g, 16.6 mmol, 2.0 equiv.) was added dropwise, maintaining the solution at -70 °C under an atmosphere of nitrogen. The reaction mixture was stirred for 2 hours at rt and then quenched by the addition of water. The resulting solution was extracted with EtOAc, 10 washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by reverse flash column with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% NH₄HCO₃), 10% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in 5-(3-(benzyloxy)-1-fluorocyclobutyl)-2-(trifluoromethyl)pyridine (2.5 g) as a pale yellow solid. LCMS Method A: [M+H]⁺ = 326.0

15 **Step 3: 3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutan-1-ol**

5-[3-(Benzyloxy)-1-fluorocyclobutyl]-2-(trifluoromethyl)pyridine (2.0 g, 6.1 mmol, 1.0 equiv.) was dissolved in MeOH (40 ml), then HCOOH (282.9 mg, 6.1 mmol, 1.0 equiv.) was added. This was followed by the addition of Pd/C (10% wt., 130.8 mg) under an atmosphere of nitrogen. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 4 hours at 40 °C. The solids were 20 removed by filtration and the filter cake was washed with MeOH. The combined filtrate was concentrated under vacuum. The residue was purified by reverse flash column with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% NH₄HCO₃), 10% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in 3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutan-1-ol (1.0 g) as a pale yellow oil. LCMS Method 25 A: [M+H]⁺ = 261.0.

Step 4: *tert*-butyl 3-((*tert*-butoxycarbonyl)amino)-5-(*trans*-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1*H*-indole-1-carboxylate and *tert*-butyl

3-((tert-butoxycarbonyl)amino)-5-(cis-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1H-indole-1-carboxylate

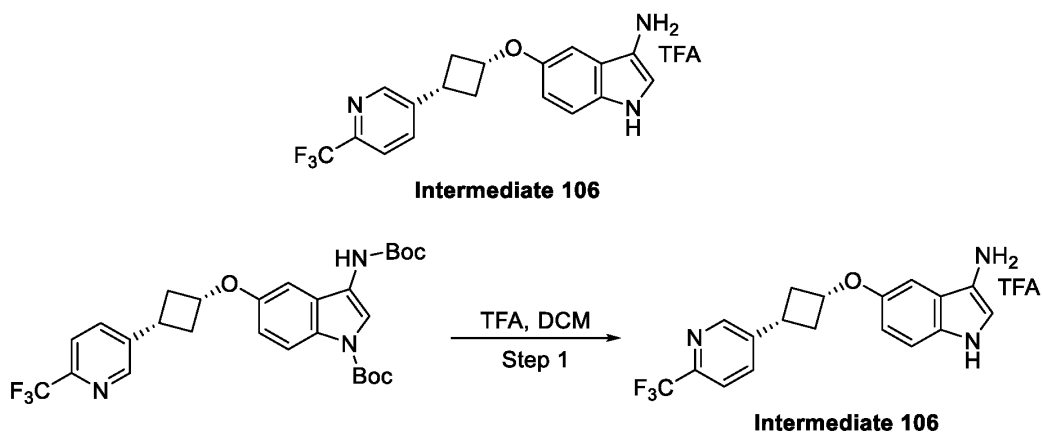
3-[6-(Trifluoromethyl)pyridin-3-yl]cyclobutan-1-ol (1.0 g, 4.6 mmol, 1.0 equiv.) was dissolved in THF (13 mL), then *tert*-butyl 3-[(*tert*-butoxycarbonyl)amino]-5-hydroxyindole-1-carboxylate (1.6 g, 4.6 mmol, 1.0 equiv.), TBUP (1.8 g, 9.2 mmol, 2.0 equiv.) and ADDP (2.3 g, 9.2 mmol, 2.0 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred for 5 hours at 70 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% NH₄HCO₃), 10% to 100% gradient in 25 min; detector, UV 254 nm. This resulted in *tert*-butyl 3-[(*tert*-butoxycarbonyl)amino]-5-(3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1H-indole-1-carboxylate (1.0 g) as a pale yellow solid. The mixture was separated by Chiral-HPLC with the following conditions: Column: JW-CHIRAL-Amylose-SA, 20*250mm, 5um; Mobile Phase A: IPA-HPLC, Mobile Phase B: Hex (0.5% 2M NH₃-MeOH)--HPLC; Flow rate: 20 mL/min; Gradient: 90% B to 90% B in 14 min; Wave Length: 220/254 nm; RT1: 8.2 min; RT2: 10.22 min. This resulted in *tert*-butyl 3-[(*tert*-butoxycarbonyl)amino]-5-(cis-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1H-indole-1-carboxylate (710.0 mg) as a pale yellow solid. LCMS Method B: [M-H]⁺ = 548. And *tert*-butyl 3-[(*tert*-butoxycarbonyl)amino]-5-(trans-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1H-indole-1-carboxylate (170.0 mg) as a pale yellow solid. LCMS Method B: [M-H]⁺ = 548.1.

Step 5: 5-(trans-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1H-indol-3-amine TFA salt

tert-Butyl 3-[(*tert*-butoxycarbonyl)amino]-5-[trans-3-[6-(trifluoromethyl)pyridin-3-yl]cyclobutoxy]indole-1-carboxylate (160.0 mg, 0.2 mmol, 1.0 equiv.) was dissolved in DCM (2 mL), then TFA (2 mL) was added. The reaction mixture was stirred for 1 hours at rt and then concentrated under vacuum to give crude 5-(trans-3-(6-

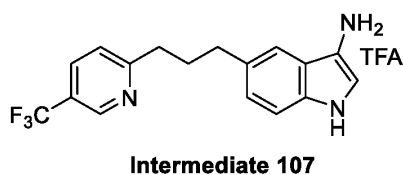
(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1*H*-indol-3-amine TFA salt (103.0 mg) as a red solid. LCMS Method B: $[M+H]^+ = 348.2$.

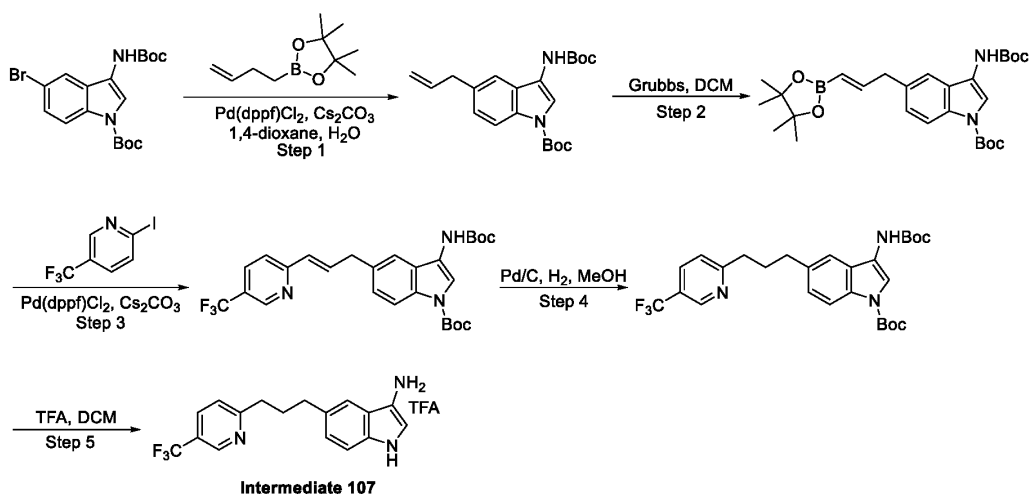
Scheme 55: Synthesis of intermediate 106 (5-(*cis*-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1*H*-indol-3-amine TFA salt)



10 *tert*-Butyl 3-[(*tert*-butoxycarbonyl)amino]-5-[*cis*-3-[6-(trifluoromethyl)pyridin-3-yl]cyclobutoxy]indole-1-carboxylate (500.0 mg, 0.9 mmol, 1.0 equiv.) was dissolved in DCM (3 mL), then TFA (3 mL) was added. The reaction mixture was stirred for 1 hour at rt and then concentrated under vacuum to give crude 5-(*trans*-3-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)-1*H*-indol-3-amine TFA salt (400.0 mg) as a brown solid. LCMS Method B: $[M+H]^+ = 348.2$

Scheme 56: Synthesis of intermediate 107 (5-(3-(5-(trifluoromethyl)pyridin-2-yl)propyl)-1*H*-indol-3-amine TFA salt)





Step 1: *tert*-butyl 5-allyl-3-((*tert*-butoxycarbonyl) amino)-1*H*-indole-1-carboxylate

tert-Butyl 5-bromo-3-((*tert*-butoxycarbonyl) amino)-1*H*-indole-1-carboxylate (4.0 g, 9.7 mmol, 1.0 equiv.), 2-(but-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3 g, 19.5 mmol, 2.0 equiv.) were dissolved in 1,4-dioxane (120 mL) and H₂O (12 mL), then Cs₂CO₃ (6.3 g, 19.5 mmol, 2.0 equiv.) and Pd(dppf)Cl₂ (0.7 g, 1.0 mmol, 0.1 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred for 4 hours at 90 °C, then cooled to rt and concentrated under vacuum. The residue was diluted with water, extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (5:1) to give *tert*-butyl 5-allyl-3-((*tert*-butoxycarbonyl) amino)-1*H*-indole-1-carboxylate (3.3 g) as a white solid. LCMS Method A: [M+H]⁺ = 373.2.

Step 2: *tert*-butyl (E)-3-((*tert*-butoxycarbonyl) amino)-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) allyl)-1*H*-indole-1-carboxylate

tert-Butyl 5-allyl-3-((*tert*-butoxycarbonyl) amino)-1*H*-indole-1-carboxylate (1.8 g, 4.8 mmol, 1.0 equiv.) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (2.2 g, 14.5 mmol, 3.0 equiv.) were dissolved in DCM (10 mL), then Grubbs 2nd (410.2 mg, 0.5 mmol, 0.1 equiv.) was added under an atmosphere of nitrogen. The reaction mixture was stirred

for 3 days at 50 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (1:1) to give *tert*-butyl (E)-3-((*tert*-butoxycarbonyl) amino)-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) allyl)-1*H*-indole-1-carboxylate (900 mg) as a yellow solid. LCMS Method A: [M+H]⁺ = 499.2.

Step 3: *tert*-butyl (E)-3-((*tert*-butoxycarbonyl) amino)-5-(3-(5-(trifluoromethyl) pyridin-2-yl) allyl)-1*H*-indole-1-carboxylate

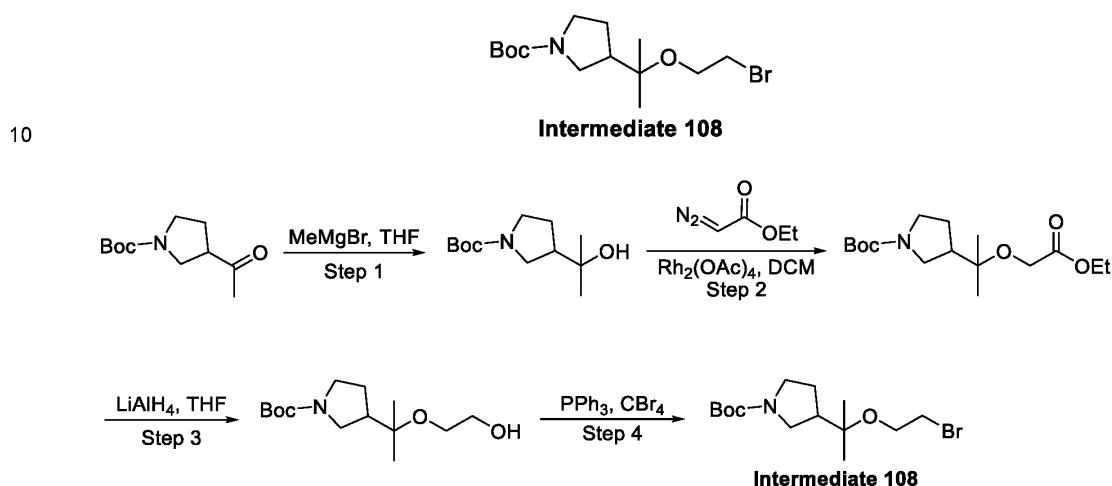
tert-Butyl (E)-3-((*tert*-butoxycarbonyl) amino)-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) allyl)-1*H*-indole-1-carboxylate (900.0 mg, 1.8 mmol, 1.0 equiv.) and 2-iodo-5-(trifluoromethyl) pyridine (985.8 mg, 3.6 mmol, 2.0 equiv.) were dissolved in 1,4-dioxane (10 mL) and H₂O (1 mL), then Pd(dppf)Cl₂ (264.2 mg, 0.4 mmol, 0.2 equiv.) and Cs₂CO₃ (1.8 g, 5.4 mmol, 3.0 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred overnight at 90 °C, then cooled to rt and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (3:1) to give *tert*-butyl (E)-3-((*tert*-butoxycarbonyl) amino)-5-(3-(5-(trifluoromethyl) pyridin-2-yl) allyl)-1*H*-indole-1-carboxylate (450.0 mg) as a pale yellow solid. LCMS Method A: [M+H]⁺ = 518.2.

Step 4: *tert*-butyl 3-((*tert*-butoxycarbonyl) amino)-5-(3-(5-(trifluoromethyl) pyridin-2-yl) propyl)-1*H*-indole-1-carboxylate

tert-Butyl (E)-3-((*tert*-butoxycarbonyl) amino)-5-(3-(5-(trifluoromethyl) pyridin-2-yl) allyl)-1*H*-indole-1-carboxylate (100.0 mg, 0.2 mmol, 1.0 equiv.) was dissolved in MeOH (10 mL), then Pd/C (10% wt, 10 mg) was added under an atmosphere of nitrogen. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 2 hours at rt. The solids were removed by filtration and the filtrate was concentrated under vacuum to give *tert*-butyl 3-((*tert*-butoxycarbonyl) amino)-5-(3-(5-(trifluoromethyl) pyridin-2-yl) propyl)-1*H*-indole-1-carboxylate (60.0 mg) as a white solid. LCMS Method A: [M+H]⁺ = 520.2.

Step 5: 5-(3-(5-(trifluoromethyl) pyridin-2-yl) propyl)-1*H*-indol-3-amine TFA salt

tert-Butyl 3-((*tert*-butoxycarbonyl) amino)-5-(3-(5-(trifluoromethyl) pyridin-2-yl) propyl)-1*H*-indole-1-carboxylate (60.0 mg, 0.1 mmol, 1.0 equiv.) was dissolved in DCM (2 mL), then TFA (0.4 mL) was added. The reaction mixture was stirred for 1 hour at rt and concentrated under vacuum to give crude 5-(3-(5-(trifluoromethyl) pyridin-2-yl) propyl)-1*H*-indol-3-amine TFA salt (65.0 mg) as a yellow oil, that was used in the next step directly without further purification. LCMS Method B: $[M+H]^+ = 320.2$.

Scheme 57: Synthesis of intermediate 108 (*tert*-butyl 3-(2-(2-bromoethoxy)propan-2-yl)pyrrolidine-1-carboxylate)**Step 1: *tert*-butyl 3-acetylpyrrolidine-1-carboxylate**

tert-Butyl 3-acetylpyrrolidine-1-carboxylate (2.0 g, 9.4 mmol, 1.0 equiv.) was dissolved in THF (20 mL) and cooled to -10 ° C, then MeMgBr (3M in THF, 6.3 mL, 18.9 mmol, 2.0 equiv.) was added dropwise, maintaining the solution at -10 ° C under an atmosphere of nitrogen. The reaction mixture was stirred for 2 hours at 0 °C, then quenched by the addition of ice-water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/petroleum

ether (5:1) to give *tert*-butyl 3-(2-hydroxypropan-2-yl) pyrrolidine-1-carboxylate (1.5 g) as a yellow oil. LCMS Method C: $[M+H]^+ = 230.1$.

Step 2: *tert*-butyl 3-(2-hydroxypropan-2-yl) pyrrolidine-1-carboxylate

tert-Butyl 3-(2-hydroxypropan-2-yl) pyrrolidine-1-carboxylate (1.3 g, 5.7 mmol, 1.0 equiv.) was dissolved in DCM (15 mL) and cooled to 0 °C, then ethyl diazoacetate (1.3 g, 11.3 mmol, 2.0 equiv.) and $Rh_2(OAc)_4$ (0.3 g, 0.6 mmol, 0.1 equiv.) were added, maintaining the solution at 0 °C under an atmosphere of nitrogen. The reaction mixture was stirred overnight at 0 °C and then quenched by the addition of ice-water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (5:1) to give *tert*-butyl 3-[2-(2-ethoxy-2-oxoethoxy) propan-2-yl] pyrrolidine-1-carboxylate (1.3 g) as a yellow oil. LCMS Method A: $[M+H]^+ = 316.2$

Step 3: *tert*-butyl 3-(2-(2-ethoxy-2-oxoethoxy) propan-2-yl) pyrrolidine-1-carboxylate

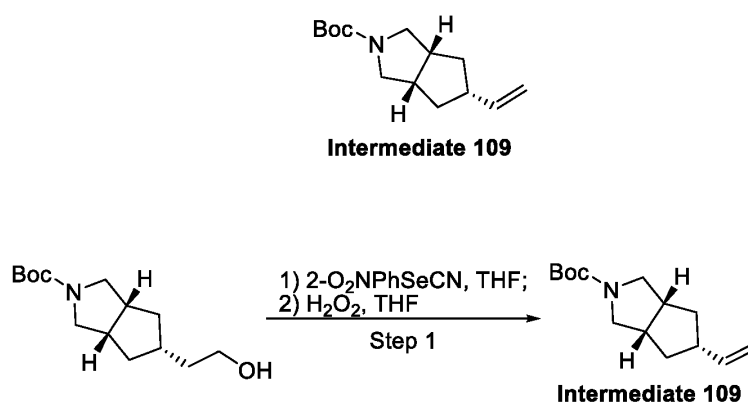
tert-Butyl 3-[2-(2-ethoxy-2-oxoethoxy) propan-2-yl] pyrrolidine-1-carboxylate (1.0 g, 3.2 mmol, 1.0 equiv.) was dissolved in THF (10 mL) and cooled to 0 °C, then $LiAlH_4$ (0.2 g, 4.8 mmol, 1.5 equiv.) was added in portions. The reaction mixture was stirred for 2 hours at rt and then quenched by the addition of ice-water at 0 °C. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na_2SO_4 and concentrated under vacuum to give *tert*-butyl 3-[2-(2-hydroxyethoxy) propan-2-yl] pyrrolidine-1-carboxylate (0.7 g) as a yellow oil. LCMS Method A: $[M+H]^+ = 274.2$.

Step 4: *tert*-butyl 3-(2-(2-hydroxyethoxy) propan-2-yl) pyrrolidine-1-carboxylate

tert-Butyl 3-[2-(2-hydroxyethoxy) propan-2-yl] pyrrolidine-1-carboxylate (1.2 g, 4.4 mmol, 1.0 equiv.) was dissolved in THF (20 mL) and cooled to 0 °C, then PPh_3 (1.7 g, 6.6 mmol, 1.5 equiv.) and CBr_4 (2.2 g, 6.6 mmol, 1.5 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred for 2 hours at 0 °C and then quenched by the

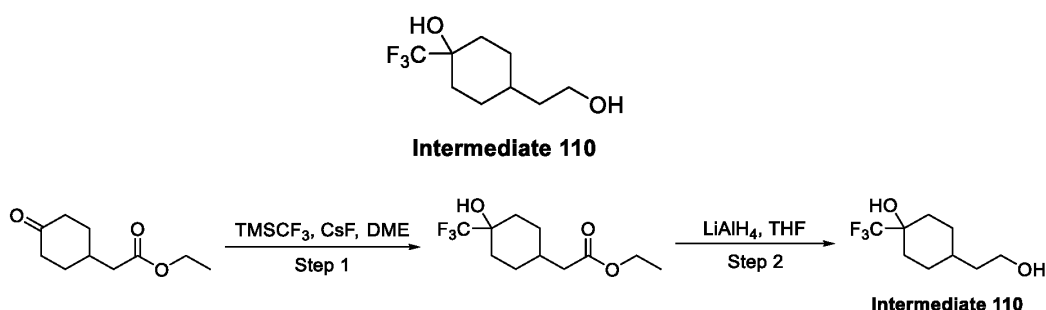
addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na_2SO_4 and concentrated under vacuum, reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (10:1) to give *tert*-butyl 3-[2-(2-bromoethoxy) propan-2-yl] pyrrolidine-1-carboxylate (0.8 g) as a yellow oil. LCMS Method C: $[\text{M}+\text{H}]^+ = 336.2$.

Scheme 58: Synthesis of intermediate 109 (*tert*-butyl (3aR,5r,6aS)-5-vinylhexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate)



tert-Butyl (3aR,5r,6aS)-5-(2-hydroxyethyl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (2.0 g, 7.8 mmol, 1.0 equiv.) and 1-nitro-2-selenocyanatobenzene (2.3 g, 10.2 mmol, 1.3 equiv.) were dissolved in THF (40 mL) and cooled to 0 °C, then TBUP (2.1 g, 10.2 mmol, 1.3 equiv.) was added under an atmosphere of nitrogen. The reaction mixture was stirred for 16 hours at rt and then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (2:1) to give intermediate product as a brown oil. Then the intermediate product was dissolved in THF (30 mL), H_2O_2 (30% wt., 6 mL) was added dropwise at 0°C. The resulting mixture was stirred for 2 hours at rt and then quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (20:1) to give *tert*-butyl (3aR,5r,6aS)-5-vinylhexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (430.0 mg) as a yellow oil. LCMS Method A: $[\text{M}+\text{H}]^+ = 238.0$.

Scheme 59: Synthesis of intermediate 110 (4-(2-hydroxyethyl)-1-(trifluoromethyl)cyclohexan-1-ol)



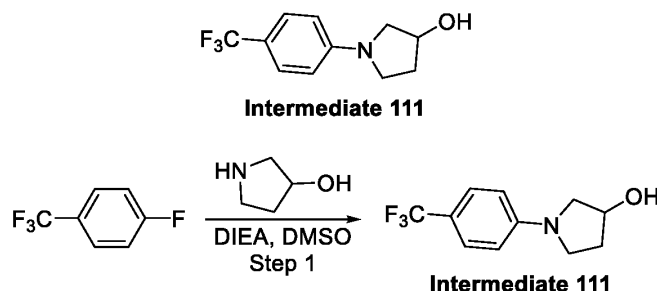
Step 1: ethyl 2-[4-hydroxy-4-(trifluoromethyl)cyclohexyl]acetate

Ethyl 2-(4-oxocyclohexyl)acetate (500.0 mg, 2.7 mmol, 1.0 equiv.) was dissolved in DME (5.0 mL), then CsF (825.0 mg, 5.4 mmol, 2.0 equiv.) and trifluoromethyltrimethylsilane (772.0 mg, 5.4 mmol, 2.0 equiv.) were added. The reaction mixture was stirred for 5 hours at rt and then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (5:1) to give ethyl 2-[4-hydroxy-4-(trifluoromethyl)cyclohexyl]acetate (200.0 mg) as a colorless oil. LCMS Method A: $[M+H]^+ = 255.1$.

Step 2: 4-(2-hydroxyethyl)-1-(trifluoromethyl)cyclohexan-1-ol

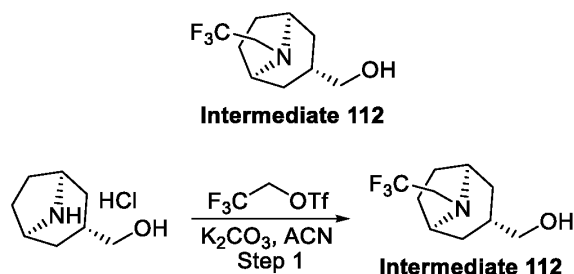
Ethyl 2-[4-hydroxy-4-(trifluoromethyl)cyclohexyl]acetate (200 mg, 0.787 mmol, 1 equiv) was dissolved in THF (4 mL) and cooled to 0 °C, then LiAlH₄ (60.0 mg, 1.6 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 5 hours at 0 °C and then quenched by the addition of ice-water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum to give 4-(2-hydroxyethyl)-1-(trifluoromethyl)cyclohexan-1-ol (170.0 mg) as a colorless oil. LCMS Method A: $[M+H]^+ = 213.2$.

Scheme 60: Synthesis of intermediate 111 (1-(4-(trifluoromethyl)phenyl)pyrrolidin-3-ol)



1-Fluoro-4-(trifluoromethyl)benzene (4.0 g, 24.3 mmol, 1.0 equiv.) was dissolved in DMSO (120 mL), then DIEA (8.0 mL, 48.7 mmol, 2.0 equiv.) and pyrrolidin-3-ol (2.1 g, 24.3 mmol, 1.0 equiv.) were added. The reaction mixture was stirred for 16 hours at 100 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (5:1) to give 1-[4-(trifluoromethyl)phenyl]pyrrolidin-3-ol (1.4 g) as a yellow solid. LCMS Method B: [M+H]⁺ = 232.2.

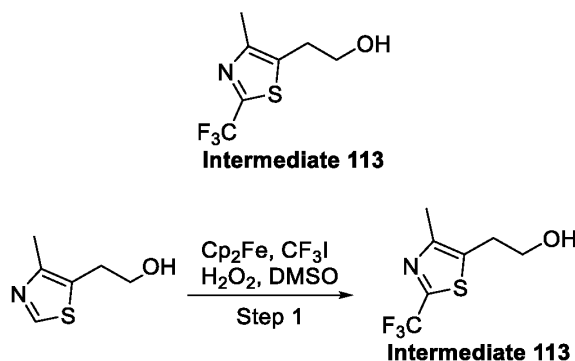
Scheme 61: Synthesis of intermediate 112 (((1R,3s,5S)-8-(2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octan-3-yl)methanol)



((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)methanol hydrochloride (500.0 mg, 2.8 mmol, 1.0 equiv.) was dissolved in ACN (10 mL), then K₂CO₃ (1.2 g, 8.4 mmol, 3.0 equiv.) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (720.0 mg, 3.1 mmol, 1.1 equiv.) were added. The reaction mixture was stirred for 2 hours at 80 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified

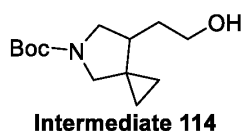
by flash column chromatography on silica gel, eluting with dichloromethane/methanol (99:1) to give [(1R,3R,5S)-8-(2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octan-3-yl]methanol (530.0 mg) as a yellow oil. LCMS Method B: $[M-H]^- = 222.1$.

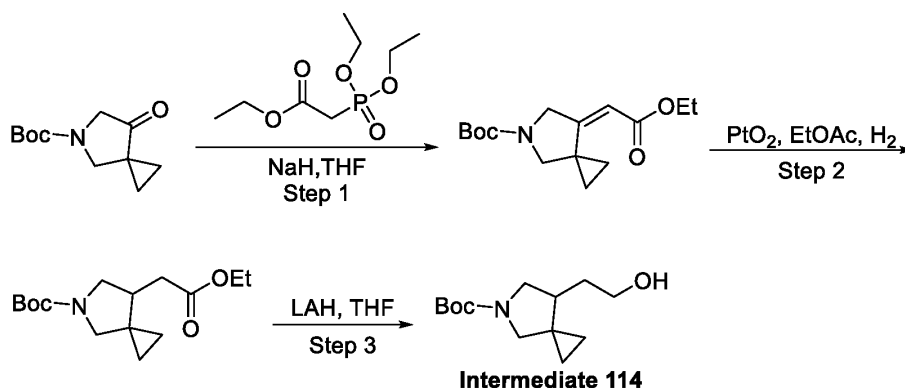
Scheme 62: Synthesis of intermediate 113 (2-(4-methyl-2-(trifluoromethyl)thiazol-5-yl)ethan-1-ol)



2-(4-Methylthiazol-5-yl) ethan-1-ol (3.0 g, 21.0 mmol, 1.0 equiv.) and ferrocene (2.2 g, 10.5 mmol, 0.5 equiv.) were dissolved in DMSO (10 mL), then CF_3I (12.3 g, 62.9 mmol, 3.0 equiv.) was added dropwise. This was followed by the addition of H_2O_2 (30%, 162.6 mL, 209.5 mmol, 10.0 equiv.) dropwise at 0 °C. The reaction mixture was stirred for 2 hours at rt and then quenched by the addition of aqueous Na_2CO_3 . The resulting solution was diluted with water, extracted with EtOAc, washed with brine, dried over anhyd. Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (1:1) to give 2-(4-methyl-2-(trifluoromethyl) thiazol-5-yl) ethan-1-ol (1.7 g) as a brown oil. LCMS Method A: $[M+H]^+ = 212.2$.

Scheme 63: Synthesis of intermediate 114 (tert-butyl 7-(2-hydroxyethyl)-5-azaspiro[2.4]heptane-5-carboxylate)





Step 1: *tert*-butyl (E)-7-(2-ethoxy-2-oxoethylidene)-5-azaspiro[2.4]heptane-5-carboxylate

5 Ethyl 2-(diethoxyphosphoryl)acetate (1.6 g, 7.1 mmol, 1.5 equiv.) was dissolved in THF (15 mL) and cooled to 0 °C, then NaH (60%, 284.0 mg, 7.1 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for 30 min at rt, then *tert*-butyl 7-oxo-5-azaspiro[2.4]heptane-5-carboxylate (1.0 g, 4.7 mmol, 1.0 equiv.) was added dropwise. The resulting mixture was stirred overnight at rt and quenched by the addition of ice-water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (1:1) to give *tert*-butyl (E)-7-(2-ethoxy-2-oxoethylidene)-5-azaspiro[2.4]heptane-5-carboxylate (750.0 mg) as a pale white solid. LCMS Method A: [M+H]⁺ = 282.2.

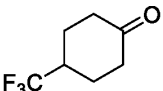
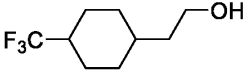
Step 2: *tert*-butyl 7-(2-ethoxy-2-oxoethyl)-5-azaspiro[2.4]heptane-5-carboxylate

15 *tert*-Butyl (E)-7-(2-ethoxy-2-oxoethylidene)-5-azaspiro[2.4]heptane-5-carboxylate (400.0 mg, 1.4 mmol, 1.0 equiv.) was dissolved in EtOAc (5.0 mL), then PtO₂ (40.0 mg, 0.2 mmol, 0.1 equiv.) was added. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 2 hours at rt. The solids were removed by filtration and the filtrate was concentrated under vacuum to give *tert*-butyl 7-(2-ethoxy-2-oxoethyl)-5-azaspiro[2.4]heptane-5-carboxylate (380.0 mg) as an off-white solid. LCMS Method A: [M+H]⁺ = 284.2.

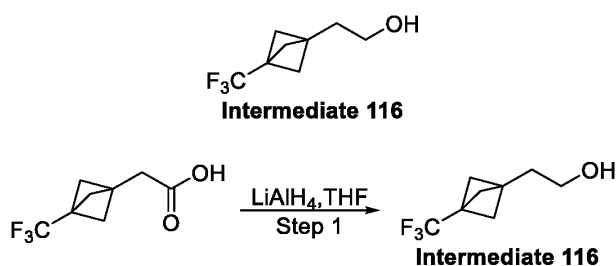
Step 3: *tert*-butyl 7-(2-hydroxyethyl)-5-azaspiro[2.4]heptane-5-carboxylate

tert-Butyl 7-(2-ethoxy-2-oxoethyl)-5-azaspiro[2.4]heptane-5-carboxylate (380.0 mg, 1.3 mmol, 1.0 equiv.) was dissolved in THF (8.0 mL) and cooled to 0 °C, then LAH (101.8 mg, 2.7 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 2 hours at rt and then quenched by the addition of Na₂SO₄·10H₂O. The resulting mixture was filtered, the filter cake was washed with EtOAc and the combined filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (1:1) to give *tert*-butyl 7-(2-hydroxyethyl)-5-azaspiro[2.4]heptane-5-carboxylate (250.0 mg) as a colorless oil. LCMS Method A: [M+H]⁺ = 242.2.

The intermediates in the following table were prepared using the same method described for Intermediates 114.

Intermediate	Starting material	Structure	LCMS data
Intermediate 115			Method A: MS-ESI: 197.2 [M+H] ⁺

Scheme 64: Synthesis of intermediate 116 (2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)ethan-1-ol)



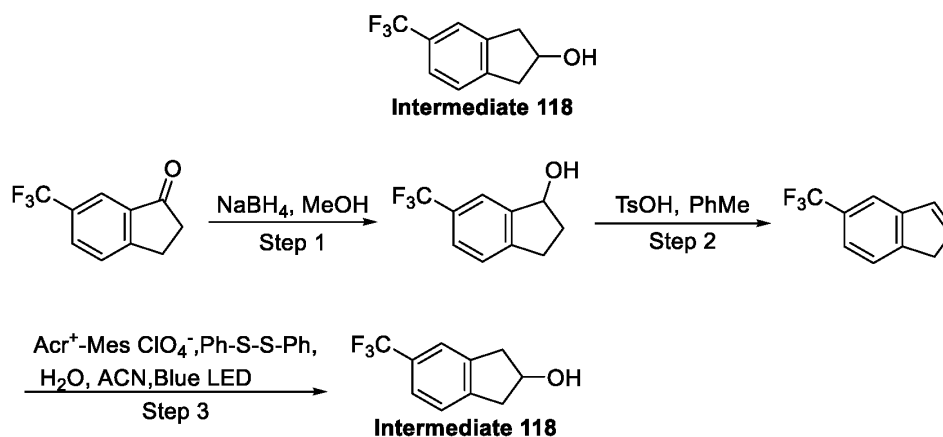
2-(3-(Trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetic acid (250.0 mg, 1.3 mmol, 1.0 equiv.) was dissolved in THF (8 mL) and cooled to 0 °C, then LiAlH₄ (97.7 mg, 2.6 mmol,

2.0 equiv.) was added. The resulting mixture was stirred for 2 hours at 0 °C and then quenched by the addition of Na₂SO₄·10H₂O. The resulting mixture was filtered and the filter cake was washed with EtOAc. The combined filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (1:1) to give 2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)ethan-1-ol (90.0 mg) as a colorless oil. LCMS Method A: [M+H]⁺ = 181.2.

The intermediates in the following table were prepared using the same method described for Intermediates 116.

Intermediate	Starting material	Structure	LCMS data
Intermediate 117			Method C: MS-ESI: 183.2 [M+H] ⁺

Scheme 65: Synthesis of intermediate 118 (5-(trifluoromethyl)-2,3-dihydro-1H-inden-2-ol)



Step 1: 6-(trifluoromethyl)-2,3-dihydro-1H-inden-1-ol

6-(Trifluoromethyl)-2,3-dihydroinden-1-one (5.0 g, 24.9 mmol, 1.0 equiv.) was dissolved in MeOH (20 mL) and cooled to 0 °C, then NaBH₄ (1.9 g, 49.9 mmol, 2.0 equiv.) was added in portions. The reaction mixture was stirred for 16 hours at rt and then quenched

by the addition of eater. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na_2SO_4 and concentrated under vacuum to give 6-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-ol (5.0 g) as a pale yellow oil. LCMS Method B: $[\text{M}-\text{H}]^- = 201.1$.

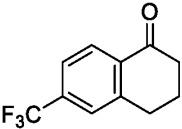
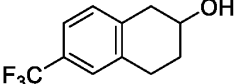
5 **Step 2: 5-(trifluoromethyl)-1*H*-indene**

6-(Trifluoromethyl)-2,3-dihydro-1*H*-inden-1-ol (1.0 g, 4.9 mmol, 1.0 equiv.) was dissolved in toluene (5 mL), then TsOH (425.8 mg, 2.5 mmol, 0.5 equiv.) was added. The reaction mixture was stirred overnight at 110 °C, then cooled to rt and concentrated under vacuum. The residue was diluted with water and the resulting solution was extracted with
10 EtOAc, washed with brine, dried over anhyd. Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether (100%) to give 5-(trifluoromethyl)-1*H*-indene (505.0 mg) as an off-white oil.

Step 3: 5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-2-ol

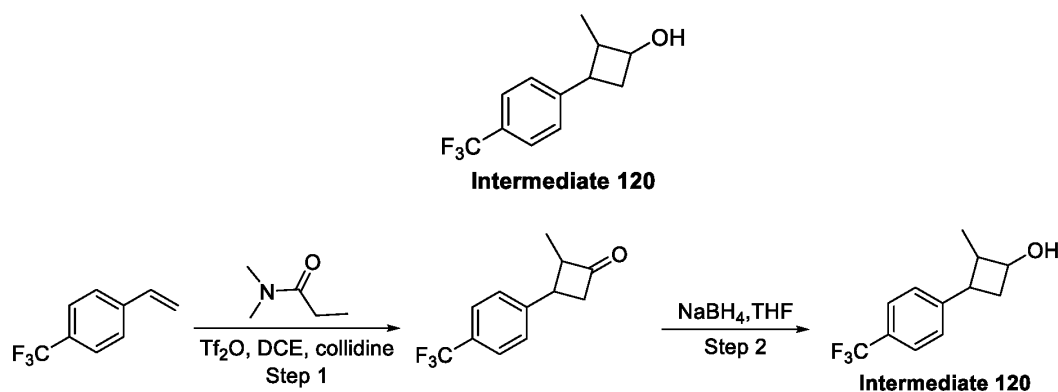
5-(Trifluoromethyl)-1*H*-indene (500.0 mg, 2.7 mmol, 1.0 equiv.) and
15 (phenyldisulfanyl)benzene (118.6 mg, 0.5 mmol, 0.2 equiv.) were dissolved in ACN (10 mL) and water (1 mL), then 9-Mesityl-10-methylacridinium Perchlorate (33.5 mg, 0.08 mmol, 0.03 equiv.) was added. The reaction mixture was stirred for 16 hours at 3 W blue LEDs at rt, then quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na_2SO_4 and concentrated under
20 vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 50% gradient in 10 min; detector, UV 254 nm. This gave 5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-2-ol (300.0 mg) as an off-white solid. LCMS Method A: $[\text{M}+\text{H}]^+ = 203.2$ 1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.56 (s, 1H), 7.48 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.43
25 (d, $J = 8.0$ Hz, 1H), 4.94 (d, $J = 3.6$ Hz, 1H), 4.57–4.52 (m, 1H), 3.13 (dd, $J = 16.4, 5.6$ Hz, 2H), 2.85–2.79 (m, 2H).

The intermediates in following table were prepared using the same method described for Intermediates 118.

Intermediate	Starting material	Structure	LCMS data
Intermediate 119			Method A: MS-ESI: 217.2 [M+H] ⁺

Scheme 66: Synthesis of intermediate 120 (2-methyl-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol)

5



Step 1: 2-methyl-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-one

1-(Trifluoromethyl)-4-vinylbenzene (5.0 g, 29.0 mmol, 1.0 equiv.) was dissolved in DCE (100 mL) and cooled to 0 °C, then Tf₂O (11.5 g, 40.7 mmol, 1.4 equiv.) was added dropwise, maintaining the solution at 0 °C. After stirred for 30 min at 0 °C, *N,N*-dimethylpropionamide (3.5 g, 34.8 mmol, 1.2 equiv.) and 2,4,6-trimethylpyridine (4.9 g, 40.6 mmol, 1.4 equiv.) was added. The reaction mixture was stirred for additional 2 hours at 80 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with dichloromethane, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (20:1) to give 2-methyl-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-one (3.0 g) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 3.52–3.42 (m, 1H), 3.42–3.34 (m, 1H), 3.33–3.24 (m, 2H), 1.18 (d, *J* = 7.2 Hz, 3H).

(15 mL), then CS₂ (1.4 g, 18.7 mmol, 2.0 equiv.) was added dropwise under an atmosphere of nitrogen. The reaction mixture was stirred for 4 hours at rt, then MeI (2.7 g, 18.7 mmol, 2.0 equiv.) was added dropwise. The resulting mixture was stirred overnight at rt and then quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (8:1) to give 2-[bis(methylsulfanyl)methylidene]-7-(trifluoromethyl)-3,4-dihydronaphthalen-1-one (1.5 g) as a yellow solid. LCMS Method A: [M+H]⁺ = 319.1.

Step 2: methyl 7-(trifluoromethyl)-3,4-dihydronaphthalene-2-carboxylate

2-[bis(methylsulfanyl)methylidene]-7-(trifluoromethyl)-3,4-dihydronaphthalen-1-one (1.5 g, 4.7 mmol, 1.0 equiv.) was dissolved in MeOH (15 mL) and cooled to 0 °C, the NaBH₄ (267.0 mg, 7.1 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for 30 min at rt, then BF₃·Et₂O (1.2 g, 85.1 mmol, 18.0 equiv.) was added dropwise. The reaction mixture was stirred overnight at 50 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (5:1) to give 2-[bis(methylsulfanyl)methylidene]-7-(trifluoromethyl)-3,4-dihydronaphthalen-1-one (810 mg) as a yellow solid. LCMS Method A: [M+H]⁺ = 257.1.

Step 3: methyl 7-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate

Methyl 7-(trifluoromethyl)-3,4-dihydronaphthalene-2-carboxylate (800.0 mg, 3.1 mmol, 1.0 equiv.) was dissolved in MeOH (10 mL), then Pd/C (166.1 mg, 1.6 mmol, 0.5 equiv.) was added under an atmosphere of nitrogen. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 5 hours at rt. The solids were removed by filtration and the filtrate was concentrated under vacuum to give methyl 7-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (705 mg) as a yellow oil. LCMS Method A: [M+H]⁺ = 259.2.

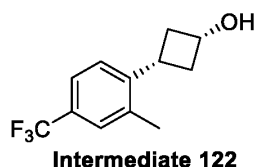
Step 4: 7-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid

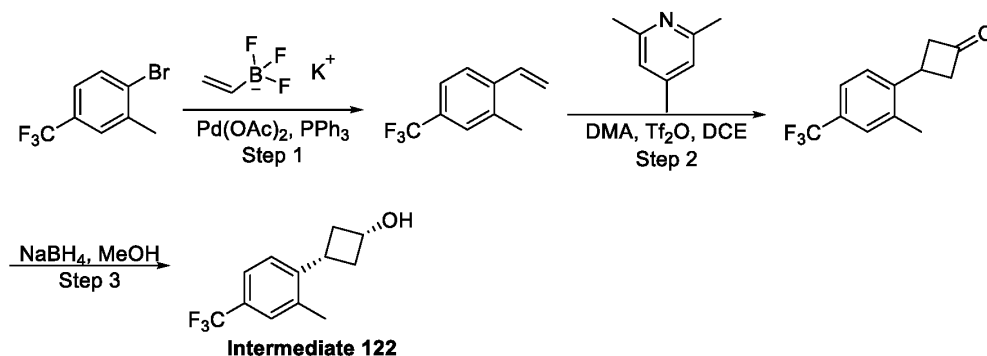
Methyl 7-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (700.0 mg, 2.7 mmol, 1.0 equiv.) was dissolved in MeOH (10 mL) and H₂O (5 mL), then NaOH (542.1 mg, 13.6 mmol, 5.0 equiv.) was added. The reaction mixture was stirred overnight at rt and concentrated under vacuum. The residue was diluted with water, adjusted to pH 5 with aqueous HCl. The precipitated solids were collected by filtration, washed with water and dried to give 7-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (350.0 mg) as an off-white solid. LCMS Method B: [M-H]⁻ = 243.1.

Step 5: (7-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)methanol

7-(Trifluoromethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (350.0 mg, 1.4 mmol, 1.0 equiv.) was dissolved in THF (5 mL) and cooled to 0 °C, then BH₃-Me₂S (181.1 mg, 7.2 mmol, 5.0 equiv.) was added. The reaction mixture was stirred for 4 hours at rt and then quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (5:1) to give (7-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (300.0 mg) as a yellow solid. ¹HNMR (400 MHz, DMSO-*d*₆) δ 7.40 (d, *J* = 9.2 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 4.62 (s, 1H), 3.38 (d, *J* = 6.4 Hz, 2H), 2.93–2.82 (m, 2H), 2.76–2.69 (m, 1H), 2.48–2.45 (m, 1H), 1.99–1.89 (m, 1H), 1.82–1.72 (m, 1H), 1.35–1.22 (m, 1H).

Scheme 68: Synthesis of intermediate 122 (cis-3-(2-methyl-4-(trifluoromethyl)phenyl)cyclobutan-1-ol)





Step 1: 2-methyl-4-(trifluoromethyl)-1-vinylbenzene

1-Bromo-2-methyl-4-(trifluoromethyl)benzene (5.0 g, 20.9 mmol, 1.0 equiv.) and potassium 1-(trifluoro-lambda4-boranyl)eth-1-ene (4.2 g, 31.6 mmol, 1.5 equiv) were dissolved in THF (40 mL) and H₂O (4 mL), then Cs₂CO₃ (13.6 g, 41.8 mmol, 2.0 equiv.), PPh₃ (1.1 g, 4.2 mmol, 0.2 N/equiv.) and Pd(OAc)₂ (0.5 g, 2.1 mmol, 0.1 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred for 4 hours at 70 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (99:1) to give 2-methyl-4-(trifluoromethyl)-1-vinylbenzene (2.2 g) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.62–7.51 (m, 2H), 7.03–6.98 (m, 1H), 5.86 (dd, *J* = 17.2 Hz, 2.1 Hz, 1H), 5.50–5.44 (m, 1H), 2.39 (s, 3H).

Step 2: 3-(2-methyl-4-(trifluoromethyl)phenyl)cyclobutan-1-one

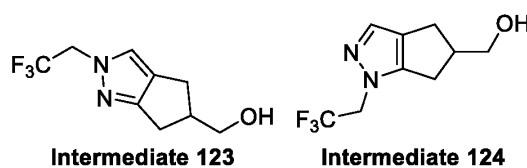
DMA (1.1 g, 12.9 mmol, 2.4 equiv.) was dissolved in DCE (10 mL) and cooled to 0 °C, then a solution of Tf₂O (6.1 g, 21.5 mmol, 4.0 equiv.) in DCE (1 mL) was added dropwise under an atmosphere of nitrogen. The reaction mixture was stirred for 30 min at 0 °C, then a mixture of 2,4,6-collidine (2.6 g, 21.5 mmol, 4.0 equiv.) and 2-methyl-4-(trifluoromethyl)-1-vinylbenzene (1.0 g, 5.4 mmol, 1.0 equiv.) was added dropwise, maintaining the solution at 0 °C. The resulting mixture was stirred for 16 hours at 80 °C, then cooled to rt and quenched by the addition of water. The resulting solution was

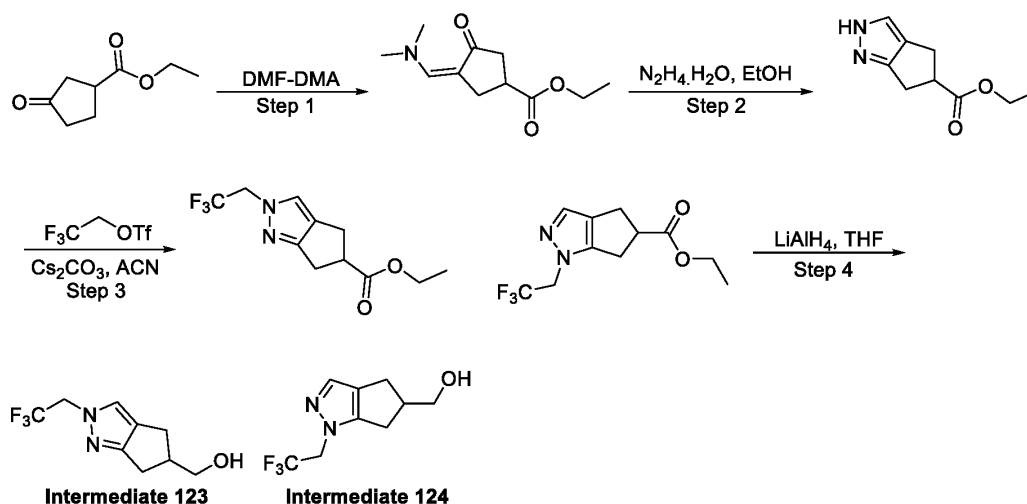
extracted with dichloromethane, washed with brine, dried over anhyd. sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (20:1) to give 3-(2-methyl-4-(trifluoromethyl)phenyl)cyclobutan-1-one (380 mg) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.62–7.60 (m, 1H), 7.56–7.53 (m, 2H), 3.88–3.79 (m, 1H), 3.50–3.41 (m, 2H), 3.30–3.24 (m, 2H), 2.37 (s, 3H).

Step 3: *cis*-3-(2-methyl-4-(trifluoromethyl)phenyl)cyclobutan-1-ol

3-(2-Methyl-4-(trifluoromethyl)phenyl)cyclobutan-1-one (380.0 mg, 1.7 mmol, 1.0 equiv.) was dissolved in MeOH (5 mL) and cooled to 0 °C, then NaBH₄ (127.0 mg, 3.3 mmol, 2.0 equiv.) was added in portions. The reaction mixture was stirred for 1 hour at 0 °C and then quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. sodium sulfate and concentrated under vacuum to give *cis*-3-(2-methyl-4-(trifluoromethyl)phenyl)cyclobutan-1-ol (300.0 mg) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.60–7.46 (m, 2H), 7.42–7.40 (m, 1H), 5.13 (d, *J* = 7.2 Hz, 1H), 4.12–4.06 (m, 1H), 3.05–2.98 (m, 1H), 2.68–2.62 (m, 2H), 2.28 (s, 3H), 1.89–1.81 (m, 2H).

Scheme 69: Synthesis of intermediate 123 ((2-(2,2,2-trifluoroethyl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-5-yl)methanol) and intermediate 124 ((1-(2,2,2-trifluoroethyl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazol-5-yl)methanol)





Step 1: ethyl (3Z)-3-[(dimethylamino)methylidene]-4-oxocyclopentane-1-carboxylate

5 Ethyl 3-oxocyclopentane-1-carboxylate (4.0 g, 25.6 mmol, 1.0 equiv.) was dissolved in DMF-DMA (40.0 mL). The reaction mixture was stirred for 4 hours at 100 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum to give ethyl (3Z)-3-[(dimethylamino)methylidene]-4-oxocyclopentane-1-carboxylate (2.0 g) as a yellow oil. LCMS Method A: [M+H]⁺ = 212.2.

10 **Step 2: ethyl 2H,4H,5H,6H-cyclopenta[c]pyrazole-5-carboxylate**

15 Ethyl (3Z)-3-[(dimethylamino)methylidene]-4-oxocyclopentane-1-carboxylate (2.0 g, 9.5 mmol, 1.0 equiv.) was dissolved in EtOH (20 mL), hydrazine (910.0 mg, 28.4 mmol, 3.0 equiv.) was added. The reaction mixture was stirred for 5 hours at rt and then quenched by the addition of FeCl₃ (900 mg). The resulting solution was filtered and the filter cake was washed with -ethanol. The combined filtrate was concentrated under vacuum. The residue was purified by Prep Chiral-HPLC with the following conditions: Column: CHIRALPAK IG, 5*15 cm, 10 μm; Mobile Phase A: CO₂, Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 200 mL/min; Gradient: isocratic 30% B; Column Temperature (°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 3.88. This resulted in ethyl

2*H*,4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazole-5-carboxylate (920.0 mg) as an off-white solid. LCMS Method A: $[M+H]^+ = 181.2$.

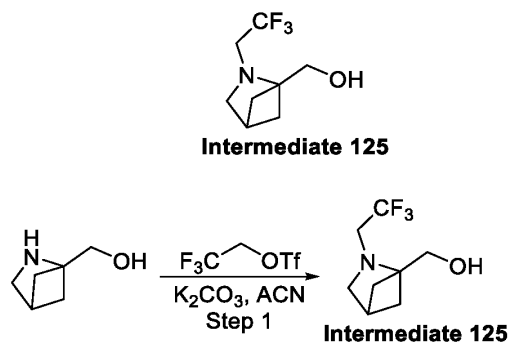
Step 3: mixture of ethyl 2-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazole-5-carboxylate and ethyl 1-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazole-5-carboxylate

Ethyl 2*H*,4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazole-5-carboxylate (900.0 mg, 5.0 mmol, 1.0 equiv.) was dissolved in ACN (10 mL), Cs₂CO₃ (3.3 g, 10.0 mmol, 2.0 equiv.) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.7 g, 7.5 mmol, 1.5 equiv.) were added. The reaction mixture was stirred for 16 hours at 65 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum to give a mixture of ethyl 2-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazole-5-carboxylate and ethyl 1-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazole-5-carboxylate (585.0 mg) as an off-white solid. LCMS Method A: $[M+H]^+ = 263.2$.

Step 4: mixture of [2-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazol-5-yl]methanol and [1-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazol-5-yl]methanol

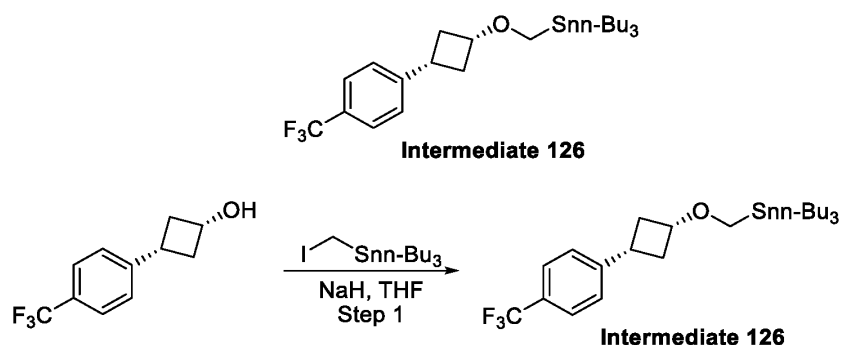
The mixture of ethyl 2-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazole-5-carboxylate and ethyl 1-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazole-5-carboxylate (200.0 mg, 0.8 mmol, 1.0 equiv.) was dissolved in THF (8 mL) and cooled to 0 °C, LiAlH₄ (44 mg, 1.2 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for 5 hours at rt and then quenched by the addition of ice-water at 0 °C. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with petroleum ether/EtOAc (5:1) to give a mixture of [2-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazol-5-yl]methanol and [1-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazol-5-yl]methanol (81.0 mg) as an off-white solid. LCMS Method A: $[M+H]^+ = 221.2$.

Scheme 70: Synthesis of intermediate 125 ((2-(2,2,2-trifluoroethyl)-2-azabicyclo[2.1.1]hexan-1-yl)methanol)



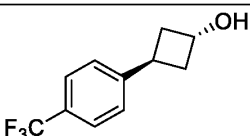
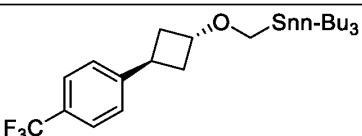
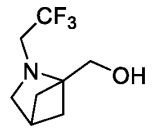
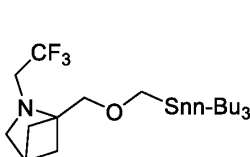
5 (2-Azabicyclo[2.1.1]hexan-1-yl)methanol (300.0 mg, 2.7 mmol, 1.0 equiv.) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (923.0 mg, 4.0 mmol, 1.5 equiv.) were dissolved in ACN (10.0 mL), K₂CO₃ (732.8 mg, 5.3 mmol, 2.0 equiv.) was added at rt. The reaction mixture was stirred for 2 h at 50 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over
 10 anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (3:1) to give (2-(2,2,2-trifluoroethyl)-2-azabicyclo[2.1.1]hexan-1-yl)methanol (400.0 mg) as a white solid. LCMS Method A: [M+H]⁺ = 196.2.

15 **Scheme 71: Synthesis of intermediate 126 (tributyl((cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)methyl)stannane)**

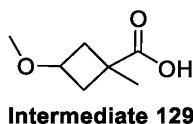


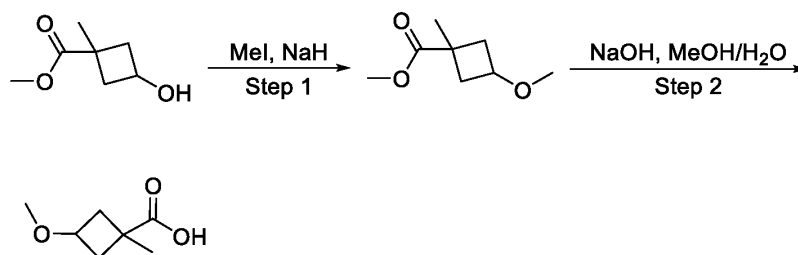
cis-3-[4-(Trifluoromethyl)phenyl]cyclobutan-1-ol (1.0 g, 4.0 mmol, 1.0 equiv.) was dissolved in THF (10 mL) and cooled to 0 °C, then NaH (60% wt., 221.0 mg, 5.5 mmol, 1.4 equiv.) was added. After stirred for 15 min at 0 °C, tributyl(iodomethyl)stannane (1.8 g, 4.2 mmol, 0.9 equiv.) was added. The reaction mixture was stirred for 2 hours at rt and then quenched by the addition of water. The resulting solution was extracted with dichloromethane, washed with brine and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (99:1) to give tributyl({[cis-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]methyl})stannane (630.0 mg) as a yellow oil.

The intermediates in the following table were prepared using the same method described for Intermediates 126.

Intermediate	Starting material	Structure	LCMS data
Intermediate 127			N/A
Intermediate 128	 Intermediate 125		N/A

Scheme 72: Synthesis of intermediate 129 (3-methoxy-1-methylcyclobutane-1-carboxylic acid)



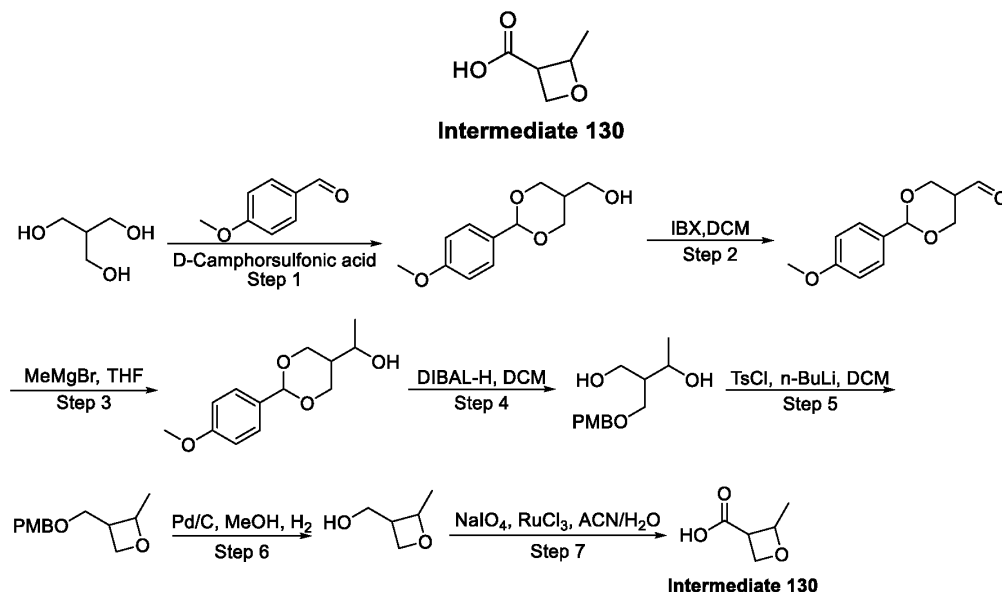
**Intermediate 129****Step 1: methyl 3-methoxy-1-methylcyclobutane-1-carboxylate**

Methyl 3-hydroxy-1-methylcyclobutane-1-carboxylate (1.5 g, 10.4 mmol, 1.0 equiv.) was dissolved in THF (30 mL) and cooled to 0 °C, then NaH (60% wt, 624.2 mg, 15.6 mmol, 1.5 equiv.) was added under an atmosphere of nitrogen. After 5 min at 0 °C, MeI (3.7 g, 26.0 mmol, 2.5 equiv.) was added. The reaction mixture was stirred for additional 1 hour at 0 °C and then quenched by the addition of ice-water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (10:1) to give methyl 3-methoxy-1-methylcyclobutane-1-carboxylate (1.3 g) as a yellow oil.

Step 2: 3-methoxy-1-methylcyclobutane-1-carboxylic acid

Methyl 3-methoxy-1-methylcyclobutane-1-carboxylate (1.3 g, 8.5 mmol, 1.0 equiv.) was dissolved in MeOH (10 mL), then aqueous NaOH (5 mL, 2 M, 10 mmol, 1.2 equiv.) was added. The reaction mixture was stirred for 1 hour at rt and concentrated under vacuum. The residue was diluted with water, adjusted to pH 3 with aqueous HCl (4M). The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum to afford 3-methoxy-1-methylcyclobutane-1-carboxylic acid (960 mg) as a colorless oil. LCMS Method B: [M-H]⁻ = 143.0.

Scheme 73: Synthesis of intermediate 130 (2-methyloxetane-3-carboxylic acid)



Step 1: (2-(4-methoxyphenyl)-1,3-dioxan-5-yl)methanol

2-(Hydroxymethyl)propane-1,3-diol (8.0 g, 75.4 mmol, 1.0 equiv.) and 4-methoxybenzaldehyde (12.3 g, 90.5 mmol, 1.2 equiv.) were dissolved in DCM (100 mL), then [(1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]methanesulfonic acid (3.5 g, 15.1 mmol, 0.2 equiv.) was added in portions. The reaction mixture was stirred for 2 days at 40 °C, then cooled to 0 °C and quenched by the addition of TEA (5.2 mL, 37.7 mmol, 0.5 equiv.). The solution was concentrated under vacuum and the residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (1:1) to give (2-(4-methoxyphenyl)-1,3-dioxan-5-yl)methanol (6.0 g) as a white solid. LCMS Method A: $[M+H]^+ = 225.1$.

Step 2: 2-(4-methoxyphenyl)-1,3-dioxane-5-carbaldehyde

(2-(4-Methoxyphenyl)-1,3-dioxan-5-yl)methanol (6.0 g, 26.8 mmol, 1.0 equiv.) was dissolved in DCM (60 mL), then IBX (15.0 g, 53.5 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for overnight at 40 °C, then cooled to rt and remove the solid by filtration. The filter cake was washed with DCM and the combined filtrate was

concentrated under vacuum to give crude 2-(4-methoxyphenyl)-1,3-dioxane-5-carbaldehyde (6.5 g) as a colorless oil. LCMS Method A: $[M+H]^+ = 223.1$.

Step 3: 1-(2-(4-methoxyphenyl)-1,3-dioxan-5-yl)ethan-1-ol

2-(4-Methoxyphenyl)-1,3-dioxane-5-carbaldehyde (6.5 g, 29.2 mmol, 1.0 equiv.) was dissolved in THF (80 mL) and cooled to 0 °C, then MgMgBr (1M in THF, 58.5 mL, 58.5 mmol, 2.0 equiv.) was added dropwise under an atmosphere of nitrogen. The reaction mixture was stirred for 4 hours at 0 °C and then quenched by the addition of saturated aqueous NH_4Cl (aq.). The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (1:1) to give 1-(2-(4-methoxyphenyl)-1,3-dioxan-5-yl)ethan-1-ol (3.2 g) as a white solid. LCMS Method A: $[M+H]^+ = 239.2$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.32–7.31 (m, 2H), 6.94–6.86 (m, 2H), 5.45 (d, $J = 1.2$ Hz, 1H), 4.66 (dd, $J = 5.6, 1.6$ Hz, 1H), 4.35–4.33 (m, 1H), 4.10–4.00 (m, 2H), 3.95–3.88 (m, 1H), 3.68–3.65 (m, 1H), 3.41 (p, $J = 6.2$ Hz, 1H), 1.26–1.15 (m, 3H).

Step 4: 2-(((4-methoxybenzyl)oxy)methyl)butane-1,3-diol

1-(2-(4-Methoxyphenyl)-1,3-dioxan-5-yl)ethan-1-ol (3.2 g, 13.4 mmol, 1.0 equiv.) was dissolved in DCM (50 mL) and cooled to 0 °C, then DIBAL-H (1M, 26.9 mL, 26.9 mmol, 2.0 equiv.) was added dropwise, maintaining the solution at 0 °C. The reaction mixture was stirred overnight at 0 °C and then quenched by the addition of $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$. The resulting mixture was filtered and the filter cake was washed with DCM. The combined filtrate was concentrated under vacuum and the residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (1:1) to give 2-(((4-methoxybenzyl)oxy)methyl)butane-1,3-diol (2.5 g) as a white solid. LCMS Method A: $[M+H]^+ = 241.2$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.23 (d, $J = 8.4$ Hz, 2H), 6.94–6.87 (m, 2H), 4.43–4.27 (m, 3H), 4.01–3.99 (m, 1H), 3.74 (s, 3H), 3.56–3.47 (m, 1H), 3.46–3.35 (m, 4H), 1.68–1.66 (m, 1H), 1.10–1.08 (m, 3H).

Step 5: 3-(((4-methoxybenzyl)oxy)methyl)-2-methyloxetane

2-(((4-Methoxybenzyl)oxy)methyl)butane-1,3-diol (2.5 g, 10.4 mmol, 1.0 equiv.) was dissolved in DCM (25 mL) and cooled to 0 °C, then n-BuLi (2.5 M in hexane, 4.2 mL, 10.4 mmol, 1.0 equiv.) was added dropwise, maintaining the solution at 0 °C under an atmosphere of nitrogen. The reaction mixture was stirred for 30 min at 0 °C, then a solution of TsCl (2.0 g, 10.4 mmol, 1.0 equiv.) in DCM (10 mL) was added dropwise at 0 °C. The resulting mixture was stirred for additional 2 hours at 0 °C, then an addition batch of n-BuLi (2.5 M in hexane, 4.2 mL, 10.4 mmol, 1.0 equiv.) dropwise. The resulting mixture was stirred overnight at 40 °C, then cooled to rt and quenched by the addition of saturated aqueous NH₄Cl at 0 °C. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (1:1) to give 3-(((4-methoxybenzyl)oxy)methyl)-2-methyloxetane (1.0 g) as an off-white solid. LCMS Method A: [M+H]⁺ = 223.1.

Step 6: (2-methyloxetan-3-yl)methanol

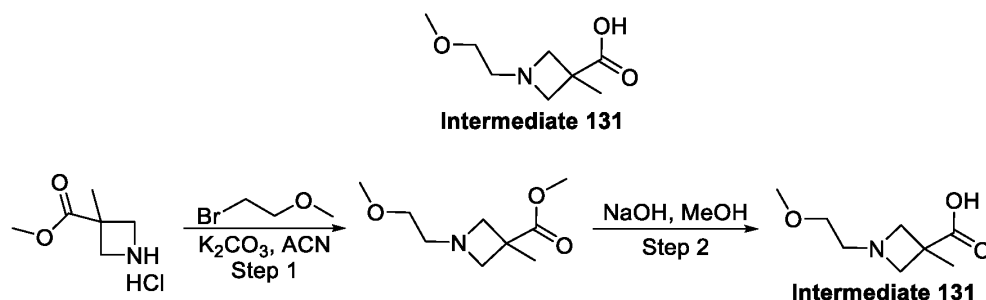
3-(((4-Methoxybenzyl)oxy)methyl)-2-methyloxetane (1.0 g, 4.5 mmol, 1.0 equiv.) was dissolved in MeOH (15 mL), then Pd/C (100.0 mg, 10% wt) was added under an atmosphere of nitrogen. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred overnight at rt. The solids were removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (1:1) to give (2-methyloxetan-3-yl)methanol (300.0 mg) as a colorless oil. LCMS Method A: [M+H]⁺ = 103.0. ¹HNMR (400 MHz, DMSO-*d*₆) δ 4.23 (t, *J* = 5.6 Hz, 1H), 4.01–3.99 (m, 1H), 3.53–3.51 (m, 1H), 3.45–3.42 (m, 3H), 1.53–1.49 (m, 1H), 1.10 (d, *J* = 6.4 Hz, 3H).

Step 7: 2-methyloxetane-3-carboxylic acid

(2-Methyloxetan-3-yl)methanol (300.0 mg, 2.9 mmol, 1.0 equiv.) was dissolved in ACN (5 mL) and H₂O (1 mL), then NaIO₄ (1.3 g, 5.9 mmol, 2.0 equiv.) and RuCl₃·H₂O (66.2 mg, 0.3 mmol, 0.1 equiv.) were added in portions. The reaction mixture was stirred overnight at rt and then quenched by the addition of water. The resulting solution was

adjusted to pH 4 with conc. HCl, extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum to give 2-methyloxetane-3-carboxylic acid (280.0 mg) as a brown oil. LCMS Method A: [M+H]⁺ = 117.2.

Scheme 74: Synthesis of intermediate 131 (1-(2-methoxyethyl)-3-methylazetidine-3-carboxylic acid)



Step 1: methyl 1-(2-methoxyethyl)-3-methylazetidine-3-carboxylate

2-Bromoethyl methyl ether (0.9 g, 6.6 mmol, 1.1 equiv.) and methyl 3-methylazetidine-3-carboxylate hydrochloride (1.0 g, 6.0 mmol, 1.0 equiv.) were dissolved in ACN (10 mL), then K₂CO₃ (1.7 g, 12.1 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 2 hours at 80 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. sodium sulfate and concentrated under vacuum to give methyl 1-(2-methoxyethyl)-3-methylazetidine-3-carboxylate (680 mg) as a yellow oil. LCMS Method A: [M+H]⁺ = 188.1.

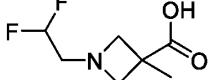
Step 2: 1-(2-methoxyethyl)-3-methylazetidine-3-carboxylic acid

Methyl 1-(2-methoxyethyl)-3-methylazetidine-3-carboxylate (680.0 mg, 3.6 mmol, 1.0 equiv.) was dissolved in MeOH (3 mL), then aqueous NaOH (3 mL, 2M, 6.0 mmol, 2.0 equiv.) was added dropwise. The reaction mixture was stirred for 2 hours at 80 °C, then cooled to rt and concentrated under vacuum. The residue was diluted with water, adjusted to pH 2 with aqueous HCl (1M). The resulting solution was extracted with dichloromethane

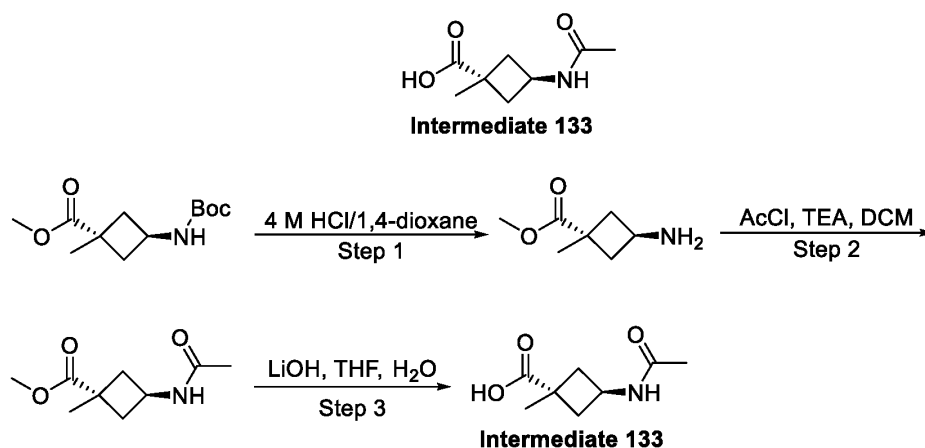
and concentrated under vacuum to give crude 1-(2-methoxyethyl)-3-methylazetidine-3-carboxylic acid (640 mg) as a yellow syrup. LCMS Method A: $[M+H]^+ = 174.2$.

The intermediates in the following table were prepared using the same method described for Intermediates 131.

5

Intermediate	Starting material	Structure	LCMS data
Intermediate 132			Method C: MS-ESI: $180.2 [M+H]^+$

Scheme 75: Synthesis of intermediate 133 (trans-3-acetamido-1-methylcyclobutane-1-carboxylic acid)



Step 1: methyl trans-3-amino-1-methylcyclobutane-1-carboxylate HCl salt

Methyl trans-3-((tert-butoxycarbonyl)amino)-1-methylcyclobutane-1-carboxylate (500.0 mg, 2.1 mmol, 1.0 equiv.) was dissolved in HCl/1,4-dioxane (5 mL). The reaction mixture was stirred for 1 hour at rt and concentrated under vacuum to give crude methyl trans-3-amino-1-methylcyclobutane-1-carboxylate (500 mg) as a white solid. LCMS Method A: $[M+H]^+ = 144.1$.

15

Step 2: methyl trans-3-acetamido-1-methylcyclobutane-1-carboxylate

Methyl *trans*-3-amino-1-methylcyclobutane-1-carboxylate (500.0 mg, 3.5 mmol, 1.0 equiv.) and TEA (2.4 mL, 17.5 mmol, 5.0 equiv.) were dissolved in DCM (10 mL) and cooled to 0 °C, then acetyl chloride (274.1 mg, 3.5 mmol, 1.0 equiv.) was added. The reaction mixture was stirred for 2 hour at rt and then quenched by the addition of water.

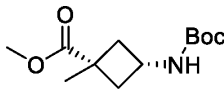
- 5 The resulting solution was extracted with dichloromethane, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum to give methyl *trans*-3-acetamido-1-methylcyclobutane-1-carboxylate (425.0 mg) as a yellow oil. LCMS Method A: [M+H]⁺ = 186.1.

Step 3: *trans*-3-acetamido-1-methylcyclobutane-1-carboxylic acid

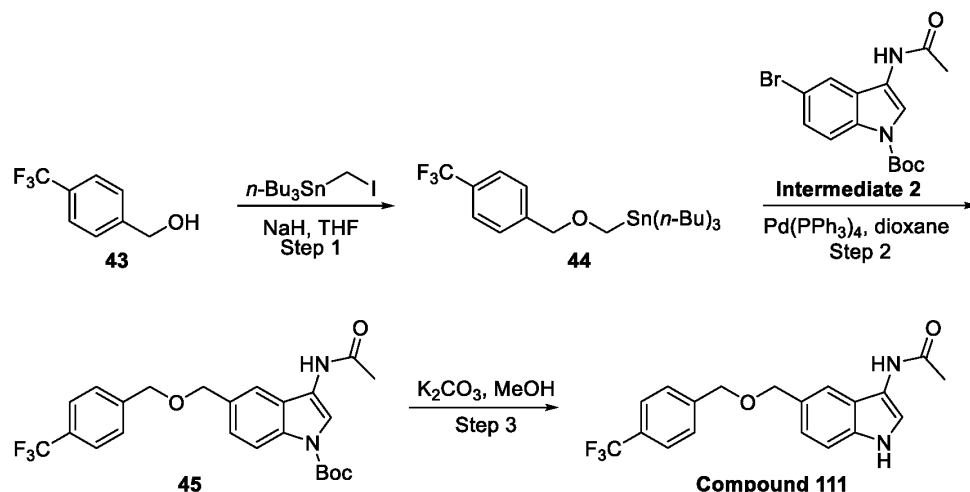
- 10 Methyl *trans*-3-acetamido-1-methylcyclobutane-1-carboxylate (425.0 mg, 2.3 mmol, 1.0 equiv.) was dissolved in THF (10 mL) and H₂O (2 mL), then LiOH (109.9 mg, 4.6 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 4 hours at rt and concentrated under vacuum. The residue was diluted with water, adjusted to pH 3 with aqueous HCl (1 M). The resulting solution was extracted with EtOAc, washed with brine,
15 dried over anhyd. Na₂SO₄ and concentrated under vacuum to afford *trans*-3-acetamido-1-methylcyclobutane-1-carboxylic acid (630 mg) as a colorless oil. LCMS Method A: [M+H]⁺ = 172.0.

The intermediates in the following table were prepared using the same method described for Intermediates 133.

20

Intermediate	Starting material	Structure	LCMS data
Intermediate 134			Method A: MS-ESI: 172.0 [M+H] ⁺

Example 1: *N*-(5-(((4-(trifluoromethyl)benzyl)oxy)methyl)-1*H*-indol-3-yl)acetamide (Compound 111)



Step 1: tributyl([4-(trifluoromethyl)phenyl]methoxy)methylstannane

5 [4-(trifluoromethyl)phenyl]methanol (3.0 g, 17.0 mmol, 1.0 equiv.) was dissolved in THF (100 mL) and cooled to 0 °C, then NaH (60% wt., 0.8 g, 15.3 mmol, 1.2 equiv.) was added. After 1 hour at 0 °C, a solution of tributyl(iodomethyl)stannane (6.6 g, 15.3 mmol, 0.9 equiv.) in THF (3 mL) was added dropwise, maintaining the solution at 0 °C. The reaction mixture was stirred for an additional 72 hours at ambient temperature, then
 10 quenched by the addition of water. The resulting solution was extracted with petroleum ether and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/ petroleum ether (1:5) to give tributyl([4-(trifluoromethyl)phenyl]methoxy)methylstannane (4.5 g) as a pale yellow oil.

Step 2: *tert*-butyl 3-acetamido-5-([4-(trifluoromethyl)phenyl]methoxy)methylindole-1-carboxylate

15 *tert*-Butyl 5-bromo-3-acetamidindole-1-carboxylate (200.0 mg, 0.6 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (5 mL), then Pd(PPh₃)₄ (65.4 mg, 0.1 mmol, 0.1 equiv.) and tributyl([4-(trifluoromethyl)phenyl]methoxy)methylstannane (407.0 mg, 0.8 mmol, 1.5 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was
 20 heated to 100 °C for 14 hours, then cooled to ambient temperature and quenched by the

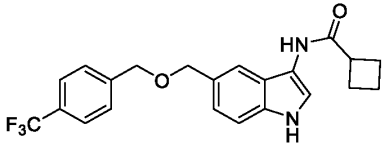
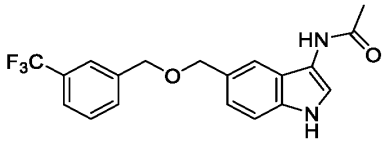
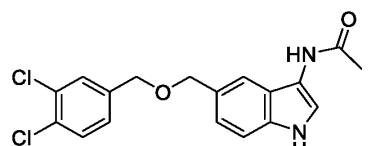
addition of water. The resulting solution was extracted with ethyl acetate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give tert-butyl 3-acetamido-5-([4-(trifluoromethyl)phenyl]methoxy)methyl)indole-1-carboxylate (100.5 mg) as a yellow semi-solid. LCMS Method A: $[M+H]^+ = 463$.

Step 3: *N*-[5-([4-(trifluoromethyl)phenyl]methoxy)methyl)-1*H*-indol-3-yl]acetamide

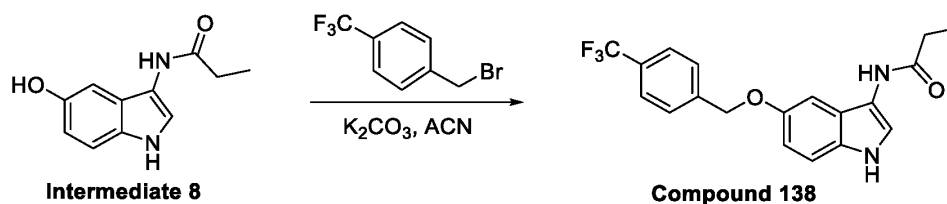
tert-Butyl 3-acetamido-5-([4-(trifluoromethyl)phenyl]methoxy)methyl)indole-1-carboxylate (90.0 mg, 0.2 mmol, 1.0 equiv.) was dissolved in MeOH (5 mL), then K₂CO₃ (80.7 mg, 0.6 mmol, 3.0 equiv.) was added. The reaction mixture was heated to 65 °C for 2 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mM NH₄HCO₃+0.1% NH₄OH), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 60% B in 8 min; Wave Length: 220 nm; RT1: 7.53 min. This resulted in *N*-[5-([4-(trifluoromethyl)phenyl]methoxy)methyl)-1*H*-indol-3-yl]acetamide (35.1 mg) as a pale yellow solid. LCMS Method D: $[M+H]^+ = 363$. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.78 (s, 1H), 9.84 (s, 1H), 7.80 (s, 1H), 7.74–7.70 (m, 3H), 7.60–7.58 (m, 2H), 7.33–7.31 (m, 1H), 7.13–7.10 (m, 1H), 4.63 (s, 4H), 2.09 (s, 3H).

The analogs prepared in the following table were prepared using the same method described for **Example 1**.

Example #	Compound No.	Starting materials Used	Structure	LCMS data
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2	109	(4-(trifluoromethyl)phenyl)methanol / Intermediate 6		Method D: MS-ESI: 401 [M-H] ⁻ .
3	106	(3-(trifluoromethyl)phenyl)methanol / Intermediate 2		Method F: MS-ESI: 361 [M-H] ⁻ .
4	101	(3,4-dichlorophenyl)methanol / Intermediate 2		Method F: MS-ESI: 370 [M+H] ⁺ .

Example 5: *N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)propionamide (Compound 138)

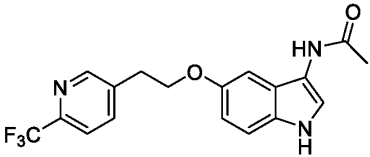
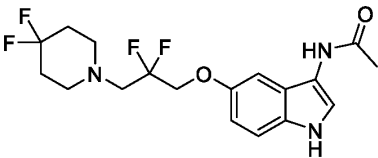


- 5 *N*-(5-hydroxy-1*H*-indol-3-yl)propionamide (160.0 mg, 0.8 mmol, 1.0 equiv.) and 1-(bromomethyl)-4-(trifluoromethyl)benzene (280.9 mg, 1.2 mmol, 1.5 equiv.) were dissolved in ACN (10 mL), then K₂CO₃ (216.6 mg, 1.6 mmol, 2.0 equiv.) was added. The reaction mixture was heated to 75 °C overnight, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate,

washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mM NH₄HCO₃+0.1% NH₄OH), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 65% B in 7 min; Wave Length: 220 nm; RT1: 6.68 min. This resulted in *N*-(5-[[4-(trifluoromethyl)phenyl]methoxy]-1*H*-indol-3-yl)propenamide (29.2 mg) as a white solid. LCMS Method D: [M+H]⁺ = 363. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.62 (s, 1H), 9.66 (s, 1H), 7.79–7.77 (m, 2H), 7.73–7.68 (m, 3H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.86–6.83 (m, 1H), 5.21 (s, 2H), 2.41–2.33 (m, 2H), 1.12 (t, *J* = 7.6 Hz, 3H).

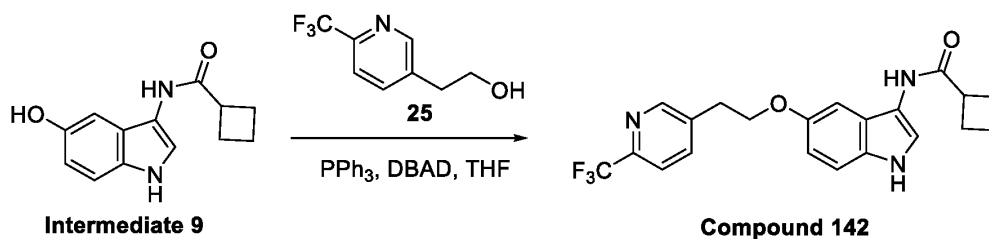
10

The analogs prepared in the following table were prepared using the same method described for **Example 5**.

Example #	Compound No.	Starting materials Used	Structure	LCMS data
6	113	Intermediate 27 / Intermediate 7		Method D: MS-ESI: 364 [M+H] ⁺ .
7	112	Intermediate 28 / Intermediate 7		Method F: MS-ESI: 388 [M+H] ⁺ .

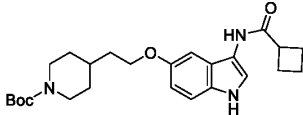
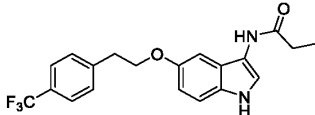
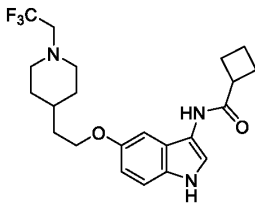
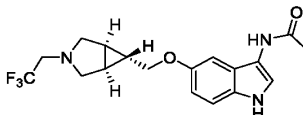
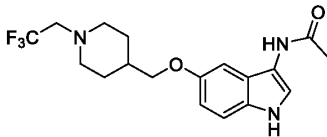
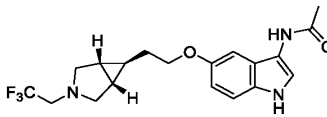
Example 8: *N*-(5-(2-(6-(trifluoromethyl)pyridin-3-yl)ethoxy)-1*H*-indol-3-yl)cyclobutanecarboxamide (Compound 142)

15



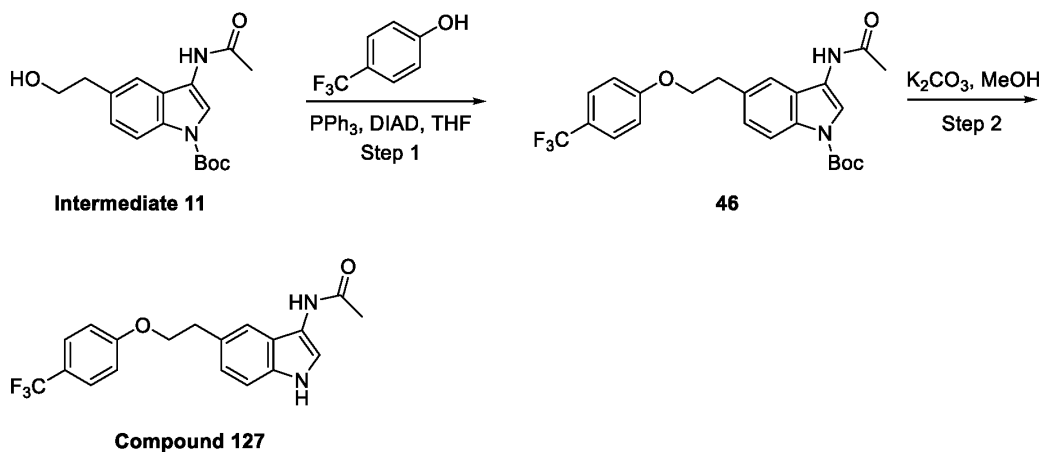
5 *N*-(5-Hydroxy-1*H*-indol-3-yl)cyclobutanecarboxamide (150.0 mg, 0.7 mmol, 1.0 equiv.) and 2-[6-(trifluoromethyl)pyridin-3-yl]ethanol (249.0 mg, 1.3 mmol, 2.0 equiv.) were dissolved in THF (10 mL), then PPh₃ (341.7 mg, 1.3 mmol, 2.0 equiv.) was added. This was followed by the addition of DBAD (300.0 mg, 1.3 mmol, 2.0 equiv.). The reaction mixture was stirred overnight at ambient temperature and then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash
 10 column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give material, that was further purified by Flash-Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30×150mm 5 μm; Mobile Phase A: Water (10 mM NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 43 B to 55 B in 8 min; 254/220 nm; RT1: 6.62 min. This resulted in *N*-(5-[2-[6-(trifluoromethyl)pyridin-
 15 3-yl]ethoxy]-1*H*-indol-3-yl)cyclobutanecarboxamide (22.3 mg) as a white solid. LCMS Method D: [M+H]⁺ = 404. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.58 (s, 1H), 9.50 (s, 1H), 8.78 (s, 1H), 8.10–8.08 (m, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 2.4 Hz, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 6.73–6.71 (m, 1H), 4.23 (t, *J* = 6.4 Hz, 2H), 3.33–3.30 (m, 1H), 3.22 (t, *J* = 6.4 Hz, 2H), 2.27–2.22 (m, 2H), 2.13–2.08 (m, 2H), 1.96–1.94
 20 (m, 1H), 1.84–1.80 (m, 1H).

The analogs prepared in the following table were prepared using the same method described for **Example 8**.

Exempl e #	Compou nd No.	Starting materials Used	Structure	Condition	LCMS data
9	140	<i>tert</i> -butyl 4-(2-hydroxyethyl) piperidine-1-carboxylate / Intermediate 9		PPh ₃ , DIAD, THF	Method D: MS-ESI: 440 [M-H] ⁻ .
10	146	2-(4-(trifluoromethyl)phenyl)ethanol / Intermediate 8		PPh ₃ , DEAD, DCM	Method D: MS-ESI: 377 [M+H] ⁺ .
11	129	Intermediate 20 / Intermediate 9		P(<i>n</i> -Bu) ₃ , ADDP, DCM	Method E: MS-ESI: 424 [M+H] ⁺ .
12	120	Intermediate 22 / Intermediate 7		PPh ₃ , DIAD, THF	Method F: MS-ESI: 368 [M+H] ⁺ .
13	119	Intermediate 21 / Intermediate 7		PPh ₃ , DIAD, THF	Method F: MS-ESI: 370 [M+H] ⁺ .
14	110	Intermediate 24 / Intermediate 7		P(<i>n</i> -Bu) ₃ , ADDP, THF	Method E: MS-ESI: 382 [M+H] ⁺ .

15	105	Intermediate 18 / Intermediate 7		P(<i>n</i> -Bu) ₃ , ADDP, DCM	Method E: MS-ESI: 402 [M+H] ⁺ .
16	104	Intermediate 19 / Intermediate 7		P(<i>n</i> -Bu) ₃ , ADDP, DCM	Method D: MS-ESI: 446 [M+H] ⁺ .
17	145	4-(trifluoromethyl)phenol / Intermediate 12		PPh ₃ , DIAD, THF	Method E: MS-ESI: 403 [M+H] ⁺ .

Example 18: *N*-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1*H*-indol-3-yl)acetamide (Compound 127)



5 Step 1: *tert*-butyl 3-acetamido-5-[2-[4-(trifluoromethyl)phenoxy]ethyl]indole-1-carboxylate (compound 46)

tert-Butyl 3-acetamido-5-(2-hydroxyethyl)indole-1-carboxylate (300.0 mg, 0.9 mmol, 1.0 equiv.) was dissolved in THF (20 mL) and cooled to 0 °C, then 4-

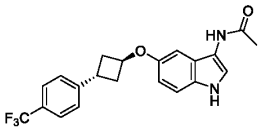
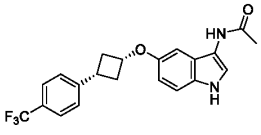
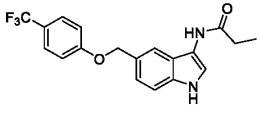
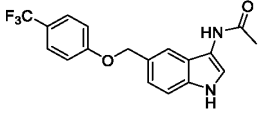
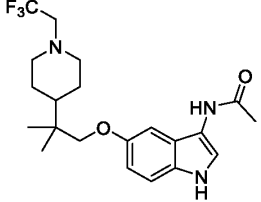
(trifluoromethyl)phenol (229.1 mg, 1.4 mmol, 1.5 equiv.) and PPh₃ (494.3 mg, 1.9 mmol, 2.0 equiv.) were added. This was followed by the dropwise addition of DIAD (0.2 mL, 1.3 mmol, 2.0 equiv.). The reaction mixture was stirred for an additional 2 hours at ambient temperature and then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give *tert*-butyl 3-acetamido-5-[2-[4-(trifluoromethyl)phenoxy]ethyl]indole-1-carboxylate (280.0 mg) as a pale yellow solid. LCMS Method A: [M+H]⁺ = 463

Step 2: *N*-(5-[2-[4-(trifluoromethyl)phenoxy]ethyl]-1*H*-indol-3-yl)acetamide

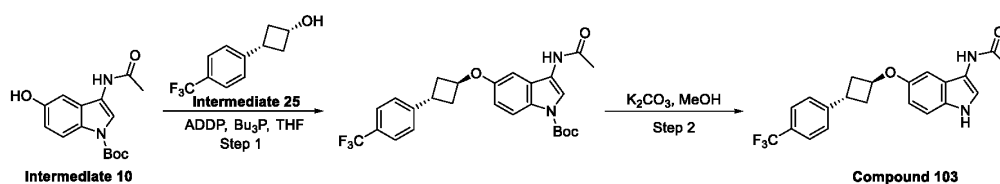
tert-Butyl 3-acetamido-5-[2-[4-(trifluoromethyl)phenoxy]ethyl]indole-1-carboxylate (100.0 mg, 0.2 mmol, 1.0 equiv.) was dissolved in MeOH (5 mL), then K₂CO₃ (64.8 mg, 0.5 mmol, 2.0 equiv.) was added. The reaction mixture was heated to 65 °C for 2 hours, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150mm 5μm; Mobile Phase A: Water (10 mM NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35%B to 65%B in 8 min, 220 nm; RT1: 7.53 min. This resulted in *N*-(5-[2-[4-(trifluoromethyl)phenoxy]ethyl]-1*H*-indol-3-yl)acetamide (36.8 mg) as a white solid. LCMS Method D: [M+H]⁺ = 363. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.67 (s, 1H), 9.75 (s, 1H), 7.69–7.63 (m, 4H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.10–7.07 (m, 1H), 4.30 (t, *J* = 7.2 Hz, 2H), 3.13 (t, *J* = 7.2 Hz, 2H), 2.09 (s, 3H).

The analogs prepared in the following table were prepared using the same method described for **Example 18**.

Examp le #	Compound No.	Starting materials Used	Structure	Condition	LCMS data

19	103	Intermediate 25 / Intermediate 10		P(<i>n</i> -Bu) ₃ , ADDP, THF	Method F: MS-ESI: 389 [M+H] ⁺ .
20	102	Intermediate 26 / Intermediate 10		P(<i>n</i> -Bu) ₃ , ADDP, THF	Method F: MS-ESI: 389 [M+H] ⁺ .
21	130	4- (trifluoromet hyl)phenol / Intermediate 14		PPh ₃ , DEAD, THF	Method D: MS-ESI: 361 [M-H] ⁻ .
22	115	4- (trifluoromet hyl)phenol / Intermediate 13		P(<i>n</i> -Bu) ₃ , ADDP, THF	Method F: MS-ESI: 347 [M-H] ⁻ .
23	108	Intermediate 23 / Intermediate 10		2- (tributylph osphoranyl idene)acet onitrile	Method F: MS-ESI: 412 [M+H] ⁺ .

Example 19: *N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)acetamide (Compound 103)



Step 1: *tert*-butyl 3-acetamido-5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indole-1-carboxylate

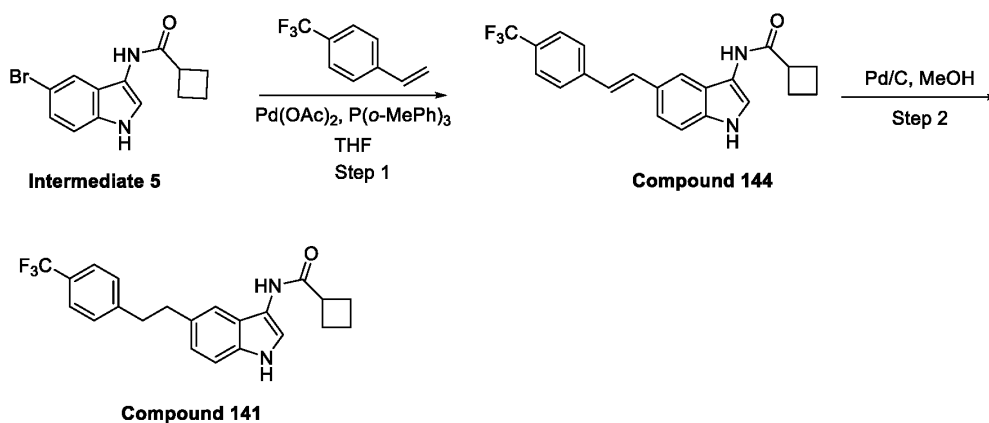
Cis-3-(4-(Trifluoromethyl)phenyl)cyclobutan-1-ol (2.5 g, 11.5 mmol, 1.0 equiv.) was dissolved in THF (40.0 mL) and cooled to 0 °C, then *tert*-butyl 3-acetamido-5-hydroxy-1*H*-indole-1-carboxylate (4.0 g, 13.8 mmol, 1.2 equiv.) and *n*-Bu₃P (3.5 g, 17.3 mmol, 1.5 equiv.) were added. This was followed by the addition of ADDP (5.7 g, 23.1 mmol, 2.0 equiv.) dropwise at 0 °C under a nitrogen atmosphere. The reaction mixture was heated to 70 °C for 3 hours, then cooled to ambient temperature and quenched by the addition of brine. The resulting solution was extracted with ethyl acetate, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with DCM/MeOH (10:1) to give *tert*-butyl 3-acetamido-5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indole-1-carboxylate (1.5 g) as a white solid. $[M+H]^+ = 489$.

Step 2: *N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)acetamide

tert-Butyl 3-acetamido-5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indole-1-carboxylate (1.5 g, 3.0 mmol, 1.0 equiv.) was dissolved in MeOH (15 mL), then K₂CO₃ (848.7 mg, 6.1 mmol, 2.0 equiv.) was added. The resulting mixture was stirred for 1 hour at 70 °C, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was further purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: water (10 mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 70% B in 7 min, 70% B; Wave Length: 220 nm; RT1(min): 7.53. This resulted in *N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-

yl)acetamide (435.0 mg) as a white solid. $[M+H]^+ = 389$. ^1H NMR (400 MHz, DMSO- d_6) δ 10.58 (s, 1H), 9.68 (s, 1H), 7.73–7.59 (m, 5H), 7.24–7.22 (m, 1H), 7.15 (d, $J = 2.0$ Hz, 1H), 6.75–6.72 (m, 1H), 4.95–4.89 (m, 1H), 3.84–3.77 (m, 1H), 2.72–2.60 (m, 4H), 2.08 (s, 3H).

- 5 **Examples** **24/25:** **(E)-N-(5-(4-(trifluoromethyl)styryl)-1H-indol-3-yl)cyclobutanecarboxamide (Compound 144) and N-(5-(4-(trifluoromethyl)phenethyl)-1H-indol-3-yl)cyclobutanecarboxamide (Compound 141)**



10

Step 1: (E)-N-(5-(4-(trifluoromethyl)styryl)-1H-indol-3-yl)cyclobutanecarboxamide

N-(5-bromo-1H-indol-3-yl)cyclobutanecarboxamide (1.0 g, 3.4 mmol, 1.0 equiv.) was dissolved in TEA (10 mL), then 1-(trifluoromethyl)-4-vinylbenzene (704.7 mg, 4.1 mmol, 1.2 equiv.), Pd(OAc)₂ (76.6 mg, 0.3 mmol, 0.1 equiv.) and tri(o-tolyl)phosphine (207.6 mg, 0.7 mmol, 0.2 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 100 °C for 16 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:2) to give material that was further purified by Flash-Prep-HPLC with the following conditions: Column: XBridge Shield RP18 OBD Column,

15

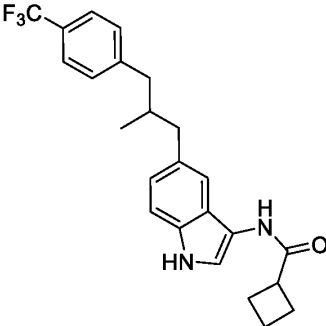
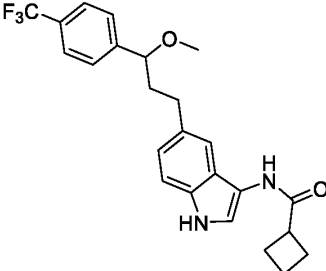
20

30*150 mm, 5 μ m; Flow rate: 60 mL/min; Gradient: 55% B to 70% B in 7 min; Wave Length: 254 nm; RT1: 6.97 min. This resulted in (E)-*N*-(5-(4-(trifluoromethyl)styryl)-1*H*-indol-3-yl)cyclobutanecarboxamide (33.3 mg) as a white solid. LCMS Method D: $[M+H]^+ = 385$. ^1H NMR (400 MHz, DMSO- d_6) δ 10.91 (s, 1H), 9.71 (s, 1H), 8.03 (s, 1H), 7.82–7.80 (m, 2H), 7.74–7.72 (m, 3H), 7.53–7.42 (m, 2H), 7.35 (d, 1H), 7.20 (d, 1H), 3.38–3.34 (m, 1H), 2.30–2.23 (m, 2H), 2.18–2.10 (m, 2H), 2.04–1.96 (m, 1H), 1.88–1.81 (m, 1H).

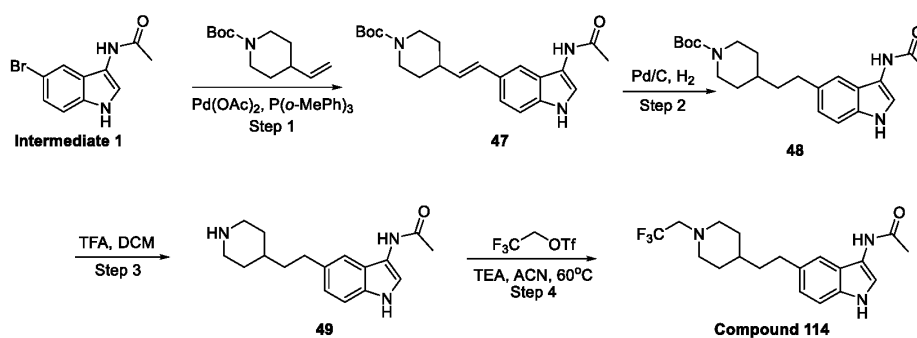
Step 2: *N*-(5-(4-(trifluoromethyl)phenethyl)-1*H*-indol-3-yl)cyclobutanecarboxamide

(E)-*N*-(5-(4-(trifluoromethyl)styryl)-1*H*-indol-3-yl)cyclobutanecarboxamide (200.0 mg, 0.5 mmol, 1.0 equiv.) was dissolved in MeOH (10 mL), then Pd/C (10%wt, 1.0 g) was added under an atmosphere of nitrogen. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 10 hours at ambient temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:3) to give material that was further purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μ m; Mobile Phase A: Water (10 mM NH_4HCO_3 +0.1% NH_4OH), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 75% B in 7 min; Wave Length: 220 nm; RT1r: 6.5 min. This resulted in *N*-(5-(4-(trifluoromethyl)phenethyl)-1*H*-indol-3-yl)cyclobutanecarboxamide (40.2 mg) as a white solid. LCMS Method D: $[M-H]^- = 385$. ^1H NMR (400 MHz, DMSO- d_6) δ 10.64 (s, 1H), 9.56 (s, 1H), 7.69 (s, 1H), 7.64–7.62 (m, 3H), 7.47 (d, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 8.4$ Hz, 1H), 7.00–6.97 (m, 1H), 3.38–3.33 (m, 1H), 3.05–2.95 (m, 4H), 2.28–2.23 (m, 2H), 2.14–2.10 (m, 1H), 2.04–1.95 (m, 1H), 1.84–1.81 (m, 1H).

The analogs prepared in following table were prepared using the same method described for **Example 25**.

Example #	Compound No.	Starting materials Used	Structure	LCMS data
26	137	Intermediate 35 / Intermediate 5		Method E: MS-ESI: 415 [M+H] ⁺ .
27	133	Intermediate 36 / Intermediate 5		Method D: MS-ESI: 431 [M+H] ⁺ .

Example 28: *N*-(5-(2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1*H*-indol-3-yl)acetamide (Compound 114)



Step 1: *tert*-butyl 4-[(*E*)-2-(3-acetamido-1*H*-indol-5-yl)ethenyl]piperidine-1-carboxylate

N-(5-bromo-1*H*-indol-3-yl)acetamide (2.0 g, 7.9 mmol, 1.0 equiv.) was dissolved in ACN (100 mL), then *tert*-butyl 4-ethenylpiperidine-1-carboxylate (2.5 g, 11.8 mmol, 1.5 equiv.), tri(*o*-tolyl)phosphine (962.0 mg, 3.2 mmol, 0.4 equiv.), Pd(AcO)₂ (177.4 mg, 0.8 mmol, 0.1 equiv.) and TEA (3.9 mL, 28.3 mmol, 3.6 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 100 °C for 10 hours, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give *tert*-butyl 4-[(*E*)-2-(3-acetamido-1*H*-indol-5-yl)ethenyl]piperidine-1-carboxylate (2.2 g) as a green solid. LCMS Method A: [M+H]⁺ = 384.

Step 2: *tert*-butyl 4-[2-(3-acetamido-1*H*-indol-5-yl)ethyl]piperidine-1-carboxylate

tert-Butyl 4-[(*E*)-2-(3-acetamido-1*H*-indol-5-yl)ethenyl]piperidine-1-carboxylate (1.3 g, 3.5 mmol, 1.0 equiv.) was dissolved in MeOH (40 mL), then Pd/C (10% wt., 270.0 mg) was added. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred overnight at ambient temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give *tert*-butyl 4-[2-(3-acetamido-1*H*-indol-5-yl)ethyl]piperidine-1-carboxylate (1.0 g) as a dark blue solid. LCMS Method A: [M+H]⁺ = 386.

Step 3: *N*-[5-[2-(piperidin-4-yl)ethyl]-1*H*-indol-3-yl]acetamide

tert-Butyl 4-[2-(3-acetamido-1*H*-indol-5-yl)ethyl]piperidine-1-carboxylate (377.0 mg, 1.0 mmol, 1.0 equiv.) was dissolved in DCM (30 mL) and TFA (10 mL). The reaction mixture was stirred overnight at ambient temperature and then concentrated under vacuum to afford *N*-[5-[2-(piperidin-4-yl)ethyl]-1*H*-indol-3-yl]acetamide (744.4 mg) as a brown oil, which was used in the next step directly without further purification. LCMS Method B: [M+H]⁺ = 286.

Step 4: *N*-(5-[2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]ethyl]-1*H*-indol-3-yl)acetamide

N-[5-[2-(piperidin-4-yl)ethyl]-1*H*-indol-3-yl]acetamide (744.0 mg, 2.6 mmol, 1.0 equiv.) was dissolved in ACN (100 mL), then 2,2,2-trifluoroethyl trifluoromethanesulfonate (726.1 mg, 3.1 mmol, 1.2 equiv.) and TEA (1.5 mL, 10.5 mmol,

4.0 equiv.) were added. The resulting mixture was heated to 60 °C overnight, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by Prep-HPLC with the following condition: Kinetex EVO C18 Column, 30*150, 5µm; Mobile Phase A: Water (10 mM NH₄HCO₃+0.1% NH₄OH), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 50% B to 70% B in 10 min; Wave Length: 220 nm. This resulted in *N*-(5-[2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]ethyl]-1*H*-indol-3-yl)acetamide (16.4 mg) as an off-white solid. LCMS Method E: [M+H]⁺ = 368. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.58 (s, 1H), 9.72 (s, 1H), 7.65–7.63 (m, 1H), 7.56–7.54 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.94–6.92 (m, 1H), 3.15–3.07 (m, 2H), 2.91–2.88 (m, 2H), 2.68–2.64 (m, 2H), 2.30–2.24 (m, 2H), 2.08 (s, 3H), 1.71–1.68 (m, 2H), 1.58–1.53 (m, 2H), 1.26–1.21 (m, 3H).

Example 29: *N*-(5-(4-(trifluoromethyl)phenoxy)-1*H*-indol-3-yl)acetamide (Compound 136)

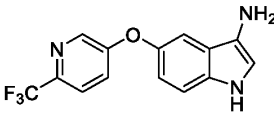
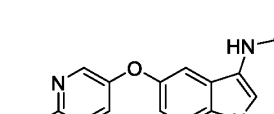
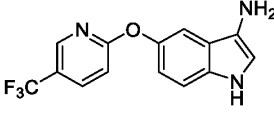
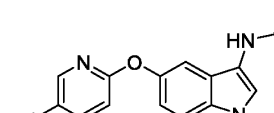
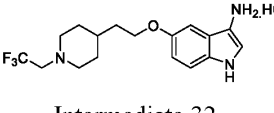
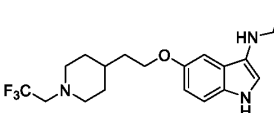
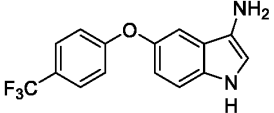
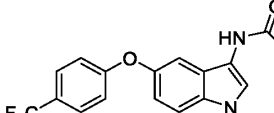


5-[2-[4-(trifluoromethyl)phenyl]ethoxy]-1*H*-indol-3-amine (350.0 mg, 1.1 mmol, 1.0 equiv.) and TEA (0.5 mL, 3.3 mmol, 3.0 equiv.) were dissolved in DCM (5 mL) and cooled to 0 °C, then acetyl chloride (0.1 mL, 1.3 mmol, 1.2 equiv.) was added, maintaining the solution at 0 °C. The reaction mixture was stirred for 30 min at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with ethyl acetate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (10:1) to give material that was further purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150mm, 5µm; Mobile Phase A: Water (10 mM NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 42 B to 56 B in 8 min; 254/220 nm; RT1: 7.35 min. This resulted in *N*-(5-[2-[4-(trifluoromethyl)phenyl]ethoxy]-1*H*-indol-3-yl)acetamide (148.3 mg) as a white solid. LCMS Method F: [M+H]⁺ = 363. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.57 (s, 1H), 9.68 (s, 1H), 7.71–7.65 (m, 2H), 7.60 (d, *J* = 8.0 Hz,

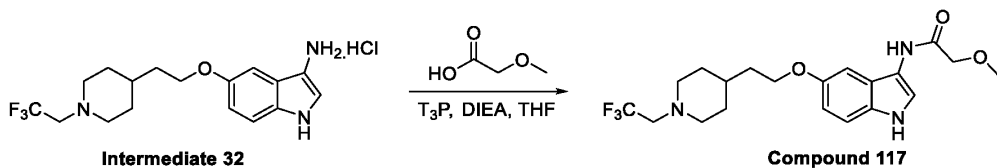
1H), 7.55–7.52 (m, 2H), 7.32 (s, 1H), 7.22–7.19 (m, 1H), 6.73–6.70 (m, 1H), 4.20 (t, $J = 6.8$ Hz, 2H), 3.18 (t, $J = 6.8$ Hz, 2H), 2.07 (s, 3H).

The analogs prepared in the following table were prepared using the same method described for **Example 29**.

5

Example #	Compound No.	Starting materials Used	Structure	LCMS data
30	123	 Intermediate 30		Method E: MS-ESI: 336 [M+H] ⁺ .
31	116	 Intermediate 31		Method D: MS-ESI: 336 [M+H] ⁺ .
32	122	 Intermediate 32		Method E: MS-ESI: 384 [M+H] ⁺ .
33	124	 Intermediate 29		Method F: MS-ESI: 335 [M+H] ⁺ .

Example 34: 2-methoxy-N-(5-(2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethoxy)-1H-indol-3-yl)acetamide (Compound 117)

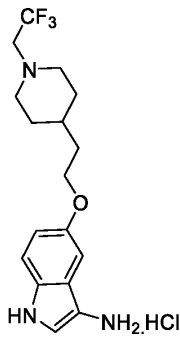
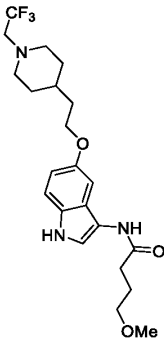
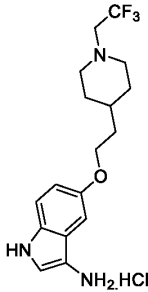
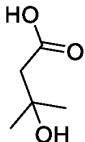
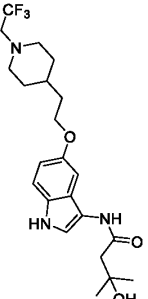
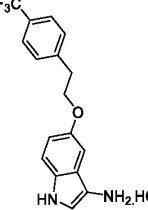
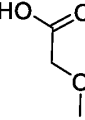
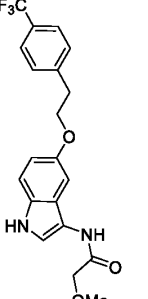


5-[2-[1-(2,2,2-Trifluoroethyl)piperidin-4-yl]ethoxy]-1*H*-indol-3-amine (200.0 mg, 0.6 mmol, 1.0 equiv.) was dissolved in THF (20 mL), then TEA (0.2 mL, 1.2 mmol, 2.0 equiv.), methoxyacetic acid (105.6 mg, 1.2 mmol, 2.0 equiv.) and T₃P (wt. 50% in ethyl acetate, 0.8 mL, 1.2 mmol, 2.0 equiv.) were added. The reaction mixture was stirred for 4 hours at ambient temperature, then concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 5% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in 2-methoxy-*N*-(5-[2-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]ethoxy]-1*H*-indol-3-yl)acetamide (88.5 mg) as a light yellow solid. LCMS Method D: [M+H]⁺ = 414. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.67 (s, 1H), 9.60 (s, 1H), 7.65 (d, *J* = 6.4 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.23–7.21 (m, 1H), 6.75–6.72 (m, 1H), 4.07 (s, 2H), 4.00 (t, *J* = 6.8 Hz, 2H), 3.37 (s, 3H), 3.17–3.09 (m, 2H), 2.93–2.90 (m, 2H), 2.34–2.28 (m, 2H), 1.71–1.68 (m, 4H), 1.53–1.47 (m, 1H), 1.30–1.27 (m, 2H).

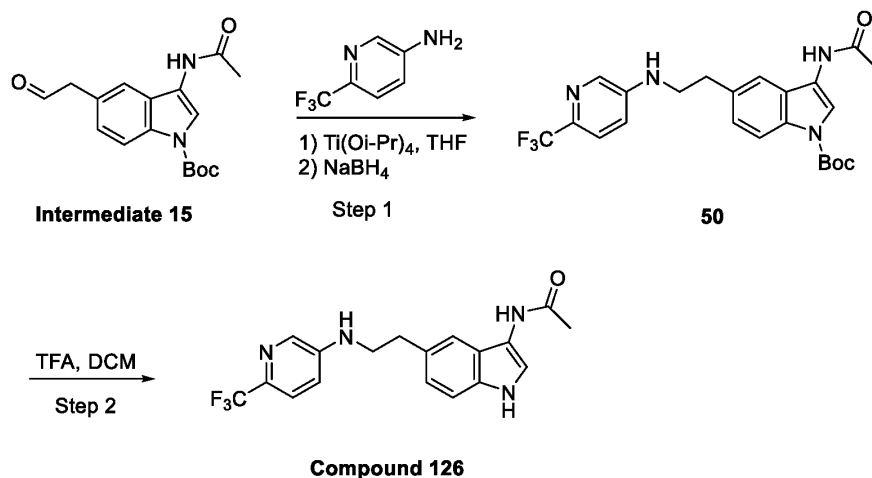
15

The analogs prepared in the following table were prepared using the same method described for **Example 34**.

Examp le #	Compou nd No.	Starting material A	Starting material B	Structure	LCMS data

35	121	 Intermediate 32			Method E: MS-ESI: 442 [M+H] ⁺ .
36	118	 Intermediate 32			Method E: MS-ESI: 442 [M+H] ⁺ .
37	107	 Intermediate 33			Method F: MS-ESI: 393 [M+H] ⁺ .

Example 38: N-(5-(2-(((6-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-1H-indol-3-yl)acetamide (Compound 126)



Step 1: *tert*-butyl 3-acetamido-5-(2-[[6-(trifluoromethyl)pyridin-3-yl]amino]ethyl)indole-1-carboxylate

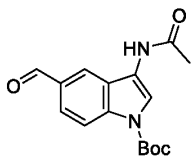
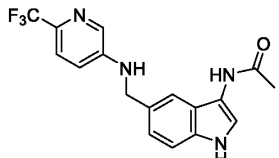
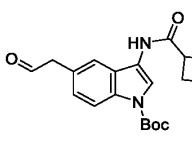
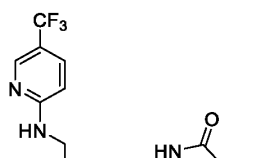
tert-Butyl 3-acetamido-5-(2-oxoethyl)indole-1-carboxylate (300.0 mg, 0.9 mmol, 1.0 equiv.) was dissolved in THF (20 mL), then 6-(trifluoromethyl)pyridin-3-amine (230.6 mg, 1.4 mmol, 1.5 equiv.) and Ti(Oi-Pr)₄ (539.0 mg, 1.9 mmol, 2.0 equiv.) were added. The reaction mixture was stirred for 2 hours at 70 °C, then cooled to ambient temperature. This was followed by the addition of NaBH₄ (71.8 mg, 1.9 mmol, 2.0 equiv.). The resulting mixture was stirred for an additional 1 hour at ambient temperature, then quenched by the addition of MeOH and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:2) to give *tert*-butyl 3-acetamido-5-(2-[[6-(trifluoromethyl)pyridin-3-yl]amino]ethyl)indole-1-carboxylate (200.0 mg) as a light yellow solid. LCMS Method B: [M+H]⁺ = 463.

Step 2: *N*-[5-(2-[[6-(trifluoromethyl)pyridin-3-yl]amino]ethyl)-1*H*-indol-3-yl]acetamide

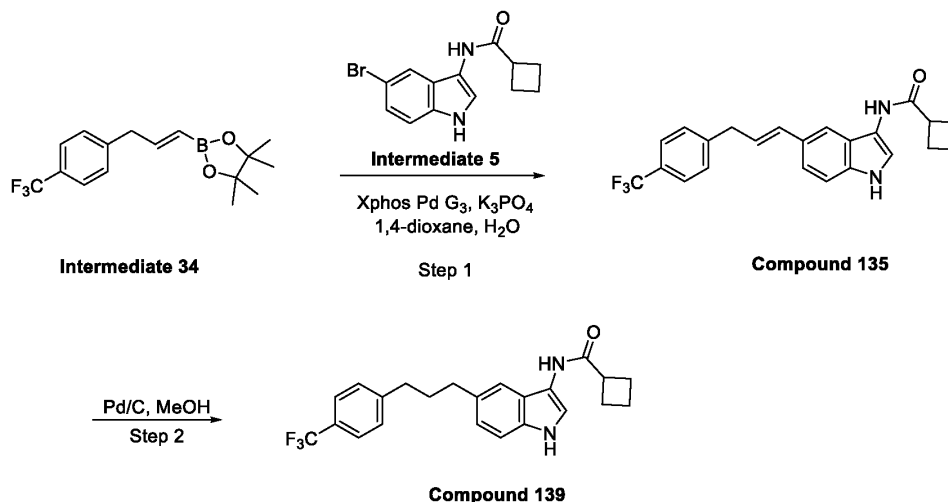
tert-Butyl 3-acetamido-5-(2-[[6-(trifluoromethyl)pyridin-3-yl]amino]ethyl)indole-1-carboxylate (100.0 mg, 0.2 mmol, 1.0 equiv.) was dissolved in DCM (10 mL) and TFA (1 mL). The reaction mixture was stirred for 1 hour at ambient temperature, then concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150mm, 5 μm; Mobile Phase A: Water (10 mM NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25 B to 55 B in 8 min; 220 nm; RT1: 7.23 min. This resulted in *N*-[5-(2-[[6-(trifluoromethyl)pyridin-3-

yl]amino]ethyl)-1*H*-indol-3-yl]acetamide (21.2 mg) as a light yellow solid. LCMS Method D: $[M+H]^+ = 363$. ^1H NMR (400 MHz, DMSO-*d*₆): δ 10.66 (s, 1H), 9.75 (s, 1H), 8.09 (d, $J = 2.8$ Hz, 1H), 7.66–7.65 (m, 2H), 7.54 (d, $J = 8.4$ Hz, 1H), 7.27 (d, $J = 8.4$ Hz, 1H), 7.06–7.03 (m, 2H), 6.77 (t, $J = 5.6$ Hz, 1H), 3.41–3.36 (m, 2H), 2.92 (t, $J = 7.2$ Hz, 2H), 2.08 (s, 3H).

The analogs prepared in the following table were prepared using the same method described for **Example 38**.

Example #	Compound No.	Intermediate	Structure	LCMS data
39	125	 Intermediate 17		Method D: MS-ESI: 349 $[M+H]^+$.
40	134	 Intermediate 16		Method E: MS-ESI: 403 $[M+H]^+$.

Example 41/42: (E)-N-(5-(3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-1*H*-indol-3-yl)cyclobutanecarboxamide (Compound 135) and N-(5-(3-(4-(trifluoromethyl)phenyl)propyl)-1*H*-indol-3-yl)cyclobutanecarboxamide (Compound 139)



Step 1: (E)-N-(5-(3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-1H-indol-3-yl)cyclobutanecarboxamide

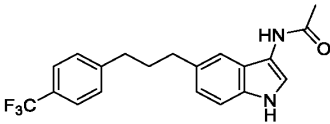
(E)-4,4,5,5-tetramethyl-2-(3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-1,3,2-dioxaborolane (150.0 mg, 0.5 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (3 mL) and water (0.3 mL), then *N*-(5-bromo-1H-indol-3-yl)cyclobutane carboxamide (169.1 mg, 0.6 mmol, 1.2 equiv.), K₃PO₄ (306.0 mg, 1.4 mmol, 3.0 equiv.) and Xphos Pd G₃ (81.4 mg, 0.1 mmol, 0.2 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 100 ° C for 4 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give material that was further purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mM NH₄HCO₃+0.1% NH₄OH), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 50% B to 80% B in 7 min; Wave Length: 220 nm; RT1: 6.02 min. This resulted in (E)-N-(5-(3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-1H-indol-3-yl)cyclobutanecarboxamide (19.0 mg) as a white solid. LCMS Method D: [M+H]⁺ = 399. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.75 (s, 1H), 9.62 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.72–7.67 (m, 3H), 7.53–7.49 (m, 2H), 7.26–7.20 (m, 2H), 6.56–6.52 (m, 1H), 6.33–6.27

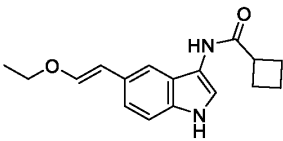
(m, 1H), 3.65 (d, $J = 7.2$ Hz, 2H), 2.34–2.33 (m, 1H), 2.27–2.22 (m, 2H), 2.14–2.09 (m, 2H), 1.96–1.92 (m, 1H), 1.84–1.81 (m, 1H).

Step 2: *N*-(5-(3-(4-(trifluoromethyl)phenyl)propyl)-1*H*-indol-3-yl)isobutyramide

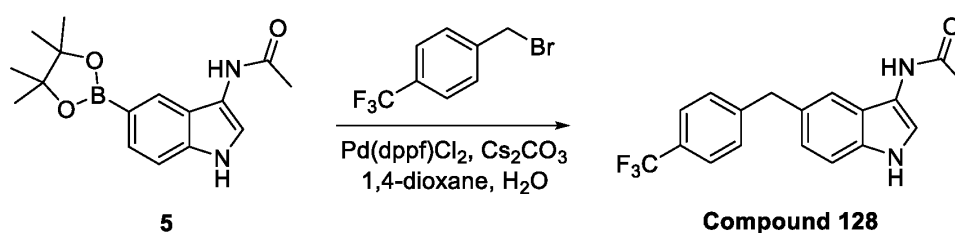
(*E*)-*N*-(5-(3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-1*H*-indol-3-yl)cyclobutanecarboxamide (150.0 mg, 0.4 mmol, 1.0 equiv.) was dissolved in MeOH (5 mL), then Pd/C (10% wt., 50.0 mg) was added under an atmosphere of nitrogen. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 10 hours at ambient temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by Flash-Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD Column, 30*50 mm, 5 μ m; Mobile Phase A: Water (10 mM NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 55% B to 70% B in 8 min; Wave Length: 254/220 nm; RT1: 7.73 min. This resulted in *N*-(5-(3-(4-(trifluoromethyl)phenyl)propyl)-1*H*-indol-3-yl)isobutyramide (30.0 mg) as a white solid. LCMS Method D: $[\text{M}+\text{H}]^+ = 401$. ^1H NMR (400 MHz, DMSO- d_6) δ 10.63 (s, 1H), 9.55 (s, 1H), 7.70–7.64 (m, 3H), 7.57 (s, 1H), 7.46 (d, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 8.4$ Hz, 1H), 6.96–6.94 (m, 1H), 3.37–3.34 (m, 1H), 2.75–2.66 (m, 4H), 2.27–2.22 (m, 2H), 2.12–2.09 (m, 2H), 2.03–1.95 (m, 3H), 1.88–1.83 (m, 1H).

The analogs prepared in the following table were prepared using the same method described for **Examples 41/42**.

Examp le #	Compou nd No.	Intermediates Used	Structure	LCMS data
43	132	Intermediate 34 Intermediate 1		Method D: MS-ESI: 359 $[\text{M}-\text{H}]^-$.

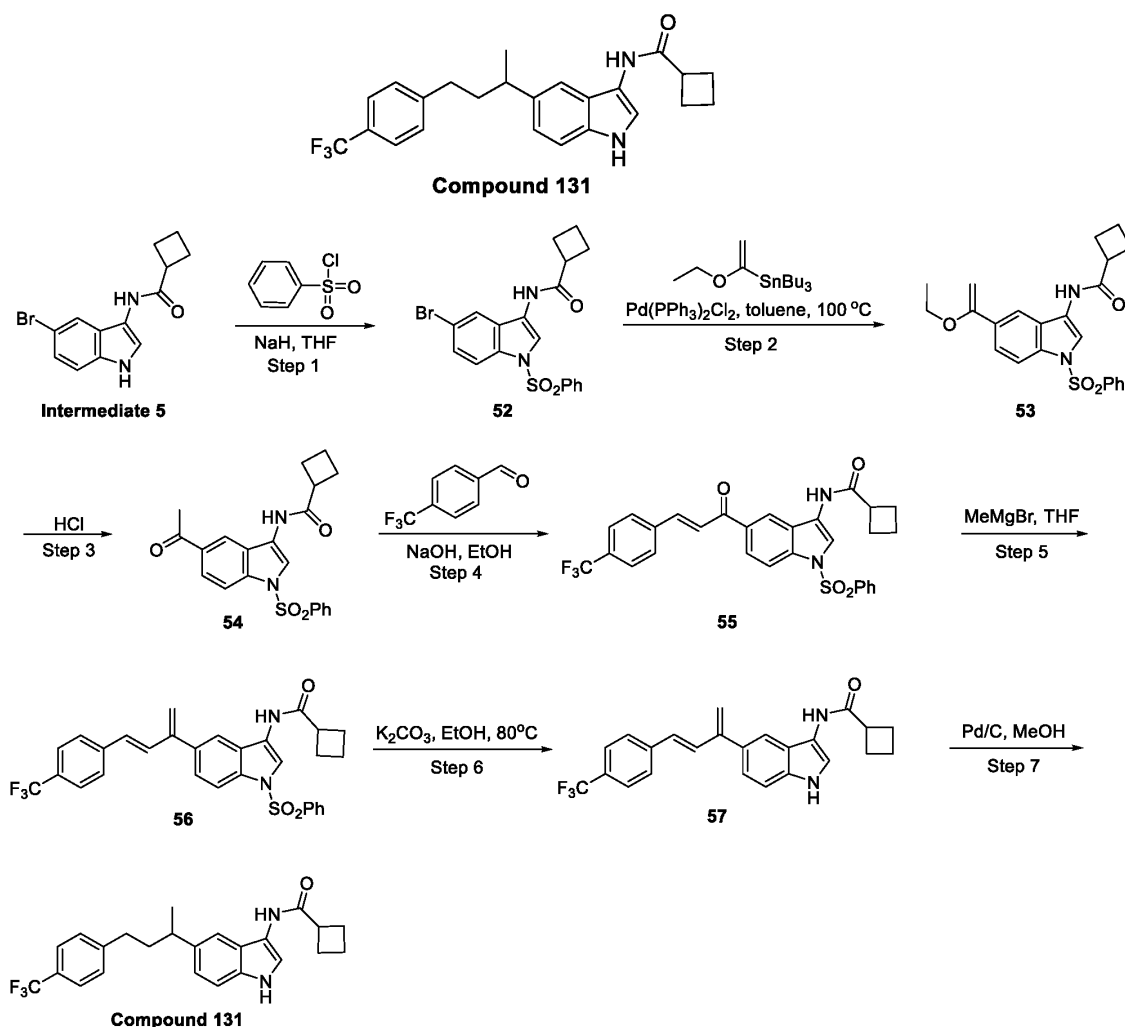
44	143	(E)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane / Intermediate 5		Method F: MS-ESI: 285 [M+H] ⁺ .
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Example 45: *N*-(5-(4-(trifluoromethyl)benzyl)-1*H*-indol-3-yl)acetamide (Compound 128)



N-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl] acetamide (296.4 mg, 1.0 mmol, 2 equiv.) and 1-(bromomethyl)-4-(trifluoromethyl)benzene (118.0 mg, 0.5 mmol, 1.0 equiv.) were dissolved in 1,4-dioxane (10 mL) and water (0.5 mL), then Cs₂CO₃ (402.1 mg, 1.2 mmol, 2.5 equiv.) and Pd(dppf)Cl₂ CH₂Cl₂ (80.4 mg, 0.1 mmol, 0.2 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 85 °C for 16 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give material that was further purified by Prep-HPLC with the following conditions: Column: YMC-Actus Triart C18 ExRS, 30 mm*150 mm, 5μm; Mobile Phase A: Water (10 mM NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 70% B in 7 min; 254/220 nm; RT1: 6.78min. This resulted in *N*-(5-[[4-(trifluoromethyl)phenyl]methyl]-1*H*-indol-3-yl)acetamide (46.3 mg) as a white solid. LCMS Method E: [M+H]⁺ = 333. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.69 (s, 1H), 9.76 (s, 1H), 7.66–7.63 (m, 4H), 7.44 (d, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 6.99–6.96 (m, 1H), 4.10 (s, 2H), 2.07 (s, 3H).

Example 46: *N*-(5-(4-(4-(trifluoromethyl)phenyl)butan-2-yl)-1*H*-indol-3-yl)cyclobutanecarboxamide (Compound 131)



Step 1: *N*-(5-bromo-1-(phenylsulfonyl)-1*H*-indol-3-yl)cyclobutanecarboxamide

N-(5-bromo-1*H*-indol-3-yl)cyclobutanecarboxamide (3.0 g, 10.2 mmol, 1.0 equiv.) was dissolved in THF (30 mL) and cooled to 0 °C, then NaH (60% wt., 0.6 g, 15.9 mmol, 1.5 equiv.) was added, maintaining the solution at 0 °C. This was followed by the dropwise addition of benzenesulfonyl chloride (1.5 mL, 12.3 mmol, 1.2 equiv.), maintaining the reaction mixture at 0 °C. The reaction mixture was stirred for 2 hours at ambient temperature and then quenched by the addition of water. The resulting solution

was extracted with ethyl acetate, washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:4) to give *N*-(5-bromo-1-(phenylsulfonyl)-1*H*-indol-3-yl)cyclobutanecarboxamide (1.2 g) as a yellow solid. LCMS Method A: [M+H]⁺ = 433.

Step 2: *N*-(5-(1-ethoxyvinyl)-1-(phenylsulfonyl)-1*H*-indol-3-yl)cyclobutanecarboxamide

N-(5-bromo-1-(phenylsulfonyl)-1*H*-indol-3-yl)cyclobutanecarboxamide (1.2 g, 2.8 mmol, 1.0 equiv.) was dissolved in toluene (20 mL), then tributyl(1-ethoxyethenyl)stannane (3.0 g, 8.4 mmol, 3.0 equiv.) and Pd(PPh₃)₂Cl₂ (380.1 mg, 0.4 mmol, 0.2 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 100 °C for 14 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give crude *N*-(5-(1-ethoxyvinyl)-1-(phenylsulfonyl)-1*H*-indol-3-yl)cyclobutanecarboxamide (920.0 mg) as a yellow solid. LCMS Method A: [M+H]⁺ = 425.

Step 3: *N*-(5-acetyl-1-(phenylsulfonyl)-1*H*-indol-3-yl)cyclobutanecarboxamide

N-[1-(benzenesulfonyl)-5-(1-ethoxyethenyl)indol-3-yl]cyclobutanecarboxamide (1.5 g, 3.5 mmol, 1.0 equiv.) was dissolved in aqueous HCl (2 N, 20 mL). The reaction mixture was stirred for 3 hours at ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give *N*-(5-acetyl-1-(phenylsulfonyl)-1*H*-indol-3-yl)cyclobutanecarboxamide (1.0 g) as a yellow solid. LCMS Method A: [M+H]⁺ = 397.

Step 4: (Z)-*N*-(1-(phenylsulfonyl)-5-(3-(4-(trifluoromethyl)phenyl)acryloyl)-1*H*-indol-3-yl)cyclobutanecarboxamide

N-[5-acetyl-1-(benzenesulfonyl)indol-3-yl]cyclobutanecarboxamide (1.0 g, 2.5 mmol, 1.0 equiv.) and 4-(trifluoromethyl)benzaldehyde (527.0 mg, 3.0 mmol, 1.2 equiv.) were dissolved in EtOH (20 mL) and cooled to 0 °C, then NaOH aqueous (2 M, 12 mL, 24.0 mmol, 10.0 equiv.) was added dropwise, maintaining the solution at 0 °C. The reaction mixture was stirred for 5 hours at ambient temperature and then quenched by the addition

of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to give (Z)-N-(1-(phenylsulfonyl)-5-(3-(4-(trifluoromethyl)phenyl)acryloyl)-1H-indol-3-yl)cyclobutanecarboxamide (1.2 g) as a yellow solid. LCMS Method B: [M-H]⁻ = 551. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.25 (s, 1H), 9.93 (s, 1H), 8.78 (s, 1H), 8.13–8.09 (m, 3H), 7.98–7.96 (m, 1H), 7.91 (d, *J* = 2.4 Hz, 1H), 7.87–7.83 (m, 3H), 7.46 (d, *J* = 8.8 Hz, 1H), 3.46–3.42 (m, 1H), 2.30–2.26 (m, 2H), 2.16–2.14 (m, 2H), 2.02–1.98 (m, 1H), 1.88–1.85 (m, 1H).

Step 5: (Z)-N-(1-(phenylsulfonyl)-5-(4-(4-(trifluoromethyl)phenyl)buta-1,3-dien-2-yl)-1H-indol-3-yl)cyclobutanecarboxamide

(E)-N-(1-(phenylsulfonyl)-5-(3-(4-(trifluoromethyl)phenyl)acryloyl)-1H-indol-3-yl)cyclobutanecarboxamide (1.2 g, 2.2 mmol, 1.0 equiv.) was dissolved in THF (50 mL) and cooled to 0 °C, then MeMgBr (3 M in THF, 2.2 mL, 6.6 mmol, 3.0 equiv.) was added dropwise, maintaining the solution at 0 °C. The reaction mixture was stirred for 18 hours at ambient temperature and then quenched by the addition of ice water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (3:2) to give (Z)-N-(1-(phenylsulfonyl)-5-(4-(4-(trifluoromethyl)phenyl)buta-1,3-dien-2-yl)-1H-indol-3-yl)cyclobutanecarboxamide (1.2 g) as a yellow solid. LCMS Method A: [M+H]⁺ = 551.

Step 6: (E)-N-(5-(4-(4-(trifluoromethyl)phenyl)buta-1,3-dien-2-yl)-1H-indol-3-yl)cyclobutanecarboxamide

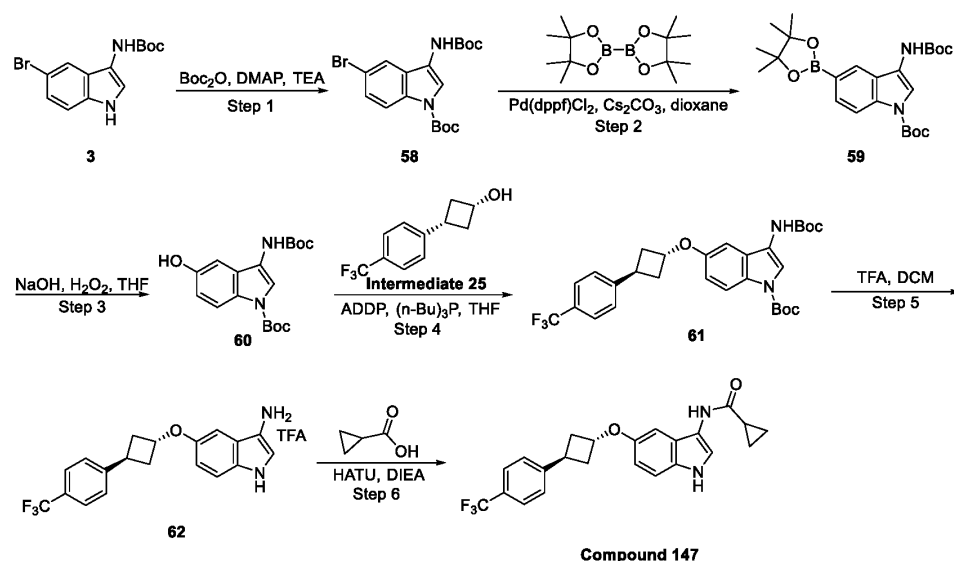
(Z)-N-(1-(phenylsulfonyl)-5-(4-(4-(trifluoromethyl)phenyl)buta-1,3-dien-2-yl)-1H-indol-3-yl)cyclobutanecarboxamide (1.2 g, 2.2 mmol, 1.0 equiv.) was dissolved in MeOH (10 mL), then K₂CO₃ (0.9 g, 6.3 mmol, 2.9 equiv.) was added. The reaction mixture was heated to 80 °C for 4 hours, then cooled to ambient temperature and quenched by the addition of ice-water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give (E)-N-(5-(4-(4-(trifluoromethyl)phenyl)buta-1,3-dien-2-yl)-1H-indol-3-

yl)cyclobutanecarboxamide (290.0 mg) as a yellow solid. LCMS Method A: $[M+H]^+ = 411$.

Step 7: *N*-(5-(4-(4-(trifluoromethyl)phenyl)butan-2-yl)-1*H*-indol-3-yl)cyclobutanecarboxamide

5 (E)-*N*-(5-(4-(4-(trifluoromethyl)phenyl)buta-1,3-dien-2-yl)-1*H*-indol-3-yl)cyclobutanecarboxamide (230.0 mg, 0.6 mmol, 1.0 equiv.) was dissolved in MeOH (10 mL), then Pd/C (10% wt., 100.0 mg) was added. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 48 hours at ambient temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give material that was further purified by Prep-HPLC with the following conditions Column: XBridge Prep OBD C18 Column, 30*150mm, 5 μ m; Mobile Phase A: Water (10 mM NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 50 % to 85 % in 8 min; 220 nm; RT1: 7.33 min. This
10 resulted in *N*-(5-(4-(4-(trifluoromethyl)phenyl)butan-2-yl)-1*H*-indol-3-yl)cyclobutanecarboxamide (32.1 mg) as a white solid. LCMS Method D: $[M+H]^+ = 415$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.63 (s, 1H), 9.58 (s, 1H), 7.71 (d, *J* = 6.4 Hz, 1H), 7.63–7.61 (m, 3H), 7.39–7.37 (m, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.00–6.97 (m, 1H), 3.39–3.33 (m, 2H), 2.76–2.74 (m, 1H), 2.60–2.54 (m, 1H), 2.28–2.23 (m, 2H), 2.13–2.10 (m,
15 2H), 1.97–1.90 (m, 3H), 1.88–1.83 (m, 1H), 1.29 (d, *J* = 7.2 Hz, 3H).

Example 47: *N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclopropanecarboxamide (Compound 147)



Step 1: *tert*-butyl 5-bromo-3-((*tert*-butoxycarbonyl)amino)-1*H*-indole-1-carboxylate

tert-Butyl (5-bromo-1*H*-indol-3-yl)carbamate (5.0 g, 16.1 mmol, 1.0 equiv.) was dissolved in THF (80.0 mL), then (Boc)₂O (4.2 g, 19.3 mmol, 1.2 equiv.), DMAP (0.2 g, 1.6 mmol, 0.1 equiv.) and TEA (4.6 mL, 32.1 mmol, 2.0 equiv.) were added. The reaction mixture was stirred for 4 hours at ambient temperature and then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give *tert*-butyl 5-bromo-3-((*tert*-butoxycarbonyl)amino)-1*H*-indole-1-carboxylate (6.5 g) as a white solid.

Step 2: *tert*-butyl 3-((*tert*-butoxycarbonyl)amino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-1-carboxylate

tert-Butyl 5-bromo-3-((*tert*-butoxycarbonyl)amino)-1*H*-indole-1-carboxylate (6.0 g, 14.6 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (100.0 mL), then 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (5.6 g, 21.9 mmol, 1.5 equiv.), Pd(dppf)Cl₂ (1.1 g, 1.5 mmol, 0.1 equiv.) and Cs₂CO₃ (9.5 g, 29.2 mmol, 2.0 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred overnight at 90 °C under nitrogen, then cooled to ambient temperature and concentrated under vacuum. The residue was

purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:4) to give *tert*-butyl 3-((*tert*-butoxycarbonyl)amino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-1-carboxylate (6.0 g) as a white solid.

Step 3: *tert*-butyl 3-((*tert*-butoxycarbonyl)amino)-5-hydroxy-1*H*-indole-1-carboxylate

tert-Butyl 3-((*tert*-butoxycarbonyl)amino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-1-carboxylate (6.0 g, 13.1 mmol, 1.0 equiv.) was dissolved in THF (80.0 mL) and cooled to 0 °C. Then NaOH (1.6 g, 39.3 mmol, 3.0 equiv.) was added at 0 °C, followed by the addition of H₂O₂ (3.0 g, 26.2 mmol, 2.0 equiv., 30%) dropwise, maintaining the reaction mixture at 0 °C. The reaction mixture was stirred for 2 hours at ambient temperature, then quenched by the addition of brine. The resulting resolution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give *tert*-butyl 3-((*tert*-butoxycarbonyl)amino)-5-hydroxy-1*H*-indole-1-carboxylate (2.2 g) as a grey solid.

Step 4: *tert*-butyl 3-((*tert*-butoxycarbonyl)amino)-5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indole-1-carboxylate

tert-Butyl 3-((*tert*-butoxycarbonyl)amino)-5-hydroxy-1*H*-indole-1-carboxylate (1.0 g, 2.9 mmol, 1.0 equiv.) and cis-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol (1.2 g, 5.7 mmol, 2.0 equiv.) were dissolved in THF (20.0 mL) and cooled to 0 °C, then *n*-Bu₃P (1.7 g, 8.6 mmol, 3.0 equiv.) was added at 0 °C under an atmosphere of nitrogen. This was followed by the addition of ADDP (2.2 g, 8.6 mmol, 3.0 equiv.) dropwise, maintaining the solution at 0 °C. The reaction mixture was heated to 50 °C for 2 hours, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase A: 0.05% NH₄HCO₃ in water; mobile phase B: Acetonitrile, 45% phase B to 70% gradient in 20 min; detector, UV 254 nm. This resulted in *tert*-butyl 3-((*tert*-

butoxycarbonyl)amino)-5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indole-1-carboxylate (1.2 g) as an off-white solid.

Step 5: 5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-amine TFA salt

5 *tert*-Butyl 3-((*tert*-butoxycarbonyl)amino)-5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indole-1-carboxylate (190.0 mg, 0.3 mmol, 1.0 equiv.) was dissolved in DCM (2.0 mL), then TFA (2.0 mL) was added. The resulting mixture was stirred for 1 hour at ambient temperature and then concentrated under vacuum to give 5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-amine TFA salt (120.0 mg) as a white solid.

10

Step 6: *N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclopropanecarboxamide

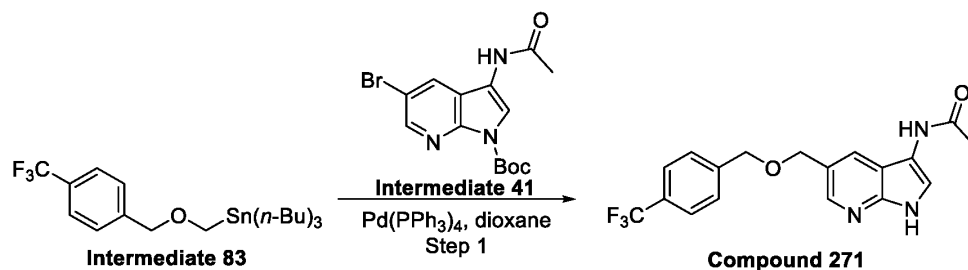
5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-amine TFA salt (100.0 mg, 0.3 mmol, 1.0 equiv.) was dissolved in THF (5.0 mL), then cyclopropanecarboxylic acid (29.8 mg, 0.3 mmol, 1.2 equiv.), HATU (131.7 mg, 0.3 mmol, 1.2 equiv.) and DIEA (0.1 mL, 0.6 mmol, 2.0 equiv.) were added. The reaction mixture was stirred for 1 hour at ambient temperature, then concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase A: 0.05% NH₄HCO₃ in water; mobile phase B: Acetonitrile, 30% to 60% gradient in 30 min; detector, UV 254 nm. The resulting material was further purified by Prep-HPLC with the following conditions: Column, XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; mobile phase, Aqueous (10 mmol/L NH₄HCO₃) and ACN (43% ACN up to 73% in 7 min). This resulted in *N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclopropanecarboxamide (12.1 mg) as a white solid. [M+H]⁺ = 415. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.57 (d, *J* = 1.6 Hz, 1H), 9.91 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 2.4 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.26–7.16 (m, 2H), 6.75–6.72 (m, 1H), 4.98–4.88 (m, 1H), 3.83–3.77 (m, 1H), 2.75–2.59 (m, 4H), 1.94–1.89 (m, 1H), 0.82–0.76 (m, 4H).

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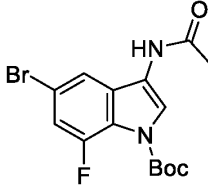
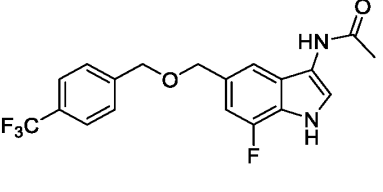
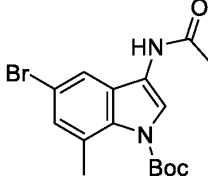
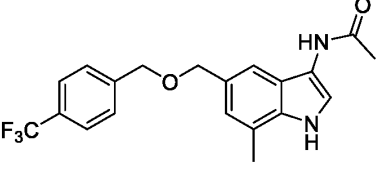
Example 48: *N*-(5-(((4-(trifluoromethyl)benzyl)oxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetamide (Compound 271)



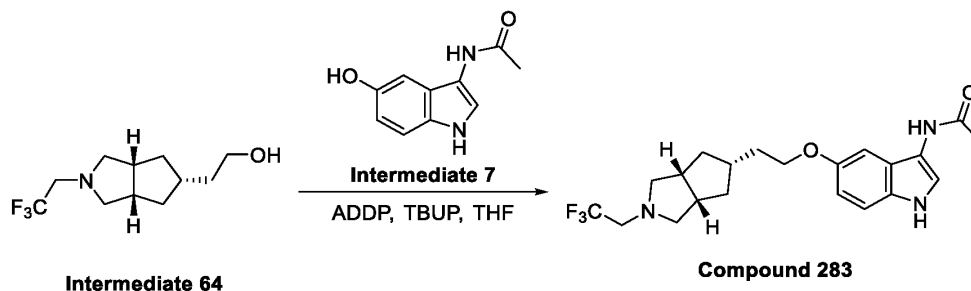
tert-Butyl 3-acetamido-5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (200.0 mg, 0.6 mmol, 1.0 equiv.) was dissolved in dioxane (5 mL), then tributyl(((4-(trifluoromethyl)benzyl)oxy)methyl)stannane (324.7 mg, 0.7 mmol, 1.2 equiv.), cataCXium A-Pd-G2 (37.8 mg, 0.1 mmol, 0.1 equiv.) and cataCXium A (40.5 mg, 0.1 mmol, 0.2 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 110 °C for 6 hours, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (10:1) to give material which was further purified by Prep-HPLC with the following conditions: Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mM NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 52% B in 8 min; Wave Length: 254/220 nm. This gave *N*-(5-(((4-(trifluoromethyl)benzyl)oxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetamide (24.0 mg) as a white solid. LCMS Method E: [M+H]⁺ = 364. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.33 (s, 1H), 9.99 (s, 1H), 8.23–8.21 (m, 2H), 7.76 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 4.68–4.66 (m, 4H), 2.08 (s, 3H).

The analogs prepared in the following table were prepared using the same method described for **Example 48**.

Example #	Compound No.	Starting materials Used	Structure	LCMS data
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49	276	 Intermediate 41		Method D: MS-ESI: 379 [M-H] ⁻ .
50	272	 Intermediate 42		Method F: MS-ESI: 375 [M-H] ⁻ .

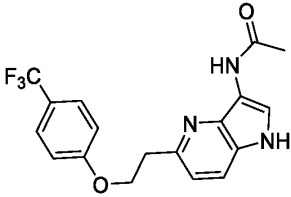
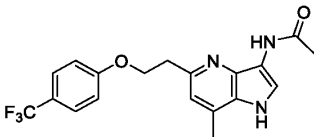
Example 51: *N*-(5-(2-((3*aR*,5*r*,6*aS*)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[*c*]pyrrol-5-yl)ethoxy)-1*H*-indol-3-yl)acetamide (Compound 283)

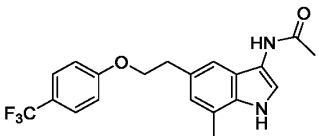
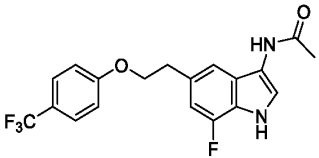
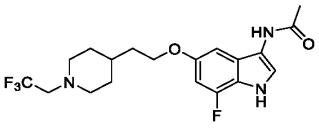
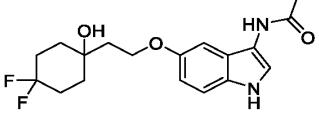
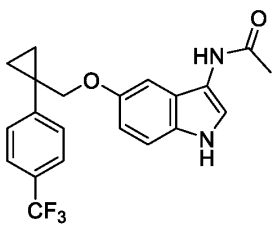
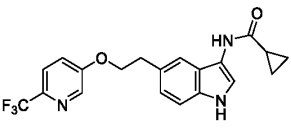


5 2-((3*aR*,5*r*,6*aS*)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[*c*]pyrrol-5-yl)ethan-1-ol (200.0 mg, 0.8 mmol, 1.0 equiv.) was dissolved in THF (8 mL), then *N*-(5-hydroxy-1*H*-indol-3-yl)acetamide (160.3 mg, 0.8 mmol, 1.0 equiv.), ADDP (422.0 mg, 1.7 mmol, 2.0 equiv.) and TBUP (340.5 mg, 1.7 mmol, 2.0 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred overnight at ambient temperature then quenched
10 by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18;

mobile phase, MeOH in water, 10% to 50% gradient in 10 min; detector, UV 254 nm. The resulting material was further purified by Prep-HPLC with the following conditions: Column: Xselect CSH C18 OBD Column 30*150mm 5 μ m, n; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21% B to 35% B in 7 min; Wave Length: 254, 220 nm; RT1: 6.23 min. This gave *N*-(5-(2-((3*aR*,5*r*,6*aS*)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[*c*]pyrrol-5-yl)ethoxy)-1*H*-indol-3-yl)acetamide (25.8 mg) as a white solid. LCMS Method D: [M+H]⁺ = 410. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.58 (s, 1H), 7.22–7.19 (m, 2H), 6.81–6.78 (m, 1H), 4.04 (t, *J* = 6.4 Hz, 2H), 3.14–3.06 (m, 2H), 2.73–2.71 (m, 2H), 2.59–2.54 (m, 2H), 2.52–2.48 (m, 2H), 2.21 (s, 3H), 2.19–2.14 (m, 2H), 2.04–1.98 (m, 1H), 1.92–1.84 (m, 2H), 1.14–1.06 (m, 2H).

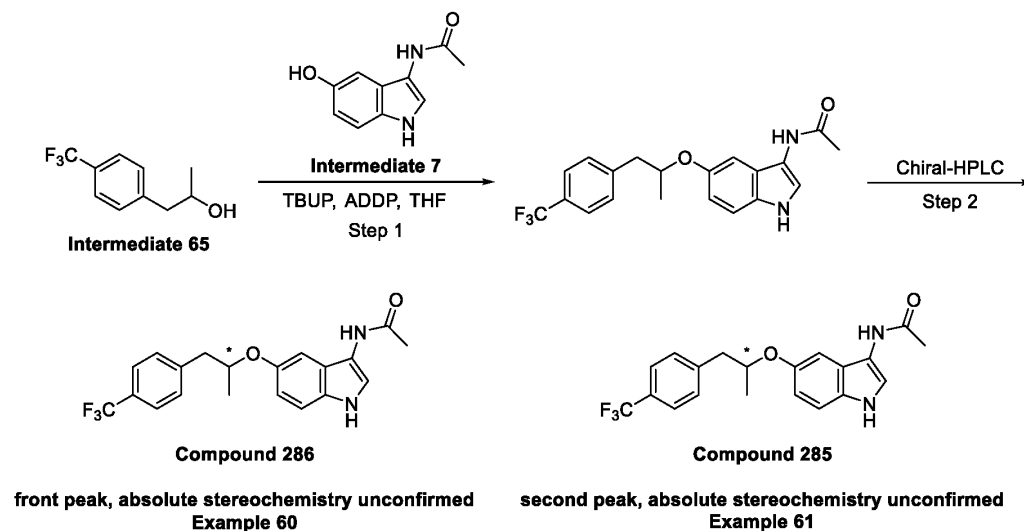
The analogs prepared in the following table were prepared using the same method described for **Example 51**.

Example #	Compound No.	Starting materials Used	Structure	Condition	LCMS data
52	255	4-(trifluoromethyl)phenol / Intermediate 51		PPh ₃ , DIAD, THF	Method G MS-ESI: 364 [M+H] ⁺ .
53	259	4-(trifluoromethyl)phenol / Intermediate 58		TBUP, ADDP, THF	Method F: MS-ESI: 378 [M+H] ⁺ .

54	264	4-(trifluoromethyl)phenol / Intermediate 50		TBUP, ADDP, THF	Method F: MS-ESI: 377 [M+H] ⁺ .
55	270	4-(trifluoromethyl)phenol / Intermediate 49		TBUP, ADDP, THF	Method D: MS-ESI: 379 [M-H] ⁻ .
56	277	Intermediate 45 / Intermediate 20		TBUP, ADDP, THF	Method F: MS-ESI: 402 [M+H] ⁺ .
57	278	Intermediate 7 / Intermediate 68		TBUP, ADDP, THF	Method E: MS-ESI: 353 [M+H] ⁺ .
58	289	Intermediate 7 / Intermediate 65		TBUP, ADDP, THF	Method G: MS-ESI: 389 [M+H] ⁺ .
59	167	Intermediate 54 / 6-(trifluoromethyl)		TBUP, ADDP, THF	Method F: MS-ESI:

		yl)pyridin-3- ol			390 [M+H] ⁺ .
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Example 60/61: *N*-(5-((1-(4-(trifluoromethyl)phenyl)propan-2-yl)oxy)-1*H*-indol-3-yl)acetamide (Compound 286) (front peak, absolute stereochemistry unconfirmed) and (Compound 285) (second peak, absolute stereochemistry unconfirmed)]



5 Step 1: *N*-[5-([1-[4-(trifluoromethyl)phenyl]propan-2-yl]oxy)-1*H*-indol-3-yl]acetamide

N-(5-hydroxy-1*H*-indol-3-yl)acetamide (500.0 mg, 2.6 mmol, 1.0 equiv.) was dissolved in THF (20 mL), then 1-[4-(trifluoromethyl)phenyl]propan-2-ol (536.8 mg, 2.6 mmol, 1.0 equiv.), TBUP (1.1 g, 5.2 mmol, 2.0 equiv.) and ADDP (1.3 g, 5.3 mmol, 2.0 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred for 16 hours at ambient temperature under nitrogen, then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give *N*-[5-([1-[4-(trifluoromethyl)phenyl]propan-2-yl]oxy)-1*H*-indol-3-yl]acetamide (33 mg) as a light yellow oil. LCMS Method A: [M+H]⁺ = 377.

Step 2: Example 60 (Compound 286) (front peak, absolute stereochemistry unconfirmed) and Example 61 (Compound 285) (second peak, absolute stereochemistry unconfirmed)

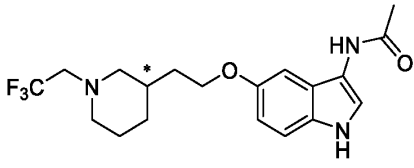
The racemic *N*-[5-([1-[4-(trifluoromethyl)phenyl]propan-2-yl]oxy)-1*H*-indol-3-yl]acetamide (20.0 mg) was separated by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK AD-H, 2*25 cm, 5 μ m; Mobile Phase A: Hex (0.5% 2M NH₃-MeOH)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 13 min; Wave Length: 220/254 nm; RT1(min): 9.03; RT2(min): 11.75. This gave **Compound 286** (front peak, 1.3 mg) as a white solid and **Compound 285** (second peak, 3.1 mg) as a white solid.

Example 60 (Compound 286): LCMS Method G: [M+H]⁺ = 377. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.56 (s, 1H), 9.66 (s, 1H), 7.68–7.64 (m, 3H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.70–6.67 (m, 1H), 4.64–4.60 (m, 1H), 3.09–3.00 (m, 2H), 2.08 (s, 3H), 1.26 (d, *J* = 6.0 Hz, 3H).

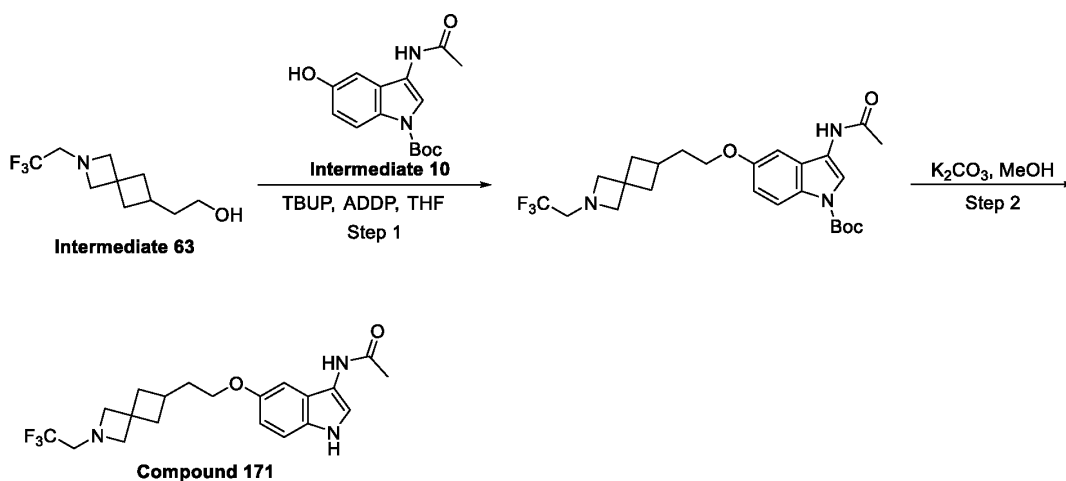
Example 61 (Compound 285): LCMS Method G: [M+H]⁺ = 377. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.56 (s, 1H), 9.66 (s, 1H), 7.68–7.64 (m, 3H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.70–6.67 (m, 1H), 4.64–4.60 (m, 1H), 3.09–3.00 (m, 2H), 2.08 (s, 3H), 1.26 (d, *J* = 6.0 Hz, 3H).

The analogs prepared in the following table were prepared using the same method described for **Example 60/61**.

Example #	Compound No.	Starting materials Used	Structure	LCMS data
62	280	Intermediate 7 / Intermediate 67	front peak, absolute stereochemistry unconfirmed	Method G: MS-ESI: 384 [M+H] ⁺ .

63	279	Intermediate 7 / Intermediate 67	 second peak, absolute stereochemistry unconfirmed	Method G: MS-ESI: 384 [M+H] ⁺ .
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Example 64: *N*-(5-(2-(2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl)ethoxy)-1*H*-indol-3-yl)acetamide (Compound 171)



Step 1: *tert*-butyl 3-acetamido-5-{2-[2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl]ethoxy}indole-1-carboxylate

2-[2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl]ethanol (180.0 mg, 0.8 mmol, 1.0 equiv.) and *tert*-butyl 3-acetamido-5-hydroxyindole-1-carboxylate (234.1 mg, 0.8 mmol, 1.0 equiv.) were dissolved in THF (4 mL), then TBUP (326.3 mg, 1.6 mmol, 2.0 equiv.) and ADDP (403.7 mg, 1.6 mmol, 2.0 equiv.) were added. The reaction mixture was heated to 70 °C for 2 hours, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, ACN in water, 10% to 100% gradient in 15 min; detector, UV 254 nm. This gave *tert*-butyl 3-acetamido-5-{2-[2-(2,2,2-trifluoroethyl)-

2-azaspiro[3.3]heptan-6-yl]ethoxy}indole-1-carboxylate (220.0 mg) as a light yellow solid. LCMS Method A: $[M+H]^+ = 496$.

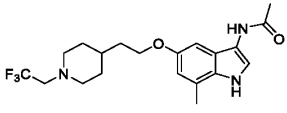
Step 2: *N*-(5-(2-(2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl)ethoxy)-1*H*-indol-3-yl)acetamide

5 *tert*-Butyl 3-acetamido-5-{2-[2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl]ethoxy}indole-1-carboxylate (200.0 mg, 0.4 mmol, 1.0 equiv.) was dissolved in MeOH (3 mL), then K_2CO_3 (167.3 mg, 1.2 mmol, 3.0 equiv.) was added. The reaction mixture was heated to 70 °C for 2 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with

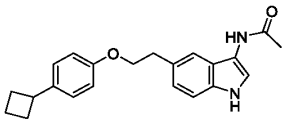
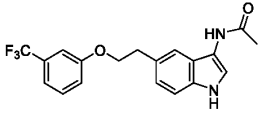
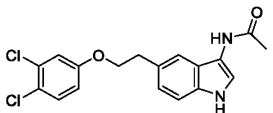
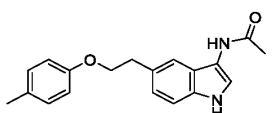
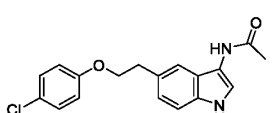
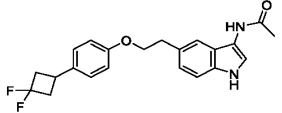
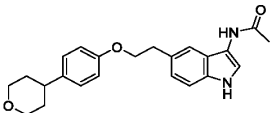
10 brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5 μ m; Mobile Phase A: Water (10 mM NH_4HCO_3 +0.1% $NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 53% B in 8 min; Wave Length: 220 nm; RT1: 7.58 min. This gave *N*-(5-(2-(2-(2,2,2-trifluoroethyl)-2-

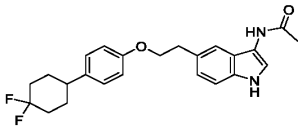
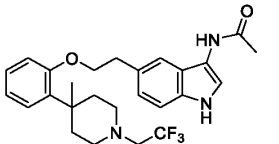
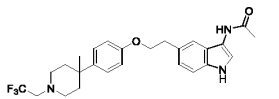
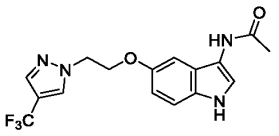
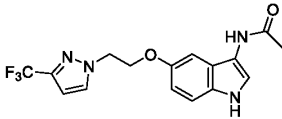
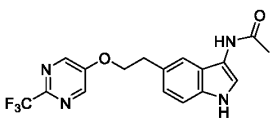
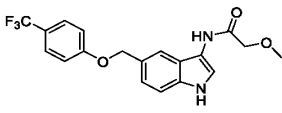
15 *azaspiro[3.3]heptan-6-yl)ethoxy)-1*H*-indol-3-yl)acetamide (110.0 mg) as a pale white solid. LCMS Method E: $[M+H]^+ = 396$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 10.54 (s, 1H), 9.68 (s, 1H), 7.64 (d, $J = 2.8$ Hz, 1H), 7.27 (d, $J = 2.8$ Hz, 1H), 7.19 (d, $J = 8.8$ Hz, 1H), 6.71–6.89 (m, 1H), 3.87 (t, $J = 6.4$ Hz, 2H), 3.35–3.33 (m, 2H), 3.24 (s, 2H), 3.14–3.06 (m, 2H), 2.33–2.24 (m, 3H), 2.08 (s, 3H), 1.81–1.79 (m, 4H).*

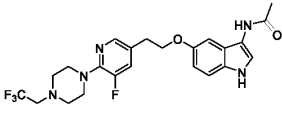
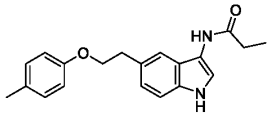
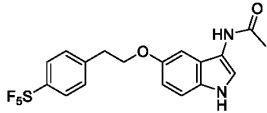
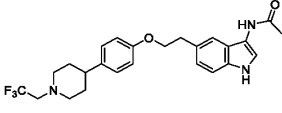
20 The analogs prepared in following table were prepared using the same method described for **Example 64**.

Example #	Compound No.	Starting materials Used	Structure	Condition	LCMS data
65	281	Intermediate 20 / Intermediate 46		TBUP, ADDP, THF	Method F: MS-ESI: 398 $[M+H]^+$.

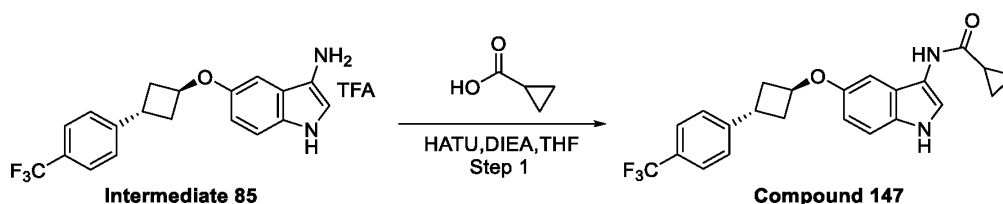
66	267	2-(4-(trifluoromethyl)phenyl)ethan-1-ol / Intermediate 47		TBUP, ADDP, THF	Method E: MS-ESI: 364 [M+H] ⁺ .
67	262	Intermediate 69 / Intermediate 10		TBUP, ADDP, THF	Method F: MS-ESI: 361 [M+H] ⁺ .
68	257	Intermediate 70 / Intermediate 10		PPh ₃ , DIAD, THF	Method F: MS-ESI: 447 [M+H] ⁺ .
69	254	Intermediate 71 / Intermediate 10		TBUP, ADDP, THF	Method G: MS-ESI: 433 [M+H] ⁺ .
70	247	(4-(trifluoromethyl)phenyl)methanol / Intermediate 10		TBUP, ADDP, THF	Method F: MS-ESI: 349 [M+H] ⁺ .
71	232	Intermediate 11 / 6-(trifluoromethyl)pyridin-3-ol		TBUP, ADDP, THF	Method F: MS-ESI: 364 [M+H] ⁺ .

72	230	Intermediate 11 / 4- cyclobutylph enol		TBUP, ADDP, THF	Method F: MS-ESI: 349 [M+H] ⁺ .
73	231	Intermediate 11 / 3- (trifluoromet hyl)phenol		TBUP, ADDP, THF	Method F: MS-ESI: 363 [M+H] ⁺ .
74	214	Intermediate 11 / 3,4- dichlorophen ol		PPh ₃ , DIAD, THF	Method F: MS-ESI: 363 [M+H] ⁺ .
75	228	Intermediate 11 / 4- methylpheno l		TBUP, ADDP, THF	Method F: MS-ESI: 309 [M+H] ⁺ .
76	229	Intermediate 11 / 4- chlorophenol		TBUP, ADDP, THF	Method F: MS-ESI: 329 [M+H] ⁺ .
77	225	Intermediate 11 / Intermediate 73		TBUP, ADDP, THF	Method E: MS-ESI: 385 [M+H] ⁺ .
78	226	Intermediate 11 / Intermediate 74		CMPB, toluene	Method F: MS-ESI: 379 [M+H] ⁺ .

79	224	Intermediate 11 / Intermediate 75		TBUP, ADDP, THF	Method F: MS-ESI: 413 [M+H] ⁺ .
80	208	Intermediate 11 / Intermediate 77		TBUP, ADDP, THF	Method F: MS-ESI: 474 [M+H] ⁺ .
81	198	Intermediate 11 / Intermediate 78		TBUP, ADDP, THF	Method F: MS-ESI: 474 [M+H] ⁺ .
82	197	Intermediate 79 / Intermediate 10		TBUP, ADDP, THF	Method F: MS-ESI: 353 [M+H] ⁺ .
83	196	Intermediate 80 / Intermediate A10		PPh ₃ , DIAD, THF	Method D: MS-ESI: 453 [M+H] ⁺ .
84	184	Intermediate 11 / 2- (trifluoromet hyl)pyrimidi n-5-ol		TBUP, ADDP, THF	Method E: MS-ESI: 365 [M+H] ⁺ .
85	273	Intermediate 57 / 4- (trifluoromet hyl)phenol		TBUP, ADDP, THF	Method F: MS-ESI: 379 [M+H] ⁺ .

86	253	Intermediate 72 / Intermediate 10		TBUP, ADDP, THF	Method G: MS-ESI: 480 [M+H] ⁺ .
87	168	Intermediate 55 / p- methylpheno 1		TBUP, ADDP, THF	Method E: MS-ESI: 323 [M+H] ⁺ .
88	169	Intermediate 62 / Intermediate 10		TBUP, ADDP, THF	Method F: MS-ESI: 419 [M-H] ⁻ .
89	170	Intermediate 11 / Intermediate 76		TBUP, ADDP, THF	Method E: MS-ESI: 460 [M+H] ⁺ .

Examples 90: N-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)cyclopropanecarboxamide (Compound 147)

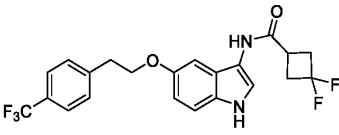
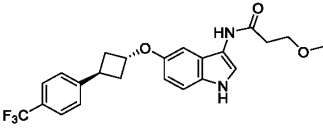
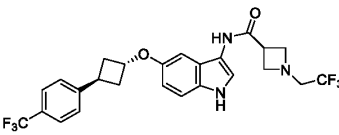
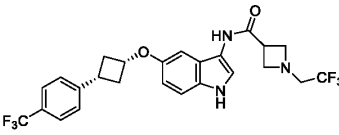
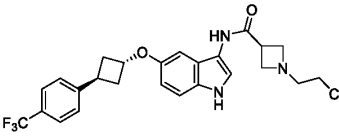
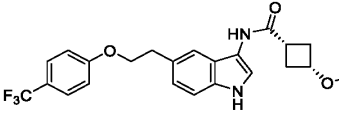


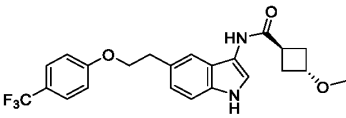
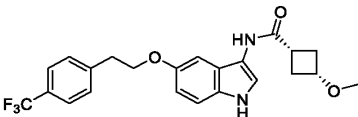
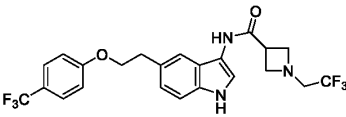
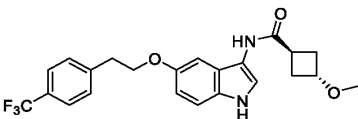
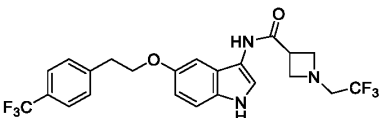
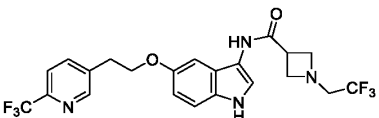
5-(trans-3-(4-(Trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-amine TFA salt (100.0 mg, 0.3 mmol, 1.0 equiv.) was dissolved in THF (5 mL), then cyclopropanecarboxylic acid (29.8 mg, 0.3 mmol, 1.2 equiv.), HATU (131.7 mg, 0.3 mmol, 1.2 equiv.) and DIEA (74.6 mg, 0.6 mmol, 2.0 equiv.) were added. The reaction mixture was stirred for 1 hour at ambient temperature and then concentrated under vacuum. The residue was purified by reverse flash chromatography with the following

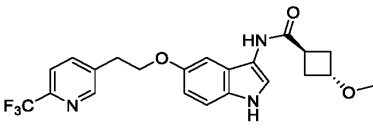
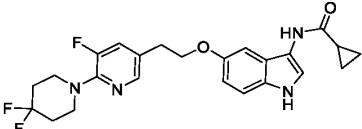
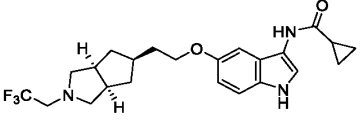
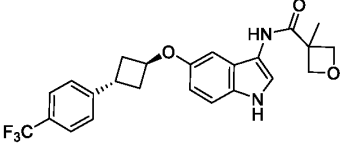
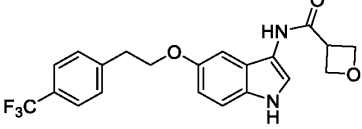
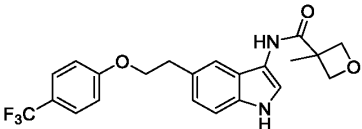
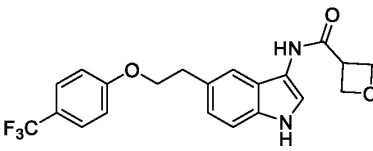
conditions: column, C18 silica gel; mobile phase A: 0.05% NH₄HCO₃ in water; mobile phase B: Acetonitrile, 30% B to 60% B gradient in 30 min; detector, UV 254 nm. The resulting crude product was further purified by Prep-HPLC with the following conditions: Column, XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; mobile phase, Water (10 mM NH₄HCO₃) and ACN (43% ACN up to 73% in 7 min). This gave *N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclopropanecarboxamide (29.8 mg) as a white solid. LCMS Method 68: [M+H]⁺ = 415. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.57 (d, *J* = 2.0 Hz, 1H), 9.91 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 2.4 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.24–7.18 (m, 2H), 6.75–6.72 (m, 1H), 4.95–4.91 (m, 1H), 3.81–3.78 (m, 1H), 2.71–2.63 (m, 4H), 1.93–1.89 (m, 1H), 0.81–0.78 (m, 4H).

The analogs prepared in the following table were prepared using the same method described for **Example 90**.

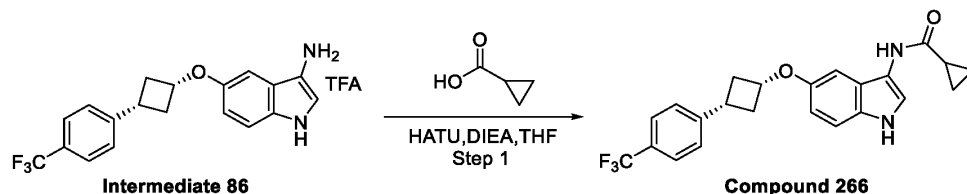
Example #	Compound No.	Starting materials Used	Structure	LCMS data
91	258	Intermediate 85 / 2-methoxyacetic acid		Method E: MS-ESI: 419 [M+H] ⁺ .
92	260	Intermediate 86 / methoxyacetic acid		Method E: MS-ESI: 419 [M+H] ⁺ .
93	252	Intermediate 33 / cyclopropanecarboxylic acid		Method F: MS-ESI: 387 [M+H] ⁺ .
94	251	Intermediate 33 / 1-methylcycloprop		Method F: MS-ESI:

		ane-1-carboxylic acid		403 [M+H] ⁺ .
95	249	Intermediate 33 / 3,3-difluorocyclobutane-1-carboxylic acid		Method F: MS-ESI: 437 [M-H] ⁻ .
96	241	Intermediate 85 / 3-methoxypropanoic acid		Method E: MS-ESI: 433 [M+H] ⁺ .
97	244	Intermediate 85 / 1-(2,2,2-trifluoroethyl)azetidine-3-carboxylic acid		Method D: MS-ESI: 512 [M+H] ⁺ .
98	243	Intermediate 86 / 1-(2,2,2-trifluoroethyl)azetidine-3-carboxylic acid		Method D: MS-ESI: 512 [M+H] ⁺ .
99	227	Intermediate 85 / Intermediate 102		Method D: MS-ESI: 524 [M-H] ⁻ .
100	221	Intermediate 92 / cis-3-methoxycyclobutane-1-carboxylic acid		Method F: MS-ESI: 433 [M+H] ⁺ .

101	220	Intermediate 92 / trans-3- methoxycyclobut ane-1-carboxylic acid		Method D: MS-ESI: 431 [M-H] ⁻ .
102	222	Intermediate 33 / cis-3- methoxycyclobut ane-1-carboxylic acid		Method F: MS-ESI: 433 [M+H] ⁺ .
103	219	Intermediate 92 / 1-(2,2,2- trifluoroethyl)aze tidine-3- carboxylic acid		Method F: MS-ESI: 486 [M+H] ⁺ .
104	211	Intermediate 33 / trans-3- methoxycyclobut ane-1-carboxylic acid		Method D: MS-ESI: 431 [M-H] ⁻ .
105	210	Intermediate 33 / 1-(2,2,2- trifluoroethyl)aze tidine-3- carboxylic acid		Method F: MS-ESI: 486 [M+H] ⁺ .
106	195	Intermediate 88 / 1-(2,2,2- trifluoroethyl)aze tidine-3- carboxylic acid		Method E: MS-ESI: 487 [M+H] ⁺ .

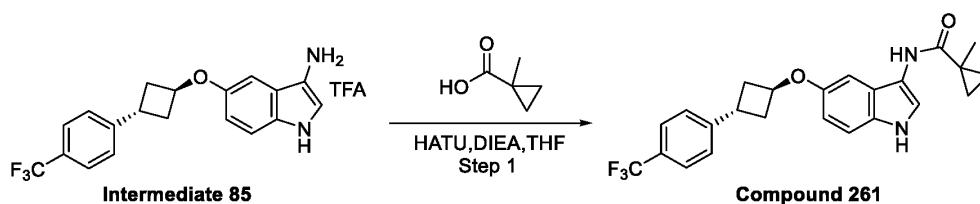
107	194	Intermediate 88 / trans-3-methoxycyclobutane-1-carboxylic acid		Method D: MS-ESI: 434 [M+H] ⁺ .
108	183	Intermediate 89 / cyclopropanecarboxylic acid		Method F: MS-ESI: 459 [M+H] ⁺ .
109	182	Intermediate 90 / cyclopropanecarboxylic acid		Method D: MS-ESI: 436 [M+H] ⁺ .
110	148	Intermediate 85 / 3-methyloxetane-3-carboxylic acid		Method E: MS-ESI: 445 [M+H] ⁺ .
111	163	Intermediate 33 / oxetane-3-carboxylic acid		Method F: MS-ESI: 405 [M+H] ⁺ .
112	165	Intermediate 92 / 3-methyloxetane-3-carboxylic acid		Method F: MS-ESI: 417 [M-H] ⁻ .
113	164	Intermediate 92 / oxetane-3-carboxylic acid		Method F: MS-ESI: 403 [M-H] ⁻ .

Examples 114: *N*-(5-(cis-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclopropanecarboxamide (Compound 266)



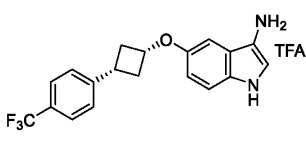
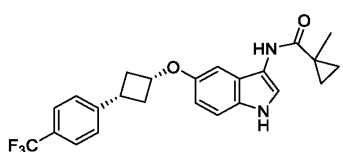
5-(cis-3-(4-(Trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-amine TFA salt (100.0 mg, 0.3 mmol, 1.0 equiv.) was dissolved in THF (5 mL), then cyclopropanecarboxylic acid (29.8 mg, 0.3 mmol, 1.2 equiv.), HATU (131.7 mg, 0.3 mmol, 1.2 equiv.) and DIEA (74.6 mg, 0.6 mmol, 2.0 equiv.) were added. The reaction mixture was stirred for 1 hour at ambient temperature and then concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase A: 0.05% NH₄HCO₃ in water; mobile phase B: Acetonitrile, 30% B to 60% B gradient in 30 min; detector, UV 254 nm. The resulting material was further purified by Prep-HPLC with the following conditions: Column, XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; mobile phase, Water (10 mM NH₄HCO₃) and ACN (43% ACN up to 73% in 7 min). This gave *N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclopropanecarboxamide (30.1 mg) as a white solid. LCMS Method E: [M+H]⁺ = 415. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.57 (d, *J* = 2.0 Hz, 1H), 9.95 (s, 1H), 7.70–7.66 (m, 3H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 6.75–6.72 (m, 1H), 4.73–4.69 (m, 1H), 3.32–3.30 (m, 1H), 3.06–2.99 (m, 2H), 2.22–2.14 (m, 2H), 1.96–1.91 (m, 1H), 0.84–0.76 (m, 4H).

Example 115: **1-methyl-*N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclopropane-1-carboxamide (Compound 261)**

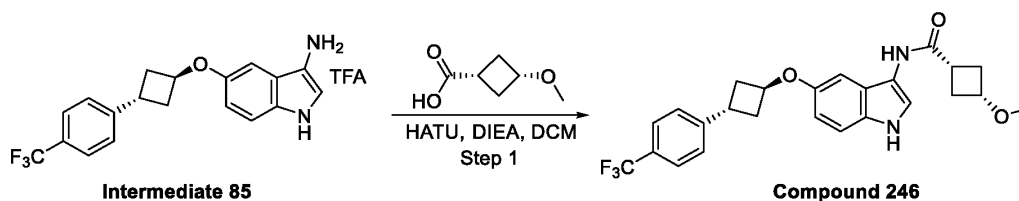


5-(trans-3-(4-(Trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-amine TFA salt (100.0 mg, 0.3 mmol, 1.0 equiv.) was dissolved in THF (5 mL), then 1-methylcyclopropane-1-carboxylic acid (34.5 mg, 0.3 mmol, 1.2 equiv.), HATU (131.7 mg, 0.3 mmol, 1.2 equiv.) and DIEA (74.6 mg, 0.6 mmol, 2.0 equiv.) were added. The reaction mixture was stirred for 1 hour at ambient temperature and then concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase A: 0.05% NH₄HCO₃ in water; mobile phase B: Acetonitrile, 30% B to 60% B gradient in 30 min; detector, UV 254 nm. The resulting crude product was further purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 75% B in 7 min; Wave Length: 220 nm. This gave 1-methyl-*N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclopropane-1-carboxamide (19.9 mg) as a white solid. LCMS Method E: [M+H]⁺ = 429. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.66 (s, 1H), 8.96 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.75–6.73 (m, 1H), 4.95–4.91 (m, 1H), 3.85–3.79 (m, 1H), 2.64–2.61 (m, 4H), 1.45 (s, 3H), 1.09–1.07 (m, 2H), 0.62–0.60 (m, 2H).

The analogs prepared in the following table were prepared using the same method described for **Example 115**.

Example #	Compound No.	Starting materials Used	Structure	LCMS data
116	263	 Intermediate 86		Method E: MS-ESI: 336 [M+H] ⁺ .

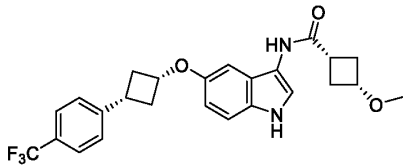
Example 117: *cis*-3-methoxy-*N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (Compound 246)



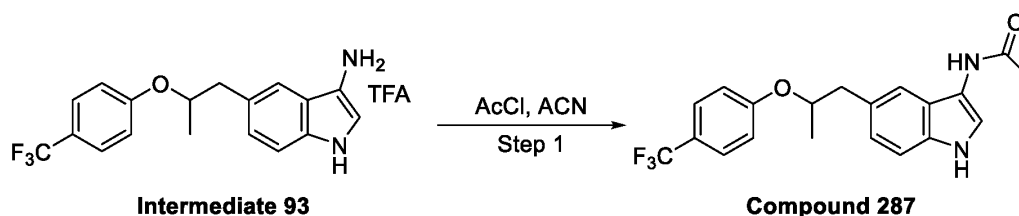
5-(trans-3-(4-(Trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-amine TFA salt (250 mg, 0.7 mmol, 1.5 equiv.) was dissolved in DCM (5 mL), then cis-3-methoxycyclobutane-1-carboxylic acid (62.6 mg, 0.4 mmol, 1.0 equiv.), HATU (274.4 mg, 0.7 mmol, 1.5 equiv.) and DIEA (310.9 mg, 2.4 mmol, 5.0 equiv.) were added. The reaction mixture was stirred for 0.5 hour at ambient temperature and then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5 μ m; Mobile Phase A: Water (10 mM NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 46% B to 69% B in 8 min; Wave Length: 220 nm. This gave cis-3-methoxy-*N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (53.9 mg) as a white solid. LCMS Method F: $[\text{M}+\text{H}]^+ = 459$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.60 (s, 1H), 9.64 (s, 1H), 7.76–7.71 (m, 3H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.22 (d, $J = 8.8$ Hz, 1H), 7.13 (d, $J = 2.4$ Hz, 1H), 6.75–6.72 (m, 1H), 4.93–4.89 (m, 1H), 3.82–3.78 (m, 2H), 3.15 (s, 3H), 2.84–2.81 (m, 1H), 2.68–2.63 (m, 4H), 2.42–2.37 (m, 2H), 2.07–2.02 (m, 2H).

The analogs prepared in the following table were prepared using the same method described for **Example 117**.

Example #	Compound No.	Starting materials Used	Structure	LCMS data
118	242	Intermediate 85 / trans-3-methoxycyclob		Method E: MS-ESI: 459 $[\text{M}+\text{H}]^+$.

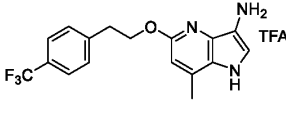
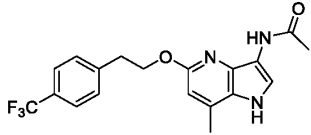
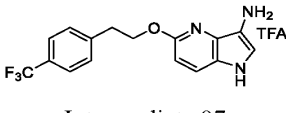
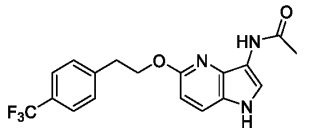
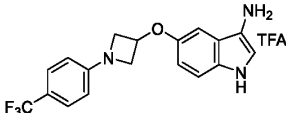
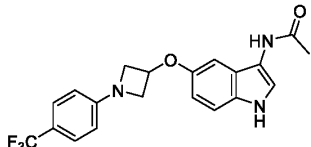
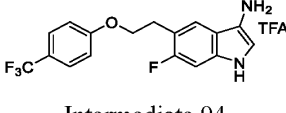
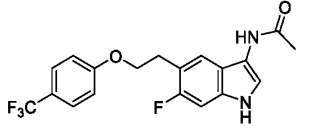
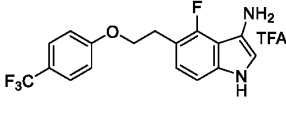
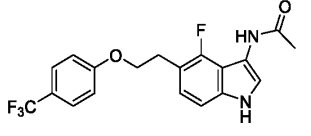
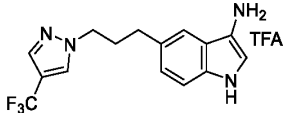
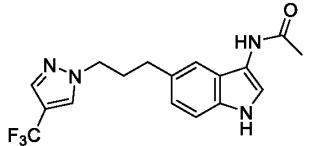
		utane-1-carboxylic acid		
119	245	Intermediate 86 / cis-3-methoxycyclobutane-1-carboxylic acid		Method E: MS-ESI: 459 [M+H] ⁺ .

Example 120: *N*-(5-(2-(4-(trifluoromethyl)phenoxy)propyl)-1*H*-indol-3-yl)acetamide (Compound 287)



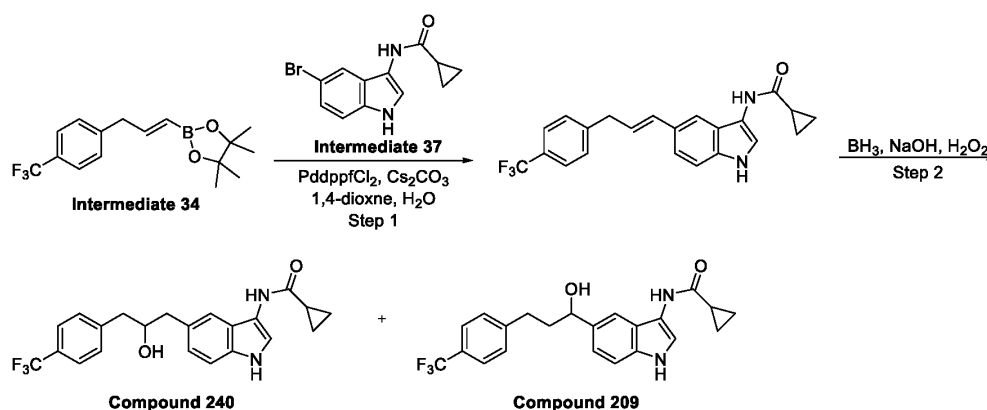
- 5-[2-[4-(Trifluoromethyl)phenoxy]propyl]-1*H*-indol-3-amine (100.0 mg, 0.2 mmol, 1.0 equiv.) and TEA (90.8 mg, 0.8 mmol, 3.0 equiv.) were dissolved in ACN (10 mL) and cooled to 0 °C, then AcCl (70.4 mg, 0.8 mmol, 3.0 equiv.) was added, maintaining the solution at 0 °C. The reaction mixture was stirred for 4 hours at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum.
- The residue was purified by Prep-HPLC with the following conditions: Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mM NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 67% B in 8 min; Wave Length: 220 nm; RT1: 7.7 min. This gave *N*-(5-[2-[4-(trifluoromethyl)phenoxy]propyl]-1*H*-indol-3-yl)acetamide (10.5 mg) as a white solid. LCMS Method E: [M-H]⁻ = 375. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.67 (d, *J* = 1.2 Hz, 1H), 9.78 (s, 1H), 7.66–7.62 (m, 4H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.06–7.04 (m, 1H), 4.82–4.76 (m, 1H), 3.14–3.09 (m, 1H), 2.92–2.87 (m, 1H), 2.09 (s, 3H), 1.27 (d, *J* = 6.0 Hz, 3H).

The analogs prepared in the following table were prepared using the same method described for **Example 120**.

Examp le #	Compou nd No.	Starting materials Used	Structure	LCMS data
121	250	 Intermediate 96		Method F: MS-ESI: 378 [M+H] ⁺ .
122	248	 Intermediate 97		Method D: MS-ESI: 364 [M+H] ⁺ .
123	233	 Intermediate 87		Method F: MS-ESI: 390 [M+H] ⁺ .
124	223	 Intermediate 94		Method F: MS-ESI: 381 [M+H] ⁺ .
125	213	 Intermediate 95		Method E: MS-ESI: 379 [M-H] ⁻ .
126	212	 Intermediate 98		Method E: MS-ESI: 351 [M+H] ⁺ .

Example 127/128: *N*-(5-(2-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1*H*-indol-3-yl)cyclopropanecarboxamide (Compound 240) and *N*-(5-(1-hydroxy-3-(4-

**(trifluoromethyl)phenyl)propyl)-1*H*-indol-3-yl)cyclopropanecarboxamide
(Compound 209)**



Step 1: (*E*)-*N*-(5-(3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-1*H*-indol-3-yl)cyclopropanecarboxamide

N-(5-Bromo-1*H*-indol-3-yl)cyclopropanecarboxamide (500.0 mg, 1.7 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (15 mL) and water (1.5 mL), then 4,4,5,5-tetramethyl-2-[(1*E*)-3-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl]-1,3,2-dioxaborolane (559.1 mg, 1.7 mmol, 1.0 equiv.), Cs₂CO₃ (1167.2 mg, 3.5 mmol, 2.0 equiv.) and Pd(dppf)Cl₂.CH₂Cl₂ (145.9 mg, 0.1 mmol, 0.1 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 100 °C for 12 hours under nitrogen, then cooled to ambient temperature and concentrated under vacuum. The residue was diluted with water, extracted with ethyl acetate, washed with water, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:5) to give (*E*)-*N*-(5-(3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-1*H*-indol-3-yl)cyclopropanecarboxamide (400.0 mg) as a white solid. LCMS Method A: [M+H]⁺ = 385.

Step 2: *N*-(5-(2-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1*H*-indol-3-yl)cyclopropanecarboxamide and *N*-(5-(1-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1*H*-indol-3-yl)cyclopropanecarboxamide

(*E*)-*N*-(5-(3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-1*H*-indol-3-yl)cyclopropanecarboxamide (150.0 mg, 0.4 mmol, 1.0 equiv.) was dissolved in THF (10

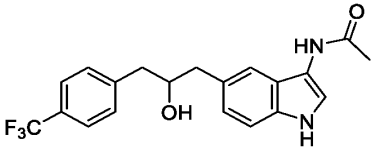
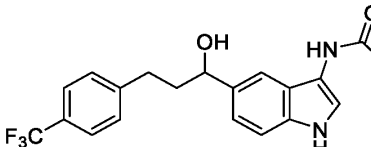
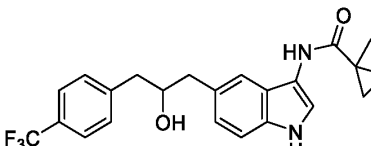
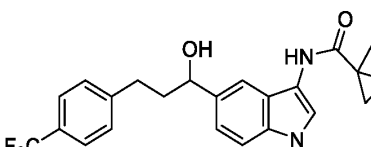
mL) and cooled to 0 °C, then BH₃-THF (1M, 1.6 mL, 1.6 mmol, 4.0 equiv.) was added dropwise. After 1 hour at ambient temperature, NaOH (31.2 mg, 0.8 mmol, 2.0 equiv.) in water (0.5 mL) and H₂O₂ (26.6 mg, 0.8 mmol, 2.0 equiv.) were added. The reaction mixture was stirred for an additional 2 hours at ambient temperature, then quenched by the addition of saturated aqueous NH₄Cl. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, ACN in water (0.5% NH₄HCO₃), 0% ACN to 100% gradient in 15 min; detector, UV 254 nm. The resulting material was further purified by Prep-HPLC with the following conditions: Column: Kinetex EVO prep C18, 30*150, 5 μm; Mobile Phase A: Water (10 mM NH₄HCO₃), Mobile Phase B: MeOH--HPLC; Flow rate: 60 mL/min; Gradient: 50% B to 70% B in 7 min; Wave Length: 220 nm. This gave *N*-(5-(2-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1*H*-indol-3-yl)cyclopropanecarboxamide (38.1 mg, Peak 1, RT = 7.65 min) as a white solid and *N*-(5-(1-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1*H*-indol-3-yl)cyclopropanecarboxamide (3.8 mg, Peak 2, RT = 8.00 min) as a white solid.

Peak 1: Compound 240: LCMS Method F: [M-H]⁺ = 401. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.62 (s, 1H), 10.01 (s, 1H), 7.63–7.61 (m, 4H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.00–6.98 (m, 1H), 4.74 (d, *J* = 6.4 Hz, 1H), 3.98–3.95 (m, 1H), 2.86–2.66 (m, 4H), 1.99–1.93 (m, 1H), 0.80–0.76 (m, 4H).

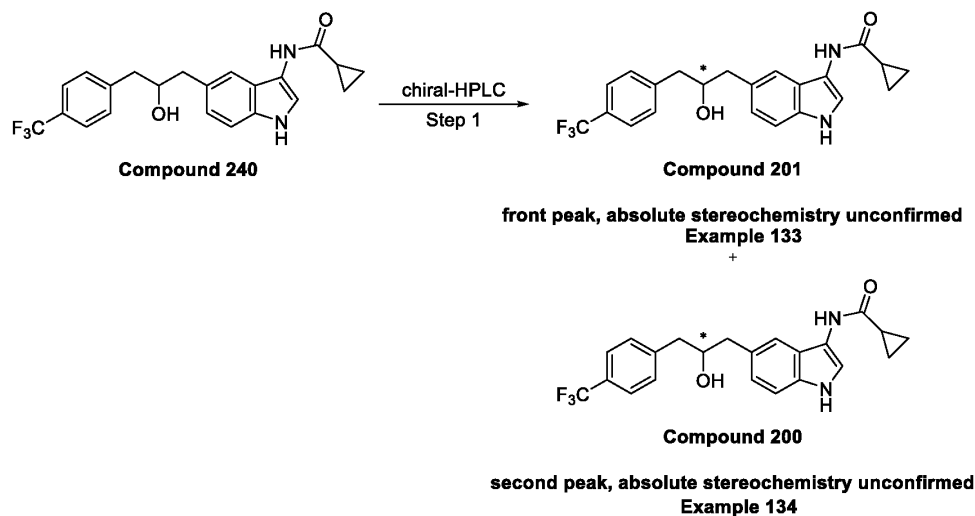
Peak 2: Compound 209: LCMS Method F: [M-H]⁺ = 401. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.64 (d, *J* = 2.0 Hz, 1H), 10.06 (s, 1H), 7.79 (s, 1H), 7.67–7.63 (m, 3H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.11–7.09 (m, 1H), 5.23 (d, *J* = 4.0 Hz, 1H), 4.62–4.58 (m, 1H), 2.73–2.68 (m, 2H), 2.03–1.94 (m, 3H), 0.80–0.75 (m, 4H).

The analogs prepared in the following table were prepared using the same method described for **Example 127/128**.

Example #	Compound No.	Starting materials Used	Structure	LCMS data

129	284	Intermediate 34 / Intermediate 1		Method F: MS-ESI: 377 [M+H] ⁺ .
130	282	Intermediate 34 / Intermediate 1		Method F: MS-ESI: 377 [M+H] ⁺ .
131	174	Intermediate 34 / Intermediate 38		Method F: MS-ESI: 417 [M+H] ⁺ .
132	172	Intermediate 34 / Intermediate 38		Method F: MS-ESI: 417 [M+H] ⁺ .

Example 133/134: *N*-(5-(2-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1*H*-indol-3-yl)cyclopropanecarboxamide [(Compound 201) (front peak, absolute stereochemistry unconfirmed) and (Compound 200) (second peak, absolute stereochemistry unconfirmed)]

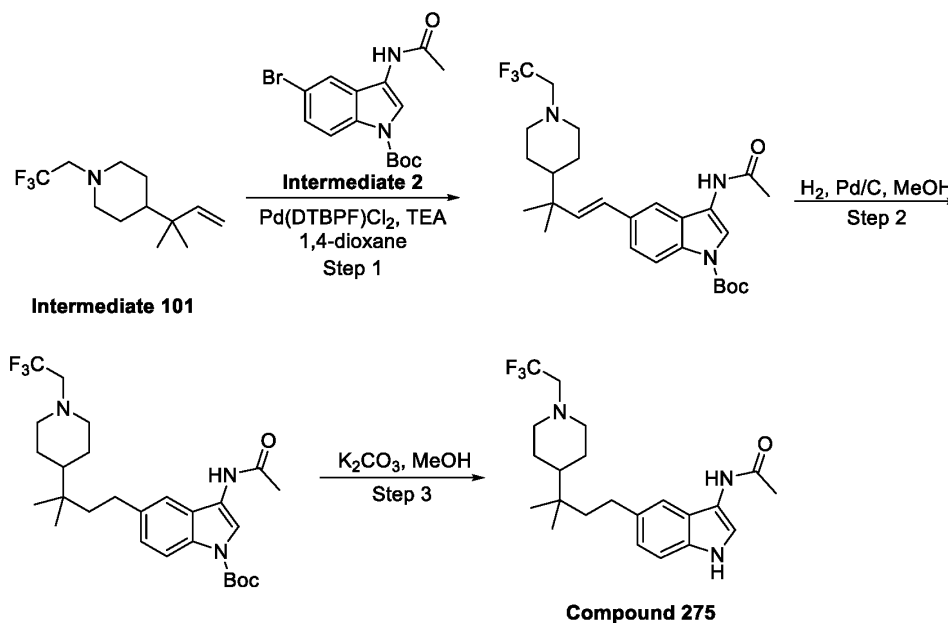


The racemic *N*-(5-(2-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-1H-indol-3-yl)cyclopropanecarboxamide (28.0 mg) was separated by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK IC, 2*25 cm, 5 μ m; Mobile Phase A: Hex(0.5% 2M NH_3 -MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 17 min; Wave Length: 220/254 nm; RT1(min): 11.732; RT2(min): 14.323. This gave (**Compound 201**) (front peak, 4.9 mg) as a white solid and (**Compound 200**) (second peak, 5.8 mg) as a white solid.

Example 133 (Compound 201) (Peak 1): LCMS Method D: $[\text{M-H}]^- = 401$. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 10.61 (s, 1H), 10.00 (s, 1H), 7.63–7.61 (m, 4H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.24 (d, $J = 8.0$ Hz, 1H), 7.00–6.98 (m, 1H), 4.74 (d, $J = 6.4$ Hz, 1H), 3.98–3.95 (m, 1H), 2.86–2.66 (m, 4H), 1.99–1.93 (m, 1H), 0.80–0.74 (m, 4H).

Example 134 (Compound 200) (Peak 2): LCMS Method D: $[\text{M-H}]^- = 401$. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 10.61 (s, 1H), 10.00 (s, 1H), 7.63–7.61 (m, 4H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.24 (d, $J = 8.0$ Hz, 1H), 7.00–6.98 (m, 1H), 4.74 (d, $J = 6.4$ Hz, 1H), 3.98–3.95 (m, 1H), 2.86–2.66 (m, 4H), 1.99–1.93 (m, 1H), 0.80–0.74 (m, 4H).

Example 135: *N*-(5-(3-methyl-3-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)butyl)-1H-indol-3-yl)acetamide (Compound 275)



Step 1: *tert*-butyl (*E*)-3-acetamido-5-(3-methyl-3-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)but-1-en-1-yl)-1*H*-indole-1-carboxylate

4-(2-Methylbut-3-en-2-yl)-1-(2,2,2-trifluoroethyl)piperidine (150.0 mg, 0.6 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (3 mL), then TEA (0.2 mL, 1.3 mmol, 2.0 equiv.), *tert*-butyl 5-bromo-3-acetamidoindole-1-carboxylate (225.2 mg, 0.6 mmol, 1.0 equiv.) and Pd(DtBPF)Cl₂ (41.6 mg, 0.1 mmol, 0.1 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was heated to 120 °C overnight, then cooled to ambient temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:3) to give *tert*-butyl (*E*)-3-acetamido-5-(3-methyl-3-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)but-1-en-1-yl)-1*H*-indole-1-carboxylate (110.0 mg) as a pale yellow solid. LCMS Method A: [M+H]⁺ = 508.

Step 2: *tert*-butyl 3-acetamido-5-(3-methyl-3-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)butyl)-1*H*-indole-1-carboxylate

tert-Butyl (*E*)-3-acetamido-5-(3-methyl-3-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)but-1-en-1-yl)-1*H*-indole-1-carboxylate (110.0 mg, 0.2 mmol, 1.0 equiv.) was dissolved in MeOH (10 mL), then Pd/C (9.2 mg, 0.1 mmol, 0.4 equiv.) was added. The mixture was

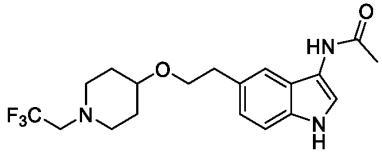
sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 3 hours at ambient temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum to give *tert*-butyl 3-acetamido-5-(3-methyl-3-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)butyl)-1*H*-indole-1-carboxylate (105.0 mg) as a pale yellow solid. LCMS Method A: $[M+H]^+ = 510$.

Step 3: *N*-(5-(3-methyl-3-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)butyl)-1*H*-indol-3-yl)acetamide

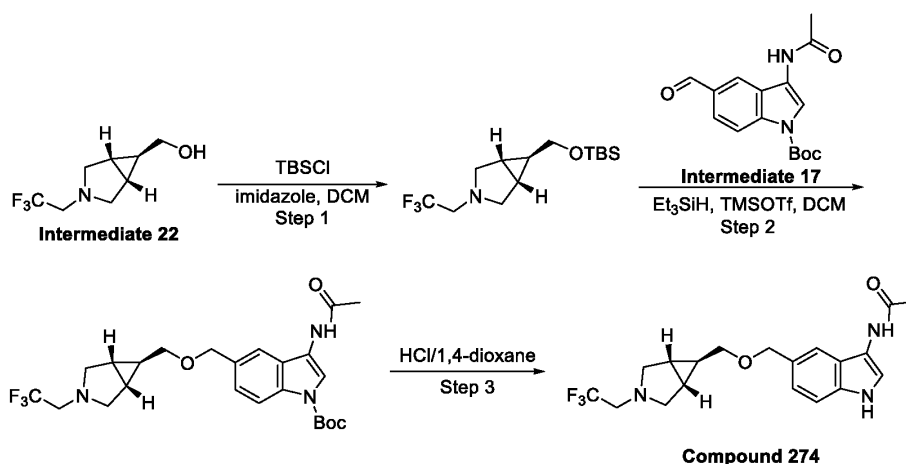
tert-Butyl 3-acetamido-5-(3-methyl-3-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)butyl)-1*H*-indole-1-carboxylate (80.0 mg, 0.2 mmol, 1.0 equiv.) was dissolved in MeOH (2 mL), then K₂CO₃ (43.4 mg, 0.3 mmol, 2.0 equiv.) was added. The reaction mixture was heated to 70 °C for 50 min, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5µm; Mobile Phase A: Water (10 mM NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 50% B to 65% B in 8 min; Wave Length: 220 nm; RT1: 7.67 min. This gave *N*-(5-[3-methyl-3-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]butyl]-1*H*-indol-3-yl)acetamide (15.9 mg) as an off-white solid. LCMS Method F: $[M+H]^+ = 410$. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.57 (s, 1H), 9.71 (s, 1H), 7.64 (s, 1H), 7.59–7.55 (m, 1H), 7.24–7.19 (m, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 3.15–3.05 (m, 2H), 3.00–2.96 (m, 2H), 2.59–2.56 (m, 2H), 2.31–2.23 (m, 2H), 2.08 (s, 3H), 1.63–1.59 (m, 2H), 1.53–1.47 (m, 2H), 1.34–1.11 (m, 3H), 0.90 (s, 6H).

The analogs prepared in the following table were prepared using the same method described for **Example 135**.

Example #	Compound No.	Starting materials Used	Structure	LCMS data

136	288	Intermediate 100 / Intermediate 2		Method F: MS-ESI: 384 [M+H] ⁺ .
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Example 137: *N*-(5-((((1*R*,5*S*,6*r*)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexan-6-yl)methoxy)methyl)-1*H*-indol-3-yl)acetamide (Compound 274)



5 Step 1: (1*R*,5*S*,6*S*)-6-[[*tert*-butyldimethylsilyl]oxy]methyl}-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexane

[(1*R*,5*S*,6*S*)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexan-6-yl]methanol (2.2 g, 11.2 mmol, 1.0 equiv.) was dissolved in DCM (100 mL), then imidazole (1.5 g, 22.5 mmol, 2.0 equiv.) and TBSCl (3.4 g, 22.5 mmol, 2.0 equiv.) were added. The reaction mixture was stirred for 2 hours at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with DCM, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give (1*R*,5*S*,6*S*)-6-[[*tert*-butyldimethylsilyl]oxy]methyl}-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexane (2.4 g) as an off-white oil. LCMS Method A: [M+H]⁺ = 310.

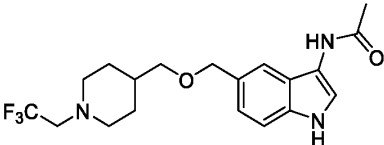
Step 2: *tert*-butyl 3-acetamido-5-([(1R,5S,6S)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexan-6-yl]methoxy)methyl)indole-1-carboxylate

(1R,5S,6S)-6-([(*tert*-butyldimethylsilyl)oxy)methyl]-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexane (200.0 mg, 0.6 mmol, 1.0 equiv.) and *tert*-butyl 5-formylindole-1-carboxylate (237.8 mg, 0.9 mmol, 1.5 equiv.) were dissolved in DCM (10 mL) and cooled to 0 °C, then Et₃SiH (165.0 mg, 1.4 mmol, 2.2 equiv.) and TMSOTf (215.0 mg, 0.9 mmol, 1.5 equiv.) were added. The reaction mixture was stirred overnight at 0 °C and then quenched by the addition of water. The resulting solution was extracted with DCM, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to give *tert*-butyl 3-acetamido-5-([(1R,5S,6S)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexan-6-yl]methoxy)methyl)indole-1-carboxylate (100.0 mg) as a grey solid. LCMS Method A: [M+H]⁺ = 482.

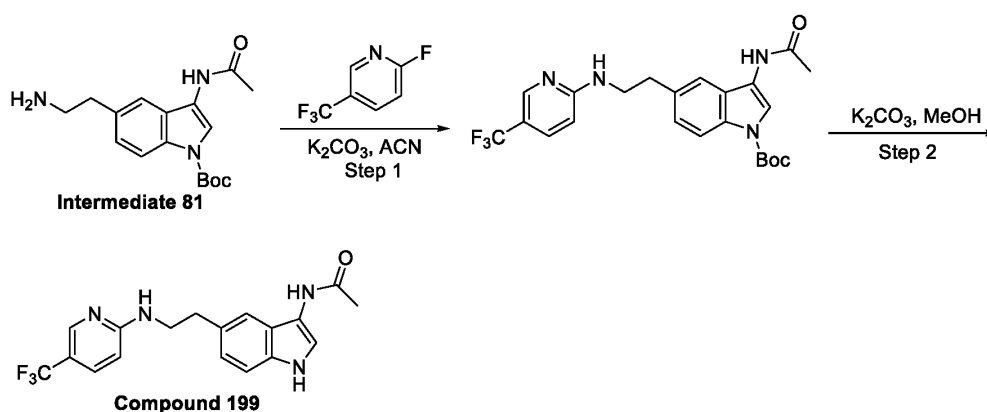
Step 3: *N*-[5-([(1R,5S,6S)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexan-6-yl]methoxy)methyl)-1H-indol-3-yl]acetamide

tert-Butyl 3-acetamido-5-([(1R,5S,6S)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexan-6-yl]methoxy)methyl)indole-1-carboxylate (100.0 mg, 0.2 mmol, 1.0 equiv.) was dissolved in ethyl acetate (2 mL), then HCl/1,4-dioxane (4 M, 1 mL) was added. The reaction mixture was stirred for 2 hours at ambient temperature and then concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: Xselect CSH C18 OBD Column 30*150mm, 5 μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 35% B in 7 min; Wave Length: 254; 220 nm; RT1: 6.47 min. This gave *N*-[5-([(1R,5S,6S)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexan-6-yl]methoxy)methyl)-1H-indol-3-yl]acetamide (1.4 mg) as a grey solid. LCMS Method E: [M+H]⁺ = 382. LCMS Method F: [M+H]⁺ = 410. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.73 (s, 1H), 9.83 (s, 1H), 7.73 (s, 1H), 7.68 (s, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 4.69–4.65 (m, 2H), 3.46–3.27 (m, 2H), 3.07–3.02 (m, 2H), 2.68–2.61 (m, 4H), 2.08 (s, 3H), 1.51–1.23 (m, 3H).

The analogs prepared in the following table were prepared using the same method described for **Example 137**.

Example #	Compound No.	Starting materials Used	Structure	LCMS data
138	268	Intermediate 21 / Intermediate 17		Method D: MS-ESI: 382 [M-H] ⁻ .

Example 139: *N*-(5-(2-((5-(trifluoromethyl)pyridin-2-yl)amino)ethyl)-1*H*-indol-3-yl)acetamide (Compound 199)



Step 1: *tert*-butyl 3-acetamido-5-(2-([5-(trifluoromethyl)pyridin-2-yl]amino)ethyl)indole-1-carboxylate

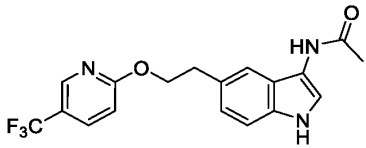
tert-Butyl 5-(2-aminoethyl)-3-acetamidindole-1-carboxylate (270.0 mg, 0.9 mmol, 1.0 equiv.) was dissolved in ACN (3 mL), then 2-fluoro-5-(trifluoromethyl)pyridine (168.5 mg, 1.0 mmol, 1.2 equiv.) and K₂CO₃ (235.1 mg, 1.7 mmol, 2.0 equiv.) were added. The reaction mixture was heated to 80 °C for 6 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:2) to give *tert*-butyl 3-acetamido-5-(2-([5-

(trifluoromethyl)pyridin-2-yl]amino}ethyl)indole-1-carboxylate (126.0 mg) as a yellow solid. LCMS Method A: $[M+H]^+ = 463$.

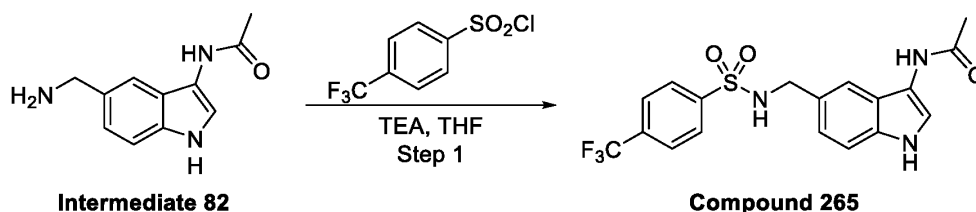
Step 2: *N*-[5-(2-{[5-(trifluoromethyl) pyridin-2-yl]amino}ethyl)-1*H*-indol-3-yl]acetamide

5 *tert*-Butyl 3-acetamido-5-(2-{[5-(trifluoromethyl) pyridin-2-yl]amino}ethyl)indole-1-carboxylate (120.0 mg, 0.3 mmol, 1.0 equiv.) was dissolved in methanol (2 mL), then K_2CO_3 (143.5 mg, 1.0 mmol, 4.0 equiv.) was added. The reaction mixture was heated to 70 °C for 3 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried
10 over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: X Bridge Prep OBD C18 Column, 30*150 mm, 5 μ m; Mobile Phase A: Water (10 mM NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 47% B in 8 min; Wave Length: 254/220 nm; RT1: 7.63 min. This gave *N*-[5-(2-{[5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-1*H*-indol-3-yl]acetamide (25.5 mg) as a white solid. LCMS Method D: $[M+H]^+ = 363$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 10.65 (s, 1H), 9.79 (s, 1H), 8.33 (s, 1H), 7.66–7.64 (m, 3H), 7.44 (t, $J = 5.6$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 1H), 7.01–6.99 (m, 1H), 6.60 (d, $J = 8.8$ Hz, 1H), 3.59–3.55 (m, 2H), 2.92–2.89 (m, 2H), 2.08 (s, 3H).

The analogs prepared in the following table were prepared using the same method
20 described for **Example 139**.

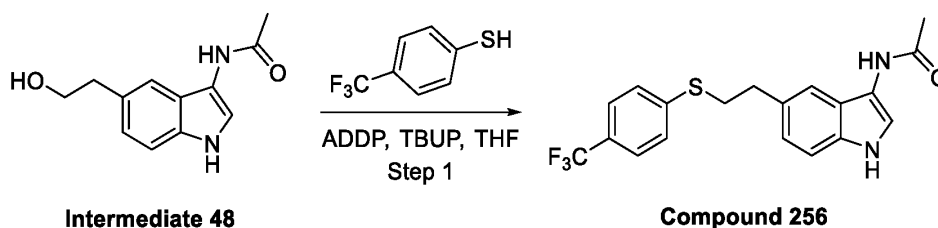
Examp le #	Compound No.	Starting materials Used	Structure	LCMS data
140	215	Intermediate 11		Method E: MS-ESI: 364 $[M+H]^+$.

Example 141: *N*-(5-(((4-(trifluoromethyl)phenyl)sulfonamido)methyl)-1*H*-indol-3-yl)acetamide (Compound 265)



N-[5-(aminomethyl)-1*H*-indol-3-yl]acetamide (50.0 mg, 0.2 mmol, 1.0 equiv.) and TEA (0.1 mL, mg, 0.5 mmol, 2.0 equiv.) were dissolved in THF (5 mL), then 4-(trifluoromethyl)benzenesulfonyl chloride (60.1 mg, 0.2 mmol, 1.0 equiv.) was added. The reaction mixture was stirred for 2 hours at ambient temperature, then concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μ m; Mobile Phase A: Water (10 mM NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 53% B in 7 min; Wave Length: 220 nm. This gave *N*-(5-[[4-(trifluoromethyl)benzenesulfonyl]amino]methyl)-1*H*-indol-3-yl)acetamide (24.5 mg) as an off-white solid. LCMS Method G: [M+H]⁺ = 412. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.72 (s, 1H), 9.82 (s, 1H), 8.32 (t, *J* = 6.0 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.67–7.65 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.06 (d, *J* = 6.0 Hz, 2H), 2.08 (s, 3H).

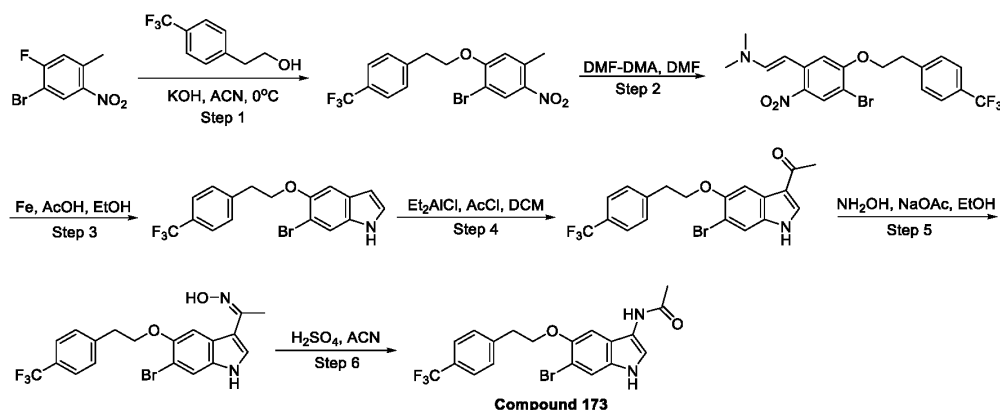
Example 142: *N*-(5-(2-((4-(trifluoromethyl)phenyl)thio)ethyl)-1*H*-indol-3-yl)acetamide (Compound 256)



N-(5-(2-hydroxyethyl)-1*H*-indol-3-yl)acetamide (254.0 mg, 1.1 mmol, 1.0 equiv.) was dissolved in THF (5 mL), then 4-(trifluoromethyl)benzenethiol (663.5 mg, 3.7 mmol, 3.2 equiv.) and TBUP (941.8 mg, 4.7 mmol, 4.0 equiv.) were added. This was followed by the addition of ADDP (582.7 mg, 2.3 mmol, 2.0 equiv.) at 0 °C under an atmosphere of nitrogen. The reaction mixture was heated to 70 °C for 2 hours, then cooled to ambient

temperature and quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μ m; Mobile Phase A: Water (10 mM NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 65% B in 8 min; Wave Length: 220 nm; RT1: 7.68 min. LCMS Method F: [M+H]⁺ = 379. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.69 (s, 1H), 9.76 (s, 1H), 7.67–7.64 (m, 4H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.05–7.03 (m, 1H), 3.38–3.34 (m, 2H), 3.00 (t, *J* = 7.6 Hz, 2H), 2.08 (s, 3H).

Example 143: *N*-(6-bromo-5-(4-(trifluoromethyl)phenethoxy)-1*H*-indol-3-yl)acetamide (Compound 173)



Step 1: 1-bromo-4-methyl-5-nitro-2-(4-(trifluoromethyl)phenethoxy)benzene

1-Bromo-2-fluoro-4-methyl-5-nitrobenzene (3.0 g, 12.8 mmol, 1.0 equiv.) and 2-(4-(trifluoromethyl)phenyl)ethan-1-ol (2.93 g, 15.4 mmol, 1.2 equiv.) were dissolved in ACN (30 mL) and cooled to 0 °C, then KOH (1.1 g, 19.2 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for 2 hours at 0 °C then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:6) to give 1-bromo-4-methyl-5-nitro-2-{2-[4-(trifluoromethyl)phenyl]ethoxy}benzene (4.7 g) as a yellow solid. LCMS Method A: [M+H]⁺ = 404.

Step 2: (*E*)-2-(4-bromo-2-nitro-5-(4-(trifluoromethyl)phenethoxy) phenyl)-*N,N*-dimethylethen-1-amine

1-Bromo-4-methyl-5-nitro-2-(4-(trifluoromethyl)phenethoxy)benzene (2.7 g, 6.6 mmol, 1.0 equiv.) was dissolved in DMF (20 mL), then DMF-DMA (10.0 mL, 75.4 mmol, 11.4 equiv.) was added. The reaction mixture was heated to 140 °C for 4 hours, then cooled to ambient temperature and concentrated under vacuum to give (*E*)-2-(4-bromo-2-nitro-5-(4-(trifluoromethyl)phenethoxy) phenyl)-*N,N*-dimethylethen-1-amine (2.5 g), which was used in the next step directly without further purification. LCMS Method A: $[M+H]^+ = 459$.

Step 3: 6-bromo-5-(4-(trifluoromethyl)phenethoxy)-1*H*-indole

(*E*)-2-(4-bromo-2-nitro-5-(4-(trifluoromethyl)phenethoxy)phenyl)-*N,N*-dimethylethen-1-amine (2.5 g, 5.4 mmol, 1.0 equiv.) was dissolved in EtOH (30 mL) and AcOH (30 mL), then Fe (5.5 g, 98.0 mmol, 18.0 equiv.) was added. The reaction mixture was heated to 90 °C for 4 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting mixture was adjusted to pH 7 with aqueous NaOH (5% wt./wt.), extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:2) to give 6-bromo-5-(4-(trifluoromethyl)phenethoxy)-1*H*-indole (850.0 mg) as a yellow solid. LCMS Method A: $[M+H]^+ = 384$.

Step 4: 1-(6-bromo-5-(4-(trifluoromethyl)phenethoxy)-1*H*-indol-3-yl)ethan-1-one

6-Bromo-5-(4-(trifluoromethyl)phenethoxy)-1*H*-indole (850.0 mg, 2.2 mmol, 1.0 equiv.) was dissolved in DCM (10 mL) and cooled to 0 °C, then diethylaluminum chloride in hexane (1M, 3.3 mL, 3.3 mmol, 1.5 equiv.) was added dropwise. After 30 min at 0 °C, AcCl (0.2 mL, 3.2 mmol, 1.0 equiv.) was added, maintaining the solution at 0 °C. The reaction mixture was stirred for additional 2 hours at ambient temperature and then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl

acetate/petroleum ether (1:3) to give 1-(6-bromo-5-(4-(trifluoromethyl)phenethoxy)-1*H*-indol-3-yl)ethan-1-one (740.0 mg) as a red solid. LCMS Method B: $[M-H]^- = 424$.

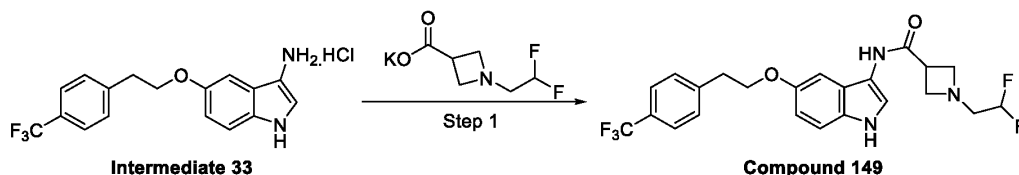
Step 5: (Z)-1-(6-bromo-5-(4-(trifluoromethyl)phenethoxy)-1*H*-indol-3-yl)ethan-1-one oxime

5 1-(6-Bromo-5-(4-(trifluoromethyl)phenethoxy)-1*H*-indol-3-yl)ethan-1-one (740.0 mg, 1.7 mmol, 1.0 equiv.) was dissolved in EtOH (10 mL), then NaOAc (284.8 mg, 3.5 mmol, 2.0 equiv.) and hydroxylamine hydrochloride (180.9 mg, 2.6 mmol, 1.5 equiv.) were added. The reaction mixture was heated to 60 °C for 5 hours, then cooled to ambient temperature and quenched by the addition of water. The resulting solution was extracted
10 with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:2) to give (Z)-1-(6-bromo-5-(4-(trifluoromethyl)phenethoxy)-1*H*-indol-3-yl)ethan-1-one oxime (620.0 mg) as a white solid. LCMS Method A: $[M+H]^+ = 441$.

15 **Step 6: *N*-(6-bromo-5-(4-(trifluoromethyl)phenethoxy)-1*H*-indol-3-yl)acetamide**

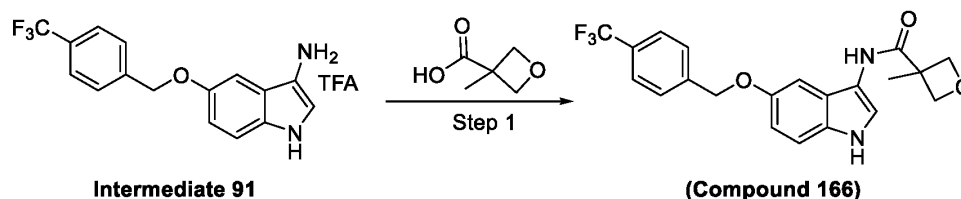
 (Z)-1-(6-Bromo-5-(4-(trifluoromethyl)phenethoxy)-1*H*-indol-3-yl)ethan-1-one oxime (300.0 mg, 0.7 mmol, 1.0 equiv.) was dissolved in ACN (5 mL) and cooled to 0 °C, then concentrated H_2SO_4 (1 mL) was added dropwise. After 2 hours at ambient temperature, the reaction was quenched by the addition of water and adjusted to pH 7 with
20 saturated aqueous $NaHCO_3$. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μ m; Mobile Phase A: Water (10 mM NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 48% B to 63% B in 8 min; Wave
25 Length: 220 nm; RT1: 7.03 min. This gave *N*-(6-bromo-5-(4-(trifluoromethyl)phenethoxy)-1*H*-indol-3-yl)acetamide (10.7 mg) as an orange solid. LCMS Method F: $[M-H]^- = 439$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 10.67 (d, $J = 1.6$ Hz, 1H), 9.75 (s, 1H), 7.71–7.69 (m, 3H), 7.65 (d, $J = 8.0$ Hz, 2H), 7.52 (s, 1H), 7.48 (s, 1H), 4.23 (t, $J = 6.8$ Hz, 2H), 3.24 (t, $J = 6.8$ Hz, 2H), 2.07 (s, 3H).

Example 144: 1-(2,2-difluoroethyl)-*N*-(5-(4-(trifluoromethyl)phenethoxy)-1*H*-indol-3-yl)azetidine-3-carboxamide (Compound 149)



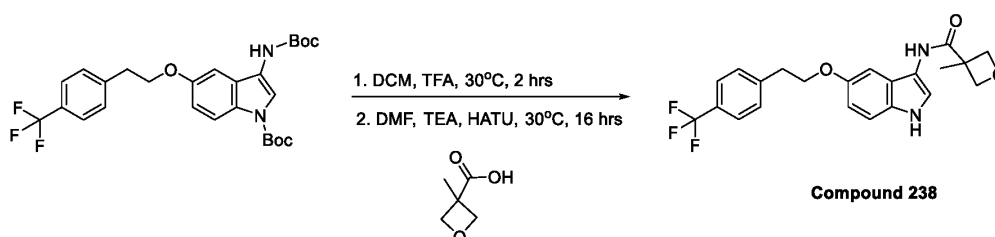
5- $\{2-[4-(\text{Trifluoromethyl})\text{phenyl}] \text{ethoxy}\}$ -1*H*-indol-3-amine hydrochloride (178.4 mg, 0.5 mmol, 1.0 equiv.) was dissolved in ACN (5 mL), then potassium 1-(2,2-difluoroethyl)azetidine-3-carboxylate (101.5 mg, 0.5 mmol, 1.0 equiv.), TCFH (210.2 mg, 0.8 mmol, 1.5 equiv.) and NMI (123.0 mg, 1.5 mmol, 3.0 equiv.) were added. The reaction mixture was stirred for 8 hours at ambient temperature and then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, ACN in water (0.5% NH_4HCO_3), 10% ACN to 50% gradient in 15 min; detector, UV 254 nm. The resulting material was further purified by Prep-HPLC with the following conditions: Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5 μm ; Mobile Phase A: Water (10 mM NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 42% B to 62% B in 8 min; Wave Length: 220 nm; RT1: 7.15 min. This gave 1-(2,2-difluoroethyl)-*N*-(5-(4-(trifluoromethyl)phenethoxy)-1*H*-indol-3-yl)azetidine-3-carboxamide (93.5 mg) as a white solid. LCMS Method F: $[\text{M}-\text{H}]^- = 466$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.62 (s, 1H), 9.69 (s, 1H), 7.72–7.69 (m, 3H), 7.60 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 2.0$ Hz, 1H), 7.21 (d, $J = 8.8$ Hz, 1H), 6.74–6.72 (m, 1H), 6.11–5.81 (t, $J_1 = 56.0$ Hz, $J_2 = 4.4$ Hz, 1H), 4.20 (t, $J = 6.8$ Hz, 2H), 3.57–3.50 (m, 3H), 3.38–3.34 (m, 2H), 3.20–3.16 (m, 2H), 2.86–2.81 (m, 2H).

Example 145: 3-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)oxetane-3-carboxamide (Compound 166)



3-Methyloxetane-3-carboxylic acid (139.0 mg, 1.2 mmol, 1.0 equiv.) and HATU (682.7 mg, 1.8 mmol, 1.5 equiv.) were dissolved in DCM (5 mL), then DIEA (1.1 mL, 6.0 mmol, 5 equiv.) was added. After 2 min, 5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-amine TFA salt (754.9 mg, 1.8 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for an additional 2 hours at ambient temperature, then quenched by the addition of water. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (10:1) to give 3-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)oxetane-3-carboxamide (91.0 mg) as a white solid. LCMS Method F: [M-H]⁻ = 403. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.73 (s, 1H), 9.49 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 2.4 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 6.88–6.86 (m, 1H), 5.21 (s, 2H), 4.88 (d, *J* = 6.0 Hz, 2H), 4.40 (d, *J* = 6.0 Hz, 2H), 1.65 (s, 3H).

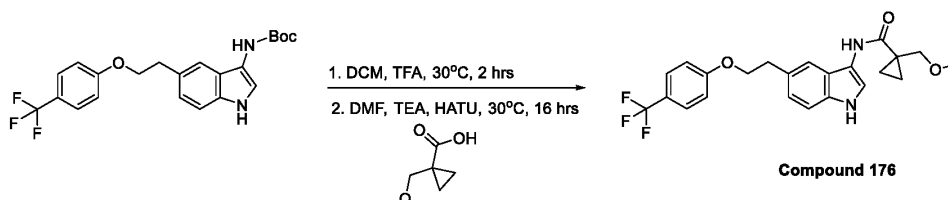
Example 146: 3-methyl-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)oxetane-3-carboxamide (Compound 238)



tert-butyl 3-[[[(tert-butoxy)carbonyl]amino}-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1H-indole-1-carboxylate (83.2 mg, 0.16 mmol, 1.0 equiv.) was dissolved in DCM (2 mL), and TFA (500 μl) was added in the mixture. The mixture was heated at 30 °C for 2 hours. The reaction mixture was concentrated by Speedvac to give a residue. The residue and 3-methyloxetane-3-carboxylic acid (37.1 mg,

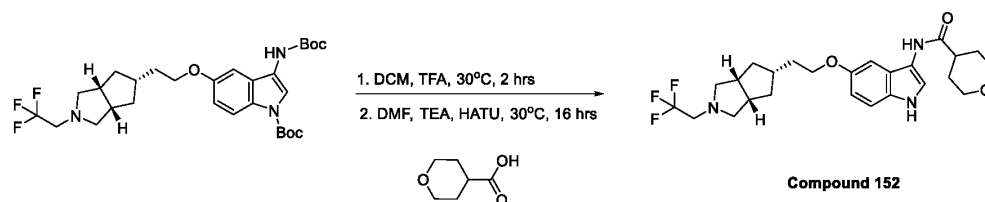
0.32 mmol, 2.0 equiv.) were dissolved in DMF (2 mL), then TEA (116 μ l, 0.8 mmol, 5.0 equiv.) and HATU (63.8 mg, 0.168 mmol, 1.05 equiv.) were added. The mixture was heated at 30 °C for 16 hours. The reaction mixture was concentrated by Speedvac to give a residue that was purified by prep HPLC to give 3-methyl-N-(5-(4-(trifluoromethyl)phenoxy)-1H-indol-3-yl)oxetane-3-carboxamide (14.5 mg, 0.035 mmol) as a powder. MS-ESI, 419.2 [M+H⁺]. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.67 (br s, 1H), 9.46 (s, 1H), 7.71–7.64 (m, 3H), 7.63–7.56 (m, 2H), 7.27–7.24 (m, 1H), 7.22 (d, *J*=8.7 Hz, 1H), 6.74 (dd, *J*=8.8 Hz, 1H), 4.85 (d, *J*=6.0 Hz, 2H), 4.38 (d, *J*=6.0 Hz, 2H), 4.21 (t, *J*=6.7 Hz, 2H), 3.23–3.10 (m, 2H), 1.63 (s, 3H).

Example 147: 1-(methoxymethyl)-N-(5-{2-[4-(trifluoromethyl)phenoxy]ethyl}-1H-indol-3-yl)cyclopropane-1-carboxamide (Compound 176)



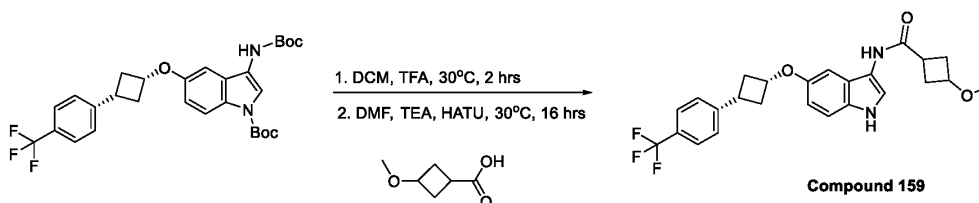
tert-butyl (5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)carbamate (83.2 mg, 0.16 mmol, 1.0 equiv.) was dissolved in DCM (2 mL), then TFA (500 μ l) was added to the mixture. The reaction mixture was heated at 30 °C for 2 hours. The reaction mixture was concentrated by Speedvac to give a residue. The residue and 1-(methoxymethyl)cyclopropane-1-carboxylic acid (41.6 mg, 0.32 mmol, 2.0 equiv.) were dissolved in DMF (2 mL), then TEA (116 μ l, 0.8 mmol, 5.0 equiv.) and HATU (63.8 mg, 0.168 mmol, 1.05 equiv.) were added. The mixture was heated at 30 °C for 16 hours. The reaction mixture was concentrated by Speedvac to give a residue that was purified by prep HPLC to give 1-(methoxymethyl)-N-(5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)cyclopropanecarboxamide (14.5 mg, 0.035 mmol) as a powder. MS-ESI, 433.2 [M+H⁺]. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.76 (br s, 1H), 9.20 (s, 1H), 7.68–7.55 (m, 3H), 7.40 (s, 1H), 7.29 (d, *J*=8.2 Hz, 1H), 7.17–7.07 (m, 3H), 4.30 (t, *J*=6.9 Hz, 2H), 3.64 (s, 2H), 3.40 (s, 3H), 3.14 (br t, *J*=6.9 Hz, 2H), 1.15–1.06 (m, 2H), 0.86–0.71 (m, 2H).

Example 148: N-(5-{2-[(3aR,5S,6aS)-2-(2,2,2-trifluoroethyl)-octahydrocyclopenta[c]pyrrol-5-yl]ethoxy}-1H-indol-3-yl)oxane-4-carboxamide (Compound 152)



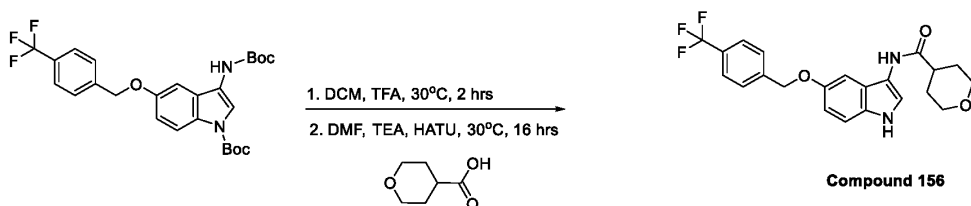
5 tert-butyl 5-{2-[(3aR,5R,6aS)-2-(2,2,2-trifluoroethyl)-octahydrocyclopenta[c]pyrrol-5-yl]ethoxy}-3-[[tert-butoxy]carbonyl]amino}-1H-indole-1-carboxylate (85.1 mg, 0.15 mmol, 1.0 equiv.) was dissolved in DCM (2 mL), then TFA (500 μ l) was added to the mixture. The reaction mixture was heated at 30 $^{\circ}$ C for 2 hours. The reaction mixture was concentrated by Speedvac to give a residue. Then the residue and tetrahydro-2H-pyran-4-carboxylic acid (39.0 mg, 0.30 mmol, 2.0 equiv.) were dissolved in DMF (2 mL), then TEA (109 μ l, 0.75 mmol, 5.0 equiv.) and HATU (59.9 mg, 0.158 mmol, 1.05 equiv.) were added. The mixture was heated at 30 $^{\circ}$ C for 16 hours. The reaction mixture was concentrated by Speedvac to give a residue that was purified by prep HPLC to give N-(5-{2-[(3aR,5S,6aS)-2-(2,2,2-trifluoroethyl)-octahydrocyclopenta[c]pyrrol-5-yl]ethoxy}-1H-indol-3-yl)oxane-4-carboxamide (14.0 mg, 0.029 mmol) as a powder. MS-ESI, 480.1 [M+H⁺]. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.55 (d, *J*=2.0 Hz, 1 H), 9.64 (s, 1H), 7.68 (d, *J*=2.5 Hz, 1H), 7.31 (d, *J*=2.3 Hz, 1H), 7.19 (d, *J*=8.8 Hz, 1H), 6.71 (dd, *J*=8.8, 2.4 Hz, 1H), 4.01–3.86 (m, 4H), 3.42–3.35 (m, 2H), 3.18 (q, *J*=10.3 Hz, 2H), 2.76–2.68 (m, 1H), 2.64 (d, *J*=8.4 Hz, 2H), 2.52 (d, *J*=1.9 Hz, 2H), 2.44–2.39 (m, 2H), 2.11–2.03 (m, 2H), 1.94–1.84 (m, 1H), 1.78 (q, *J*=6.5 Hz, 2H), 1.74–1.66 (m, 4H), 1.02–0.91 (m, 2H).

Example 149: 3-methoxy-N-{5-[(1S,3S)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}cyclobutane-1-carboxamide (Compound 159)



tert-butyl 3-{[(tert-butoxy)carbonyl]amino}-5-[(1S,3S)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indole-1-carboxylate (81.9 mg, 0.15 mmol, 1.0 equiv.) was dissolved in DCM (2 mL), then TFA (500 μ l) was added to the mixture. The reaction mixture was heated at 30 °C for 2 hours. The reaction mixture was concentrated by Speedvac to give a residue. The residue and 3-methoxycyclobutane-1-carboxylic acid (39.0 mg, 0.30 mmol, 2.0 equiv.) were dissolved in DMF (2 mL), then TEA (109 μ l, 0.75 mmol, 5.0 equiv.) and HATU (59.9 mg, 0.158 mmol, 1.05 equiv.) were added. The mixture was heated at 30 °C for 16 hours. The reaction mixture was concentrated by Speedvac to give a residue that was purified by prep HPLC to give 3-methoxy-N-{5-[(1S,3S)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}cyclobutane-1-carboxamide (32.8 mg, 0.071 mmol) as a powder. MS-ESI, 459.3 [M+H⁺]. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.60 (br s, 1H), 9.68 (s, 1H), 7.74–7.65 (m, 3H), 7.53 (d, J=8.1 Hz, 2H), 7.28–7.18 (m, 2H), 6.71 (dd, J=8.7, 2.2 Hz, 1H), 4.68 (q, J=7.2 Hz, 1H), 3.93–3.68 (m, 1H), 3.31–3.26 (m, 1H), 3.18–3.12 (m, 3H), 3.05–2.96 (m, 2H), 2.92–2.76 (m, 1H), 2.43–2.37 (m, 2H), 2.20–2.03 (m, 4H).

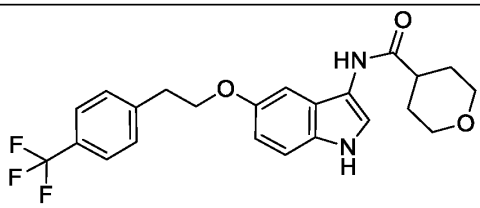
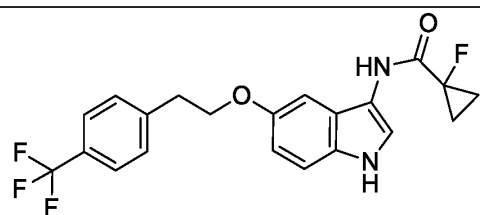
Example 150: 3-methoxy-N-{5-[(1S,3S)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}cyclobutane-1-carboxamide (Compound 156)

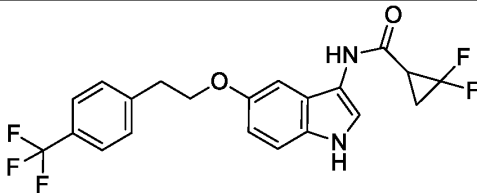
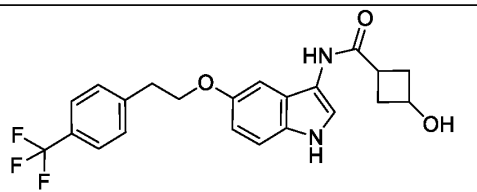
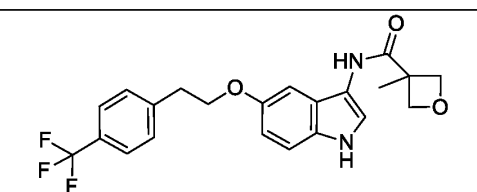
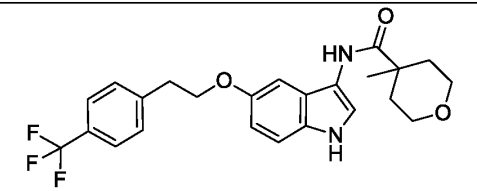


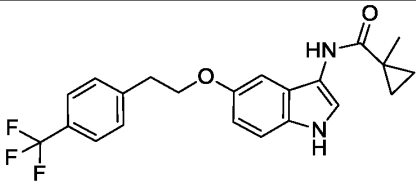
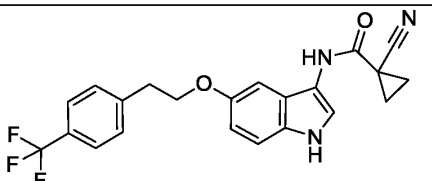
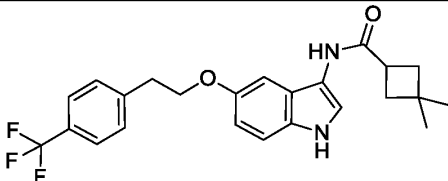
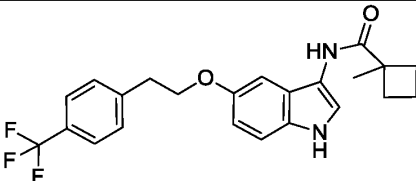
tert-butyl 3-{[(tert-butoxy)carbonyl]amino}-5-{[4-(trifluoromethyl)phenyl]methoxy}-1H-indole-1-carboxylate (86.0 mg, 0.17 mmol, 1.0 equiv.) was dissolved in DCM (2 mL), then TFA (500 μ l) was added to the mixture. The

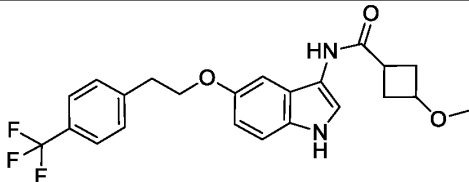
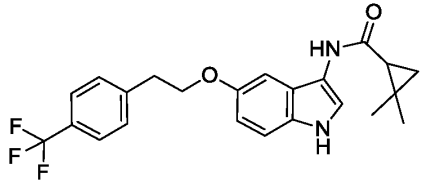
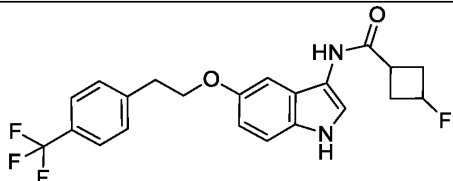
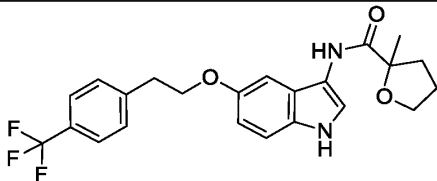
reaction mixture was heated at 30 °C for 2 hours. The reaction mixture was concentrated by Speedvac to give the residue. Then the residue and tetrahydro-2H-pyran-4-carboxylic acid (44.2 mg, 0.34 mmol, 2.0 equiv.) were dissolved in DMF (2 mL), then TEA (123 μ L, 0.85 mmol, 5.0 equiv.) and HATU (68.0 mg, 0.179 mmol, 1.05 equiv.) were added. The mixture was heated at 30 °C for 16 hours. The reaction mixture was concentrated by Speedvac to give a residue that was purified by prep HPLC to give N-(5-{[4-(trifluoromethyl)phenyl]methoxy}-1H-indol-3-yl)oxane-4-carboxamide (33.16 mg, 0.079 mmol) as a powder. MS-ESI, 419.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 10.67–10.60 (m, 1H), 9.68 (s, 1H), 7.80–7.75 (m, 2H), 7.73–7.68 (m, 3H), 7.45 (d, $J=2.3$ Hz, 1H), 7.24 (d, $J=8.8$ Hz, 1H), 6.84 (dd, $J=8.8, 2.3$ Hz, 1H), 5.21 (s, 2H), 3.97–3.89 (m, 2H) 3.42–3.35 (m, 2H), 2.78–2.68 (m, 1H), 1.77–1.63 (m, 4H).

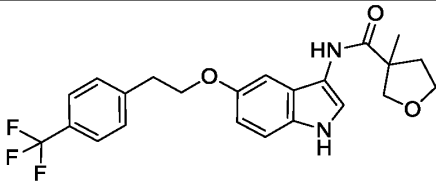
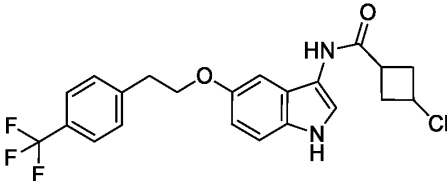
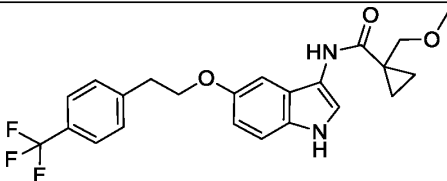
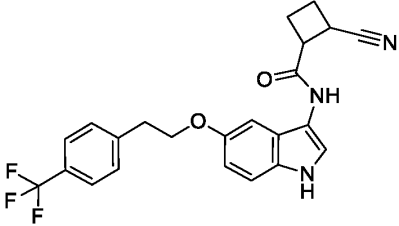
The analogs prepared in the following table were prepared using the above procedures with the appropriate starting material.

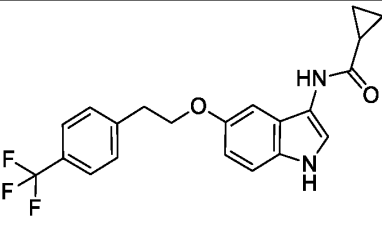
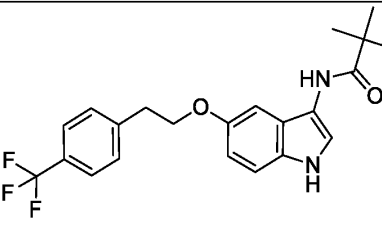
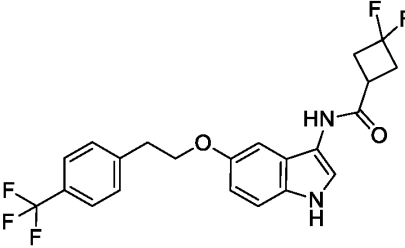
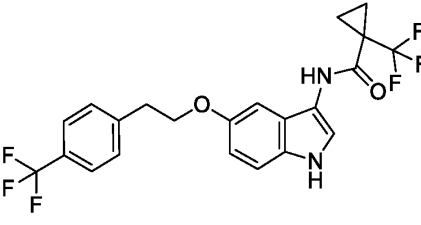
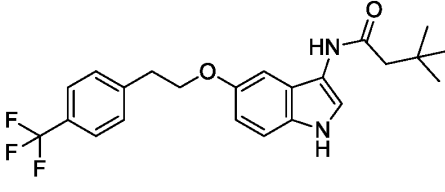
Example #	Compound No.	Structure	LC-MS, MS-ESI, - - $[M+H]^+$.
151	239		433.2
152	218		407.2

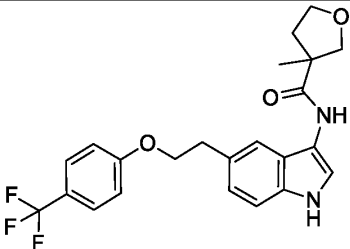
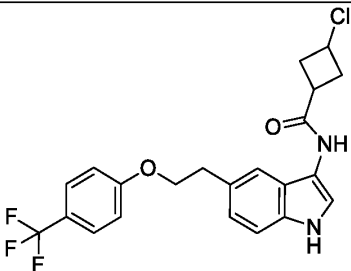
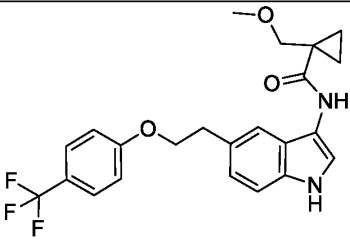
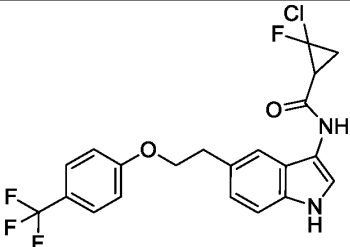
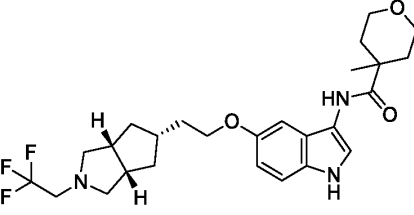
153	181		425.2
154	180		419.2
155	238		419.2
156	237		447.2

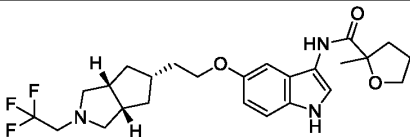
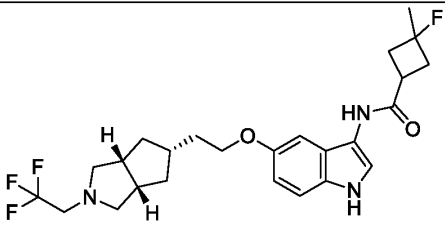
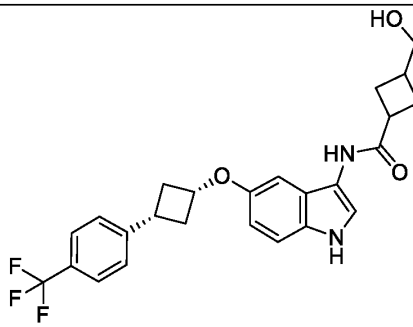
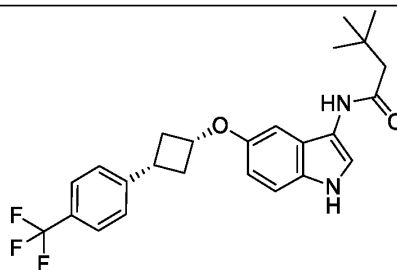
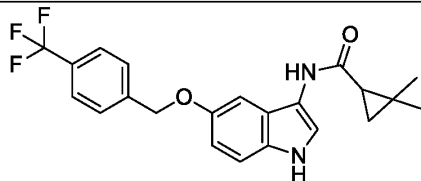
157	251		403.2
158	193		414.2
159	236		431.2
160	235		417.2

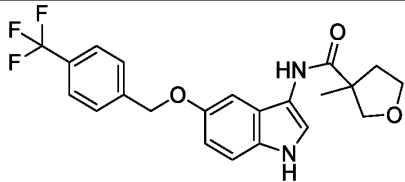
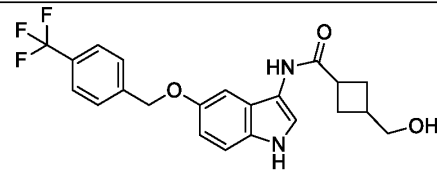
161	234		433.2
162	192		417.1
163	207		421.2
164	191		433.2

165	189		433.2
166	217		437.1
167	204		433.2
168	187		428.1

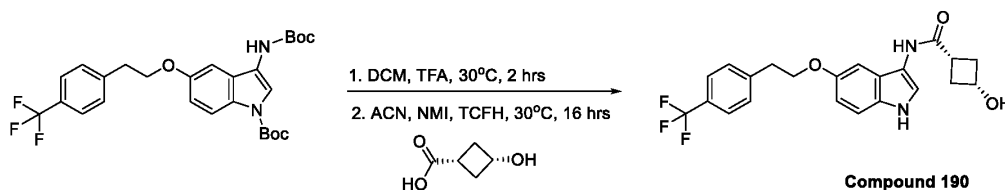
169	252		389.3
170	186		405.1
171	249		439.2
172	185		457.1
173	202		419.2

174	178		433.3
175	177		437.2
176	176		433.2
177	175		441.1
178	161		494.4

179	160		480.3
180	151		482.1
181	158		459.3
182	157		445.4
183	155		403.3

184	154		419.3
185	153		419.3

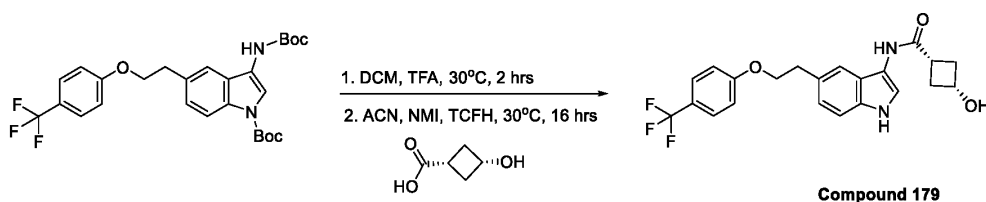
Example 186: (1S,3S)-3-hydroxy-N-(5-(4-(trifluoromethyl)phenethoxy)-1H-indol-3-yl)cyclobutanecarboxamide (Compound 190)



tert-butyl 3-[[[(tert-butoxy)carbonyl]amino]-5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1H-indole-1-carboxylate (83.2 mg, 0.16 mmol, 1.0 equiv.) was dissolved in DCM (2 mL), and TFA (500 μ l) was added in the mixture. The mixture was heated at 30 $^{\circ}$ C for 2 hours. The reaction mixture was concentrated by Speedvac to give a residue. Then the residue and (1S,3S)-3-hydroxycyclobutane-1-carboxylic acid (37.1 mg, 0.32 mmol, 2.0 equiv.) were dissolved in ACN (2 mL), then NMI (0.5 mL) and TCFH (53.8 mg, 0.19 mmol, 1.2 equiv.) were added. The mixture was heated at 30 $^{\circ}$ C for 16 hours. The reaction mixture was concentrated by Speedvac to give a residue that was purified by prep HPLC to give (1S, 3S)-3-hydroxy-N-(5-{2-[4-(trifluoromethyl)phenyl]ethoxy}-1H-indol-3-yl)cyclobutane-1-carboxamide (27.0 mg, 0.064 mmol) as a powder. MS-ESI, 419.1 [M+H⁺]. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.61–10.52 (m, 1H), 9.57 (s, 1H), 7.69 (dd, *J*=5.2, 2.6 Hz, 3H), 7.59 (d, *J*=8.0 Hz, 2H), 7.31 (d, *J*=2.2 Hz, 1H), 7.19 (d, 1H), 6.71 (dd, *J*=8.8, 2.3 Hz, 1H), 5.14 (br d, *J*=6.4 Hz,

1H), 4.19 (t, $J=6.7$ Hz, 2H), 4.04–3.92 (m, 1H), 3.25–3.09 (m, 2H), 2.73–2.63 (m, 1H), 2.39–2.25 (m, 2H), 2.15–1.97 (m, 2H).

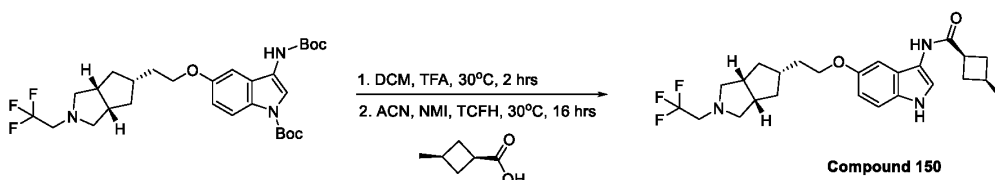
Example 187: (1S,3S)-3-hydroxy-N-(5-{2-[4-(trifluoromethyl)phenoxy]ethyl}-1H-indol-3-yl)cyclobutane-1-carboxamide (Compound 179)



tert-butyl (5-(2-(4-(trifluoromethyl)phenoxy)ethyl)-1H-indol-3-yl)carbamate (83.2 mg, 0.16 mmol, 1.0 equiv.) was dissolved in DCM (2 mL), then TFA (500 μ l) was added to the mixture. The reaction mixture was heated at 30 °C for 2 hours. The reaction mixture was concentrated by Speedvac to a residue. Then the residue and (1S,3S)-3-hydroxycyclobutane-1-carboxylic acid (37.1 mg, 0.32 mmol, 2.0 equiv.) were dissolved in ACN (2 mL), then NMI (0.5 mL) and TCFH (53.8 mg, 0.192 mmol, 1.2 equiv.) were added. The mixture was heated at 30 °C for 16 hours. The mixture was heated at 30 °C for 16 hours. The reaction mixture was concentrated by Speedvac to give a residue that was purified by prep HPLC to give (1S,3S)-3-hydroxy-N-(5-{2-[4-(trifluoromethyl)phenoxy]ethyl}-1H-indol-3-yl)cyclobutane-1-carboxamide (14.52 mg, 0.035 mmol) as a powder. MS-ESI, 419.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 10.72–10.65 (m, 1H), 9.68 (s, 1H), 7.72–7.60 (m, 4H), 7.26 (d, $J=8.3$ Hz, 1H), 7.16–7.05 (m, 3H), 5.14 (d, $J=7.0$ Hz, 1H), 4.29 (t, $J=7.0$ Hz, 2H), 4.04–3.92 (m, 1H), 3.16–3.07 (m, 2H), 2.78–2.68 (m, 1H), 2.39–2.27 (m, 2H), 2.15–1.95 (m, 2H).

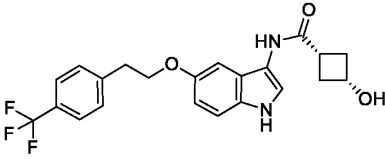
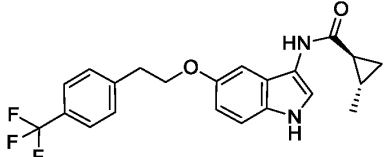
15

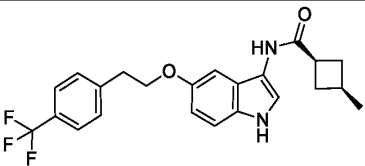
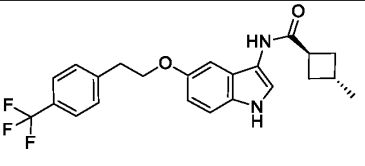
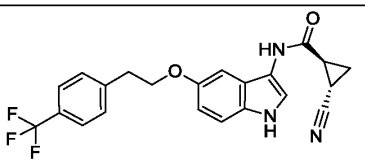
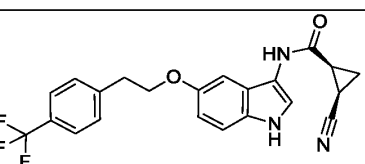
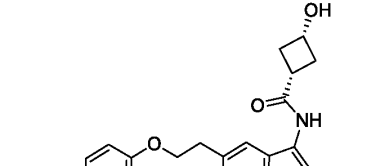
Example 188: (1R,3S)-N-(5-{2-[(3aR,5S,6aS)-2-(2,2,2-trifluoroethyl)-octahydrocyclopenta[c]pyrrol-5-yl]ethoxy}-1H-indol-3-yl)-3-methylcyclobutane-1-carboxamide (Compound 150)



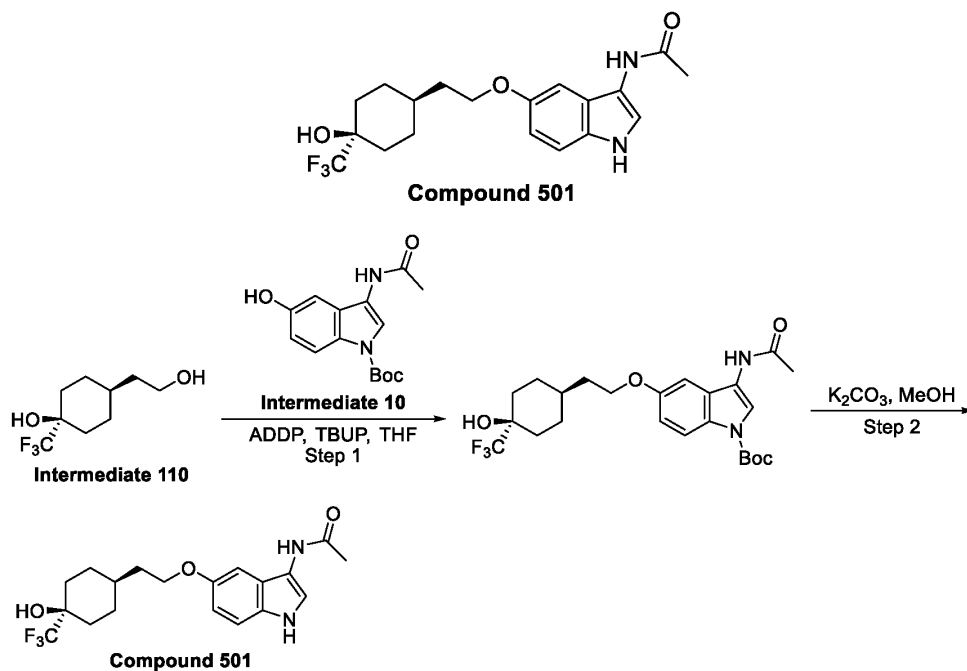
tert-butyl 3-[[[(tert-butoxy)carbonyl]amino}-5-[(1S,3S)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indole-1-carboxylate (81.9 mg, 0.15 mmol, 1.0 equiv.) was dissolved in DCM (2 mL), then TFA (500 μ l) was added to the mixture. The reaction mixture was heated at 30 °C for 2 hours. The reaction mixture was concentrated by Speedvac to give a residue. Then the residue and (1R,3S)-3-methylcyclobutane-1-carboxylic acid (34.2 mg, 0.30 mmol, 2.0 equiv.) were dissolved in ACN (2 mL), then NMI (0.5 mL) and TCFH (50.4 mg, 0.18 mmol, 1.2 equiv.) were added. The mixture was heated at 30 °C for 16 hours. The reaction mixture was concentrated by Speedvac to give a residue that was purified by prep HPLC to give (1R,3S)-N-(5-{2-[(3aR,5S,6aS)-2-(2,2,2-trifluoroethyl)-octahydrocyclopenta[c]pyrrol-5-yl]ethoxy}-1H-indol-3-yl)-3-methylcyclobutane-1-carboxamide (30.5 mg, 0.066 mmol) as a powder. MS-ESI, 464.4 [M+H⁺]. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.57–10.51 (m, 1H), 9.51 (s, 1H), 7.68 (d, *J*=2.4 Hz, 1H), 7.29 (d, *J*=2.3 Hz, 1H), 7.18 (d, *J*=8.8 Hz, 1H), 6.70 (dd, *J*=8.8, 2.3 Hz, 1H), 3.95 (t, *J*=6.5 Hz, 2H), 3.22–3.09 (m, 3H), 2.68–2.61 (m, 2H), 2.46–2.39 (m, 3H), 2.39–2.16 (m, 4H), 2.11–2.02 (m, 2H), 1.94–1.74 (m, 5H), 1.04 (d, *J*=6.3 Hz, 3H), 0.96 (td, *J*=11.7, 8.4 Hz, 2H).

The analogs prepared in the following table were prepared using the above procedures with the appropriate starting material.

Example #	Compound No.	Structure	LC-MS, MS-ESI, -- [M+H ⁺].
189	190		419.1
190	206		403.2

191	162		417.3
192	205		417.3
193	203		414.2
194	188		414.2
195	179		419.2

Example 196: *N*-(5-(2-(*cis*-4-hydroxy-4-(trifluoromethyl)cyclohexyl)ethoxy)-1*H*-indol-3-yl)acetamide (compound 501)



5

Step 1: *tert*-butyl 3-acetamido-5-{2-[4-hydroxy-4-(trifluoromethyl)cyclohexyl]ethoxy}indole-1-carboxylate

4-(2-hydroxyethyl)-1-(trifluoromethyl)cyclohexan-1-ol (132.0 mg, 0.6 mmol, 1.2 equiv.) and *tert*-butyl 3-acetamido-5-hydroxyindole-1-carboxylate (150.0 mg, 0.5 mmol, 1.0 equiv.) were dissolved in THF (10 mL), then TBUP (209.0 mg, 1.0 mmol, 2.0 equiv.) and ADDP (259.0 mg, 1.0 mmol, 2.0 equiv.) were added at 0 °C under an atmosphere of nitrogen. The reaction mixture was stirred for 16 hours at rt and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with petroleum ether/EtOAc (5:1) to afford *tert*-butyl 3-acetamido-5-{2-[4-hydroxy-4-(trifluoromethyl)cyclohexyl]ethoxy}indole-1-carboxylate (200.0 mg) as a pale white solid.

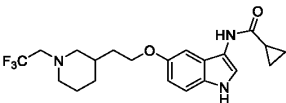
LCMS Method A: $[M+H]^+ = 485.1$.

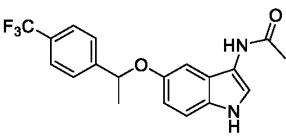
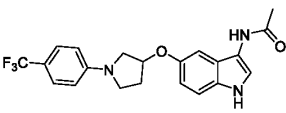
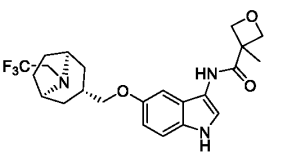
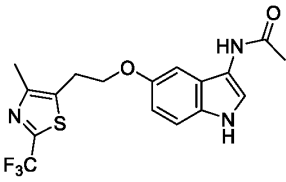
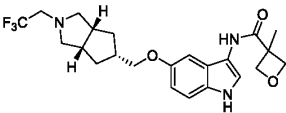
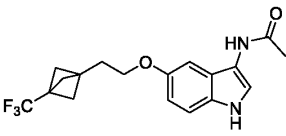
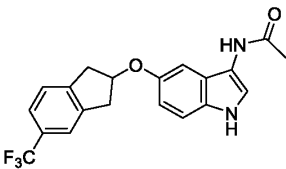
15

Step 2: *N*-(5-(2-(*cis*-4-hydroxy-4-(trifluoromethyl)cyclohexyl)ethoxy)-1*H*-indol-3-yl)acetamide

tert-Butyl 3-acetamido-5-{2-[4-hydroxy-4-(trifluoromethyl)cyclohexyl]ethoxy} indole-1-carboxylate (200.0 mg, 0.4 mmol, 1.0 equiv.) was dissolved in MeOH (5 mL), then K₂CO₃ (115.4 mg, 0.8 mmol, 2.0 equiv.) was added. The reaction mixture was heated to 60 °C for 16 hours, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 46% B in 8 min; Wave Length: 254; 220 nm; RT1: 6.83min. This gave *N*-(5-(2-(*cis*-4-hydroxy-4-(trifluoromethyl)cyclohexyl)ethoxy)-1*H*-indol-3-yl)acetamide (37.5 mg) as a pale white solid. LCMS Method D: [M+H]⁺ = 385.1. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.55 (s, 1H), 9.67 (s, 1H), 7.64 (d, *J* = 2.4 Hz, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 6.73–6.71 (m, 1H), 5.66 (s, 1H), 4.00 (t, *J* = 6.4 Hz, 2H), 2.08 (s, 3H), 1.90–1.70 (m, 7H), 1.54–1.45 (m, 4H).

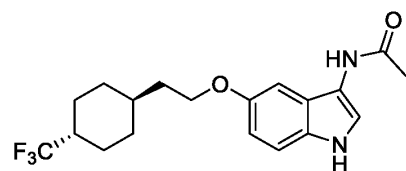
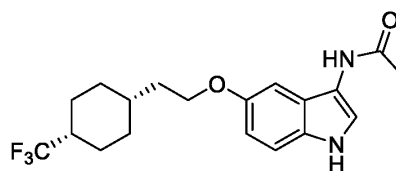
The analogs prepared in the following table were prepared using the same method described for Example 196.

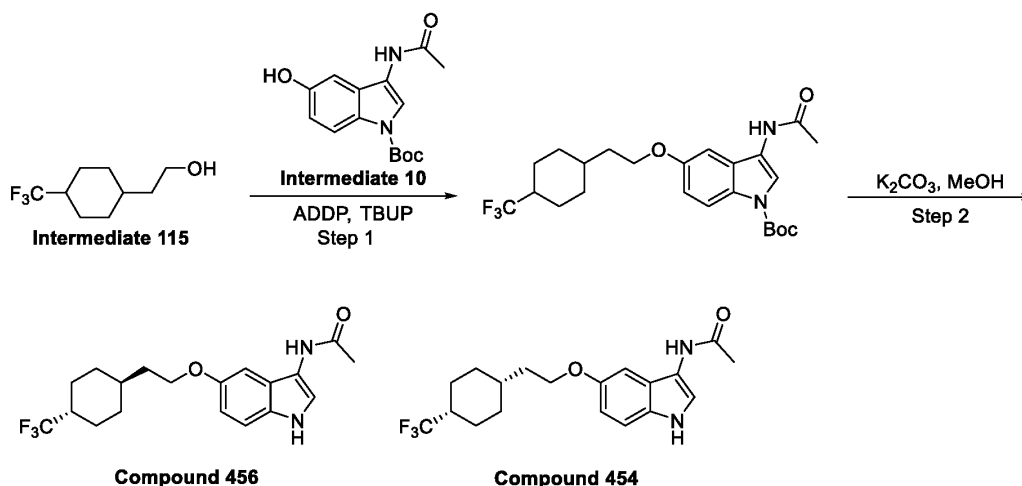
example #	Compound #	Starting materials Used	Structure	Condition	LCMS data
197	498	Intermediate 67 /Intermediate 104		TBUP, ADDP, THF	Method F: MS-ESI: 410.2 [M+H] ⁺ .

198	497	1-(4-(trifluoromethyl)phenyl)ethan-1-ol /Intermediate 10		TBUP, ADDP, THF	Method E: MS-ESI: 361.1 [M-H]⁺.
199	494	Intermediate 111 /Intermediate 10		PPh ₃ , DEAD, THF	Method F: MS-ESI: 404.0 [M+H]⁺.
200	485	Intermediate 112 /Intermediate 104		TBUP, ADDP, THF	Method F: MS-ESI: 452.1[M+H]⁺.
201	484	Intermediate 113 /Intermediate 10		PPh ₃ , DIAD, Py, THF	Method D: MS-ESI: 382.1[M-H]⁺.
202	479	Intermediate 64 /Intermediate 104		TBUP, ADDP, THF	Method F: MS-ESI: 452.2 [M+H]⁺.
203	474	Intermediate 116 /Intermediate 10		TBUP, ADDP, THF	Method F: MS-ESI: 353.2 [M+H]⁺.
204	473	Intermediate 118 /Intermediate 10		CMPB, toluene	Method F: MS-ESI: 375.3[M+H]⁺.

205	472	Intermediate 117 /Intermediate 10		TBUP, ADDP, THF	Method F: MS-ESI: 355.3 [M+H]⁺.
206	458	2-(bicyclo[1.1.1]pentan-1-yl)ethan-1-ol /Intermediate 10		TBUP, ADDP, THF	Method F: MS-ESI: 285.2[M+H]⁺.
207	437	Intermediate 121 /Intermediate 10		TBUP, ADDP, THF	Method F: MS-ESI: 401.1[M-H]⁺.
208	436	Intermediate 119 /Intermediate 10		DBAD, PPh ₃ , THF	Method F: MS-ESI: 389.1[M+H]⁺.
209	435	Intermediate 122 /Intermediate 10		TBUP, ADDP, THF	Method E: MS-ESI: 403.2[M+H]⁺.

Examples 210/211: *N*-(5-(2-(trans-4-(trifluoromethyl)cyclohexyl)ethoxy)-1*H*-indol-3-yl)acetamide [(compound 456) and *N*-(5-(2-(cis-4-(trifluoromethyl)cyclohexyl)ethoxy)-1*H*-indol-3-yl)acetamide (compound 454)

**Compound 456****Compound 454**



Step 1: *tert*-butyl 3-acetamido-5-(2-(4-(trifluoromethyl)cyclohexyl)ethoxy)-1*H*-indole-1-carboxylate

tert-Butyl 3-acetamido-5-hydroxy-1*H*-indole-1-carboxylate (488.2 mg, 1.7 mmol, 1.0 equiv.) and 2-(4-(trifluoromethyl)cyclohexyl)ethan-1-ol (330.0 mg, 1.7 mmol, 1.0 equiv.) were dissolved in THF (5 mL) and cooled to 0 °C, then TBUP (1.4 g, 6.7 mmol, 4.0 equiv.) and ADDP (842.1 mg, 3.3 mmol, 2.0 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred for 2 hours at 70 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with petroleum ether/EtOAc (1:1) to afford *tert*-butyl 3-acetamido-5-(2-(4-(trifluoromethyl)cyclohexyl)ethoxy)-1*H*-indole-1-carboxylate (500.0 mg) as a brown solid. LCMS Method A: [M+H]⁺ = 469.2.

Step 2: *N*-(5-(2-(*trans*-4-(trifluoromethyl)cyclohexyl)ethoxy)-1*H*-indol-3-yl)acetamide (front peak) and *N*-(5-(2-(*cis*-4-(trifluoromethyl)cyclohexyl)ethoxy)-1*H*-indol-3-yl)acetamide (second peak)

tert-Butyl 3-acetamido-5-(2-(4-(trifluoromethyl)cyclohexyl)ethoxy)-1*H*-indole-1-carboxylate (480 mg, 1.0 mmol, 1.0 equiv.) was dissolved in MeOH (5 mL), then K₂CO₃ (283.2 mg, 2.1 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 1 hour

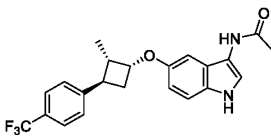
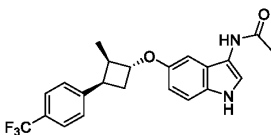
at 70 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. sodium sulfate and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: Xselect CSH C18 OBD Column 30*150mm 5µm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 47% B to 57% B in 9 min, 57% B; Wave Length: 254; 220 nm; RT1: 7.75 min, RT2: 8.15 min. This resulted in *N*-(5-(2-(trans-4-(trifluoromethyl)cyclohexyl)ethoxy)-1*H*-indol-3-yl)acetamide (front peak, absolute stereochemistry unconfirmed, assigned as Compound 456 (14.2 mg, 3.7%) as a white solid and *N*-(5-(2-(cis-4-(trifluoromethyl)cyclohexyl)ethoxy)-1*H*-indol-3-yl)acetamide (second peak, absolute stereochemistry unconfirmed, assigned as Compound 454 (16.3 mg, 4.1%) as a white solid.

Compound 456: LCMS Method E: $[M+H]^+ = 369.4$. ^1H NMR (400 MHz, DMSO- d_6): δ 10.57 (s, 1H), 9.70 (s, 1H), 7.65 (d, $J = 2.4$ Hz, 1H), 7.31 (d, $J = 2.4$ Hz, 1H), 7.20 (d, $J = 8.8$ Hz, 1H), 6.73–6.71 (m, 1H), 3.99 (t, $J = 6.4$ Hz, 2H), 2.31–2.29 (m, 1H), 2.08 (s, 3H), 1.92–1.90 (m, 1H), 1.81–1.76 (m, 2H), 1.67–1.60 (m, 8H).

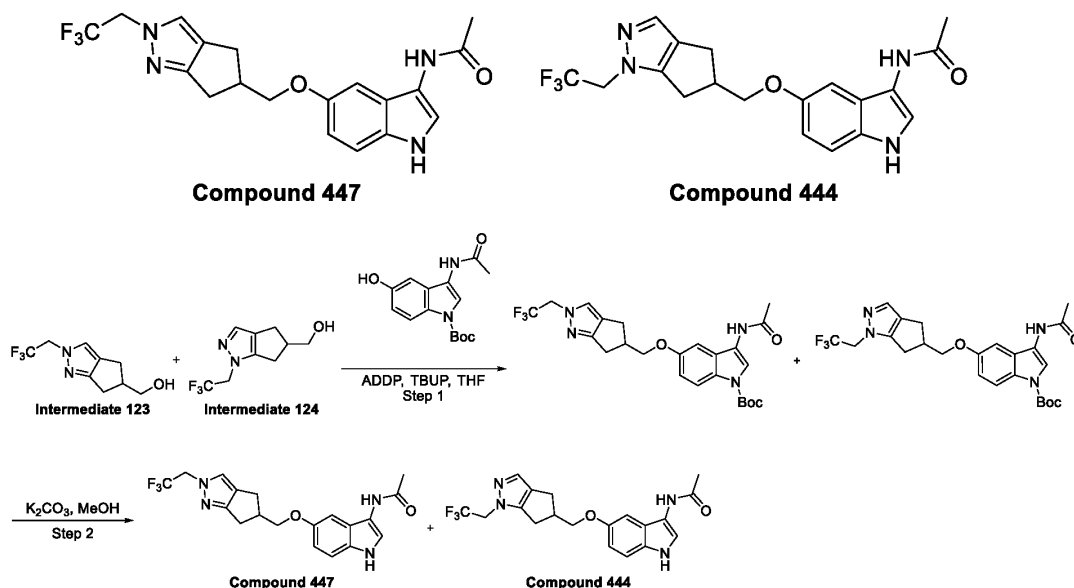
Compound 454: LCMS Method E: $[M+H]^+ = 369.4$. ^1H NMR (400 MHz, DMSO- d_6): δ 10.57 (s, 1H), 9.70 (s, 1H), 7.65 (d, $J = 2.4$ Hz, 1H), 7.31 (d, $J = 2.4$ Hz, 1H), 7.20 (d, $J = 8.8$ Hz, 1H), 6.73–6.71 (m, 1H), 4.00 (t, $J = 6.4$ Hz, 2H), 2.24–2.18 (m, 1H), 2.09 (s, 3H), 1.90–1.87 (m, 4H), 1.70–1.65 (m, 2H), 1.55–1.41 (m, 2H), 1.31–1.19 (m, 2H), 1.11–1.02 (m, 2H).

The analogs prepared in following table were prepared using the same method described for Example 210/211.

Compound d	Compound #	Starting materials Used	Structure	LCMS data
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212	448	Intermediate 120 /Intermediate 10		Method F: MS-ESI: 401.0 [M-H] ⁺ .
213	596	Intermediate 120 /Intermediate 10		Method E: MS-ESI: 401.1 [M-H] ⁺ .

Examples 214/215: *N*-(5-((2-(2,2,2-trifluoroethyl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-5-yl)methoxy)-1*H*-indol-3-yl)acetamide (compound 447) and *N*-(5-((1-(2,2,2-trifluoroethyl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazol-5-yl)methoxy)-1*H*-indol-3-yl)acetamide (compound 444)



Step 1: mixture of *tert*-butyl 3-acetamido-5-([2-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[c]pyrazol-5-yl]methoxy)indole-1-carboxylate and *tert*-butyl 3-acetamido-5-[1-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[c]pyrazol-5-yl]methoxy]indole-1-carboxylate

A mixture of [2-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazol-5-yl]methanol and [1-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazol-5-yl]methanol (200.0 mg, 0.9 mmol, 1.0 equiv.) and *tert*-butyl 3-acetamido-5-hydroxyindole-1-carboxylate (264.0 mg, 0.9 mmol, 1.0 equiv.) were dissolved in THF (8 mL) and cooled to 0 °C, then TBUP (368.0 mg, 1.8 mmol, 2.0 equiv.) and ADDP (455.0 mg, 1.8 mmol, 2.0 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred for 16 hours at rt and then concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with petroleum ether/EtOAc (5:1) to give a mixture of *tert*-butyl 3-acetamido-5-{[2-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazol-5-yl]methoxy}indole-1-carboxylate and *tert*-butyl 3-acetamido-5-{[1-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazol-5-yl]methoxy}indole-1-carboxylate (150.0 mg) as an off-white solid. LCMS Method A: [M+H]⁺ = 493.2.

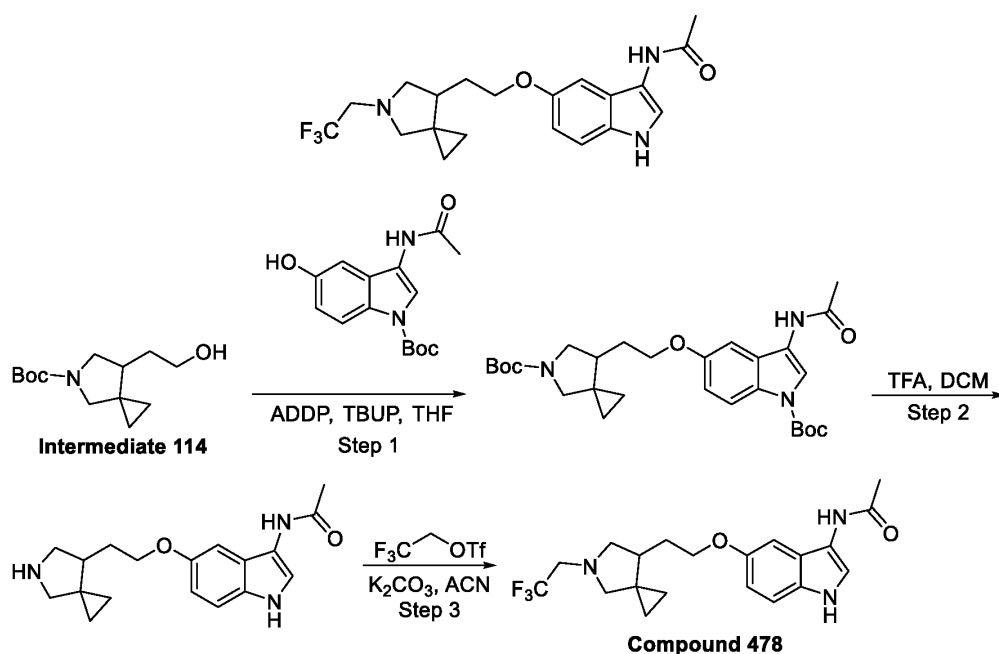
Step 2: *N*-(5-((2-(2,2,2-trifluoroethyl)-2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-5-yl)methoxy)-1*H*-indol-3-yl)acetamide and *N*-(5-((1-(2,2,2-trifluoroethyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-5-yl)methoxy)-1*H*-indol-3-yl)acetamide

tert-Butyl 3-acetamido-5-{[2-(2,2,2-trifluoroethyl)-4*H*,5*H*,6*H*-cyclopenta[*c*]pyrazol-5-yl]methoxy}indole-1-carboxylate (169.7 mg, 0.3 mmol, 1.0 equiv) was dissolved in MeOH (8 mL), K₂CO₃ (97 mg, 0.915 mmol, 3.0 equiv.) was added. The reaction mixture was stirred for 5 hours at 60 °C, then cooled to rt and removed the solid by filtration. The filter cake was washed with MeOH, and the combined filtrate was concentrated under vacuum. The resulting mixture was separated by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH₃-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 15 min; Wave Length: 220/254 nm; RT1: 10.14 min, RT2: 14.00 min. This resulted in *N*-(5-((2-(2,2,2-trifluoroethyl)-2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-5-yl)methoxy)-1*H*-indol-3-yl)acetamide (34.3 mg) as an off-white solid and *N*-(5-((1-(2,2,2-trifluoroethyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-5-yl)methoxy)-1*H*-indol-3-yl)acetamide (11.0 mg) as an off-white solid.

Compound 447: LCMS Method E: $[M+H]^+ = 393.1$. ^1H NMR (400 MHz, DMSO- d_6): δ 10.57 (s, 1H), 9.70 (s, 1H), 7.66 (d, $J = 2.4$ Hz, 1H), 7.45 (s, 1H), 7.34 (d, $J = 2.4$ Hz, 1H), 7.21 (d, $J = 8.8$ Hz, 1H), 6.77–6.75 (m, 1H), 5.00 (q, $J = 9.2$ Hz, 2H), 4.00 (d, $J = 6.8$ Hz, 2H), 3.27–3.22 (m, 1H), 2.92–2.82 (m, 2H), 2.60–2.54 (m, 2H), 2.08 (s, 3H).

5 **Compound 444:** LCMS Method E: $[M+H]^+ = 393.4$. ^1H NMR (400 MHz, DMSO- d_6): δ 10.58 (s, 1H), 9.69 (s, 1H), 7.65 (d, $J = 2.4$ Hz, 1H), 7.34 (d, $J = 2.4$ Hz, 1H), 7.26 (s, 1H), 7.21 (d, $J = 8.8$ Hz, 1H), 6.77–6.74 (m, 1H), 5.02 (q, $J = 9.2$ Hz, 2H), 4.99–4.00 (m, 2H), 3.46–3.43 (m, 1H), 3.02–2.96 (m, 1H), 2.86–2.80 (m, 1H), 2.72–2.67 (m, 1H), 2.52–2.50 (m, 1H), 2.08 (s, 3H).

10 **Example 216:** *N*-(5-(2-(5-(2,2,2-trifluoroethyl)-5-azaspiro[2.4]heptan-7-yl)ethoxy)-1*H*-indol-3-yl)acetamide (compound 478)



15 **Step 1: *tert*-butyl 3-acetamido-5-(2-(5-(*tert*-butoxycarbonyl)-5-azaspiro[2.4]heptan-7-yl)ethoxy)-1*H*-indole-1-carboxylate**

tert-Butyl 3-acetamido-5-hydroxy-1*H*-indole-1-carboxylate (150.0 mg, 0.5 mmol, 1.0 equiv.) and *tert*-butyl 7-(2-hydroxyethyl)-5-azaspiro[2.4]heptane-5-carboxylate (249.4 mg, 1.0 mmol, 2.0 equiv.) were dissolved in THF (5 mL) and cooled to 0 °C, then TBUP

(209.1 mg, 1.0 mmol, 2.0 equiv.) and ADDP (258.7 mg, 1.0 mmol, 2.0 equiv.) were added, maintaining the solution at 0 °C. The reaction mixture was stirred for 4 hours at rt and then concentrated under vacuum. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 30% to 70% gradient in 30 min; detector, UV 254 nm. This resulted in *tert*-butyl 3-acetamido-5-(2-(5-(*tert*-butoxycarbonyl)-5-azaspiro[2.4]heptan-7-yl)ethoxy)-1*H*-indole-1-carboxylate (120.0 mg) as an off-white solid. LCMS Method A: [M+H]⁺ = 514.2.

Step 2: *N*-(5-(2-(5-azaspiro[2.4]heptan-7-yl)ethoxy)-1*H*-indol-3-yl)acetamide

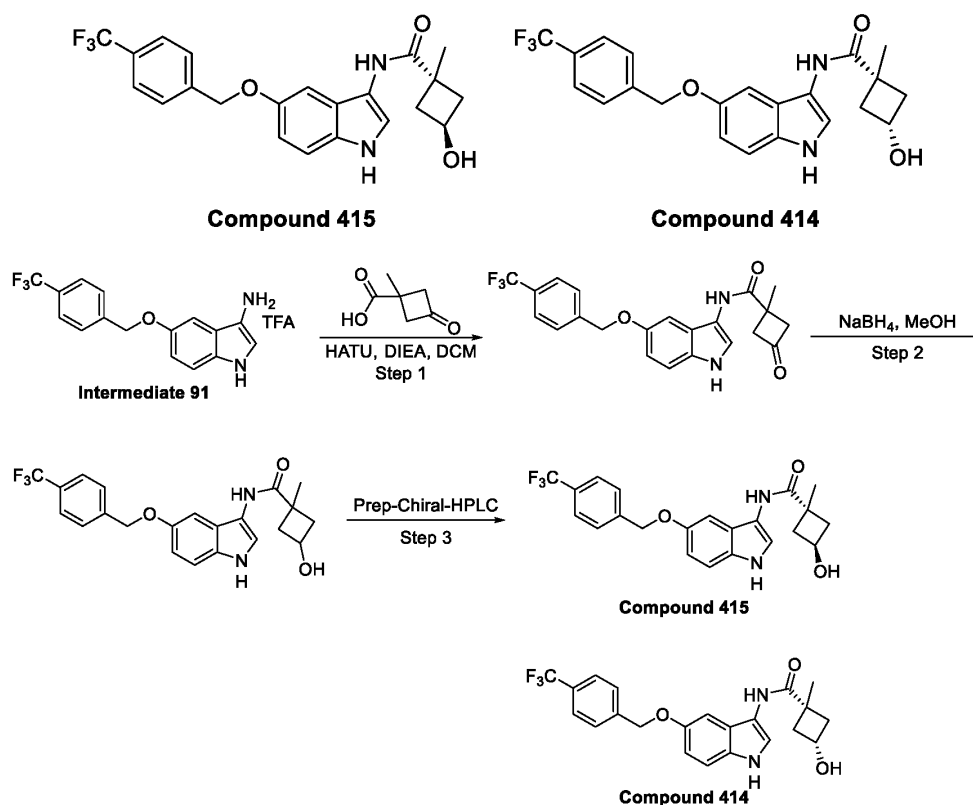
tert-Butyl 3-acetamido-5-(2-(5-(*tert*-butoxycarbonyl)-5-azaspiro[2.4]heptan-7-yl)ethoxy)-1*H*-indole-1-carboxylate (110.0 mg, 0.2 mmol, 1.0 equiv.) was dissolved in DCM (3.0 mL), then TFA (0.6 mL) was added. The reaction mixture was stirred for 2 hours at rt and then concentrated under vacuum to give *N*-(5-(2-(5-azaspiro[2.4]heptan-7-yl)ethoxy)-1*H*-indol-3-yl)acetamide (60.0 mg) as a colorless oil. LCMS Method A: [M+H]⁺ = 314.2.

Step 3: *N*-(5-(2-(5-(2,2,2-trifluoroethyl)-5-azaspiro[2.4]heptan-7-yl)ethoxy)-1*H*-indol-3-yl)acetamide

N-(5-(2-(5-azaspiro[2.4]heptan-7-yl)ethoxy)-1*H*-indol-3-yl)acetamide (60.0 mg, 0.2 mmol, 1.0 equiv.) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (66.7 mg, 0.3 mmol, 1.5 equiv.) were dissolved in ACN (5.0 mL), then K₂CO₃ (79.4 mg, 0.6 mmol, 3.0 equiv.) was added. The reaction mixture was stirred for 2 hours at 60 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column, XBridge Shield RP18 OBD Column, 30*150 mm, 5µm; mobile phase, Water (10 mmol/L NH₄HCO₃+0.1% NH₃.H₂O) and ACN (33% ACN up to 57% in 7 min). This resulted in *N*-(5-(2-(5-(2,2,2-trifluoroethyl)-5-azaspiro[2.4]heptan-7-yl)ethoxy)-1*H*-indol-3-yl)acetamide (15.0 mg) as a white solid. LCMS Method F: [M+H]⁺ = 396.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.56 (d, *J* = 1.6 Hz, 1H), 9.68 (s, 1H), 7.64 (d, *J* = 2.4 Hz, 1H), 7.28 (d, *J* = 2.0 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 6.72–6.69 (m, 1H), 3.93–3.89 (m, 2H), 3.25–3.21 (m, 3H), 2.74 (d, *J*

= 8.8 Hz, 1H), 2.69 (d, J = 8.8 Hz, 1H), 2.62–2.57 (m, 1H), 2.15–2.13 (m, 1H), 2.08 (s, 3H), 1.65–1.52 (m, 2H), 0.72–0.69 (m, 1H), 0.61–0.59 (m, 1H), 0.48–0.46 (m, 1H), 0.40–0.36 (m, 1H).

Example 217/218: *trans*-3-hydroxy-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (compound 415) and *cis*-3-hydroxy-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (compound 414)



Step 1: 1-methyl-3-oxo-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide

5-((4-(Trifluoromethyl)benzyl)oxy)-1*H*-indol-3-amine TFA salt (500.0 mg, 1.6 mmol, 1.0 equiv.) and 1-methyl-3-oxocyclobutane-1-carboxylic acid (209.1 mg, 1.6 mmol, 1.0 equiv.) were added in DCM (10 mL), then DIEA (0.5 mL, 3.2 mmol, 2.0 equiv.) and HATU (931.1 mg, 2.4 mmol, 1.5 equiv.) were added. The reaction mixture was stirred for

1 hour at rt and then quenched by the addition of water. The resulting solution was extracted with dichloromethane, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with petroleum ether/EtOAc (3:1) to afford 1-methyl-3-oxo-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (500.0 mg) as a black solid. LCMS Method A: [M+H]⁺ = 417.2.

Step 2: 3-hydroxy-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide

1-Methyl-3-oxo-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (500.0 mg, 1.2 mmol, 1.0 equiv.) was dissolved in MeOH (10 mL) and cooled to 0 °C, then NaBH₄ (181.7 mg, 4.8 mmol, 4.0 equiv.) was added. The reaction mixture was stirred for 1 hour at rt and then quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 10% to 50% gradient in 10 min; detector, UV 254 nm.). This resulted in 3-hydroxy-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (410.0 mg) as a white solid. LCMS Method A: [M+H]⁺ = 419.2.

Step 3: *trans*-3-hydroxy-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide and *cis*-3-hydroxy-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide

The racemic 3-hydroxy-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (400.0 mg) was separated by Chiral-HPLC with the following conditions: Column: JW-CHIRALPAK-ID, 2*25cm; 5μm; Mobile Phase A: Hex(0.5% 2M NH₃-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 11.5 min; Wave Length: 220/254 nm; RT1: 6.942 min, RT2: 7.015 min. This resulted in *trans*-3-hydroxy-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (125.5 mg) as an

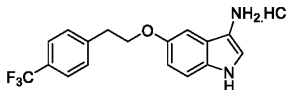
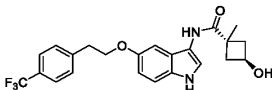
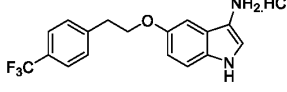
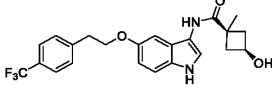
off-white solid and *cis*-3-hydroxy-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (92.4 mg) as an off-white solid.

Compound 415: LCMS Method E: $[M+H]^+ = 419.2$. ^1H NMR (400 MHz, DMSO-*d*₆): δ 10.67 (d, *J* = 1.6 Hz, 1H), 9.20 (s, 1H), 7.78–7.70 (m, 4H), 7.60 (d, *J* = 2.4 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.85–6.83 (m, 1H), 5.20 (s, 2H), 5.03 (d, *J* = 6.0 Hz, 1H), 4.03–3.89 (m, 1H), 2.84–2.79 (m, 2H), 1.82–1.77 (m, 2H), 1.49 (s, 3H).

Compound 414: LCMS Method E: $[M+H]^+ = 419.2$. ^1H NMR (400 MHz, DMSO-*d*₆): δ 10.67 (d, *J* = 2.0 Hz, 1H), 9.03 (s, 1H), 7.80–7.70 (m, 4H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 6.86–6.83 (m, 1H), 5.20 (s, 2H), 4.99 (d, *J* = 6.8 Hz, 1H), 4.18–4.13 (m, 1H), 2.27–2.19 (m, 4H), 1.41 (s, 3H).

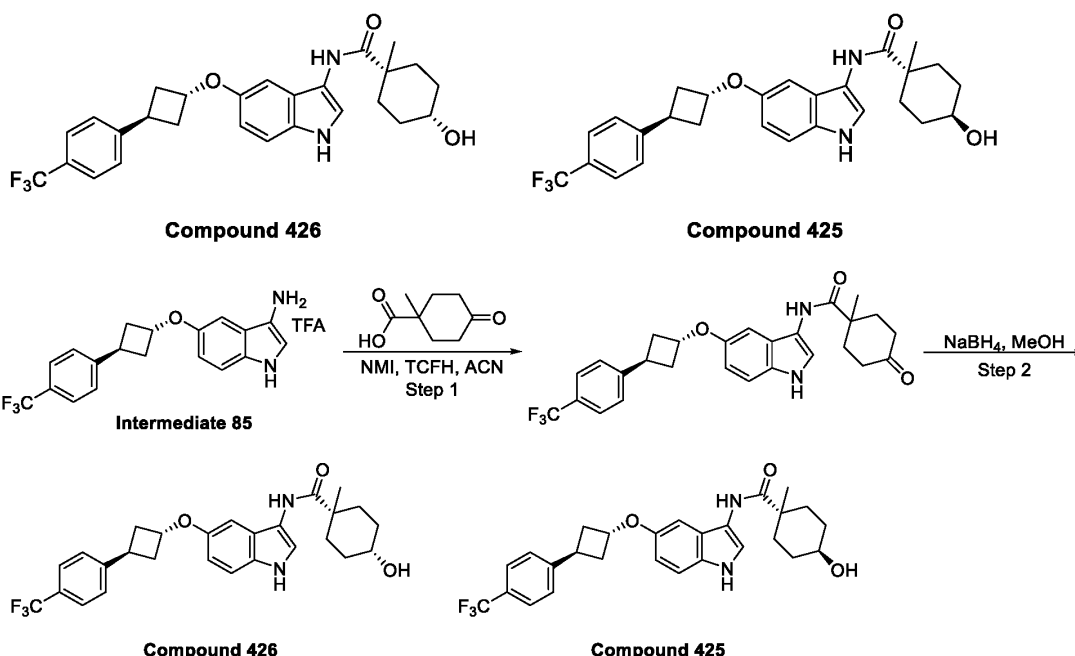
The analogs prepared in the following table were prepared using the same method described for Example 217/218.

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Example #	Compound #	Starting materials Used	Structure	LCMS data
219	446	 Intermediate 33		Method F: MS-ESI: 433.1[M+H] ⁺
220	445	 Intermediate 33		Method D: MS-ESI: 433.1[M+H] ⁺

Example 221/222: *cis*-4-hydroxy-1-methyl-*N*-(5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclohexane-1-carboxamide (compound 426) and *trans*-4-hydroxy-1-methyl-*N*-(5-(*trans*-3-(4-

(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclohexane-1-carboxamide
(compound 425)



5 **Step 1: 1-methyl-4-oxo-*N*-(5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclohexane-1-carboxamide**

5-[*trans*-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1*H*-indol-3-amine TFA salt (300.0 mg, 0.9 mmol, 1.0 equiv.) and 1-methyl-4-oxocyclohexane-1-carboxylic acid (135.3 mg, 0.9 mmol, 1.0 equiv.) were dissolved in ACN (5 mL), then TCFH (1.5 g, 5.2 mmol, 6.0 equiv.) and NMI (87.6 mg, 0.9 mmol, 1.0 equiv.) were added at 0 °C. The reaction mixture was stirred for 2 hours at rt and then concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 70% gradient in 20 min; detector, UV 254 nm. This resulted in 1-methyl-4-oxo-*N*-(5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclohexane-1-carboxamide (140.0 mg) as a yellow green solid. LCMS Method B: [M+H]⁺ = 485.2.

Step 2: *cis*-4-hydroxy-1-methyl-*N*-(5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclohexane-1-carboxamide (front peak,

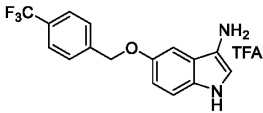
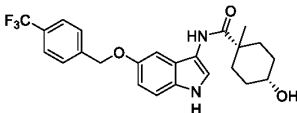
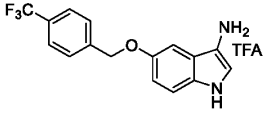
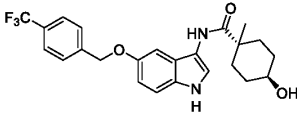
stereochemistry unconfirmed) and *trans*-4-hydroxy-1-methyl-*N*-(5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclohexane-1-carboxamide (second peak, stereochemistry unconfirmed)

1-Methyl-4-oxo-*N*-(5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclohexane-1-carboxamide (200.0 mg, 0.4 mmol, 1.0 equiv.) was dissolved in MeOH (4 mL) and cooled to 0 °C, then NaBH₄ (31.2 mg, 0.8 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 2 hours at rt and then quenched by the addition of ice-water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: SunFire C18 OBD Prep Column, 19*250 mm, 5µm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 45% B to 65% B in 6 min; Wave Length: 254/210 nm; RT1: 6.1 min, RT2: 6.7 min. This resulted in *cis*-4-hydroxy-1-methyl-*N*-(5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclohexane-1-carboxamide (front peak, absolute stereochemistry unconfirmed, assigned as compound 426) (20.1 mg) as a white solid and *trans*-4-hydroxy-1-methyl-*N*-(5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)cyclohexane-1-carboxamide (second peak, absolute stereochemistry unconfirmed, assigned as compound 425) (48.5 mg) as a white solid.

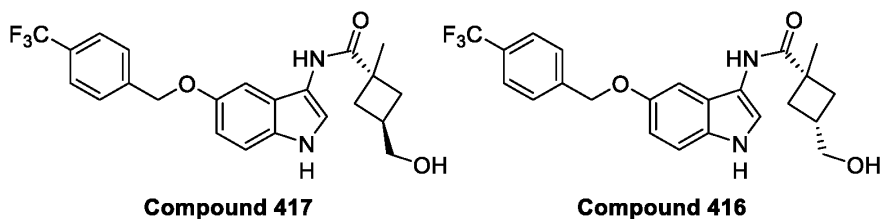
Compound 426: LCMS Method F: [M+H]⁺ = 487.3. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.65 (s, 1H), 8.86 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.74–6.72 (m, 1H), 4.92–4.87 (m, 1H), 4.41 (d, *J* = 4.0 Hz, 1H), 3.82–3.78 (m, 1H), 3.57–3.55 (m, 1H), 2.61 (t, *J* = 6.8 Hz, 4H), 1.88–1.81 (m, 2H), 1.70–1.65 (m, 4H), 1.49–1.42 (m, 2H), 1.24 (s, 3H).

Compound 425: LCMS Method F: [M+H]⁺ = 487.3. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.68 (s, 1H), 8.94 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.74–6.72 (m, 1H), 4.92–4.86 (m, 1H), 4.46 (d, *J* = 4.4 Hz, 1H), 3.84–3.78 (m, 1H), 3.45–3.41 (m, 1H), 2.61 (t, *J* = 6.8 Hz, 4H), 2.32–2.29 (m, 2H), 1.72–1.68 (m, 4H), 1.36–1.30 (m, 2H), 1.27–1.16 (m, 5H).

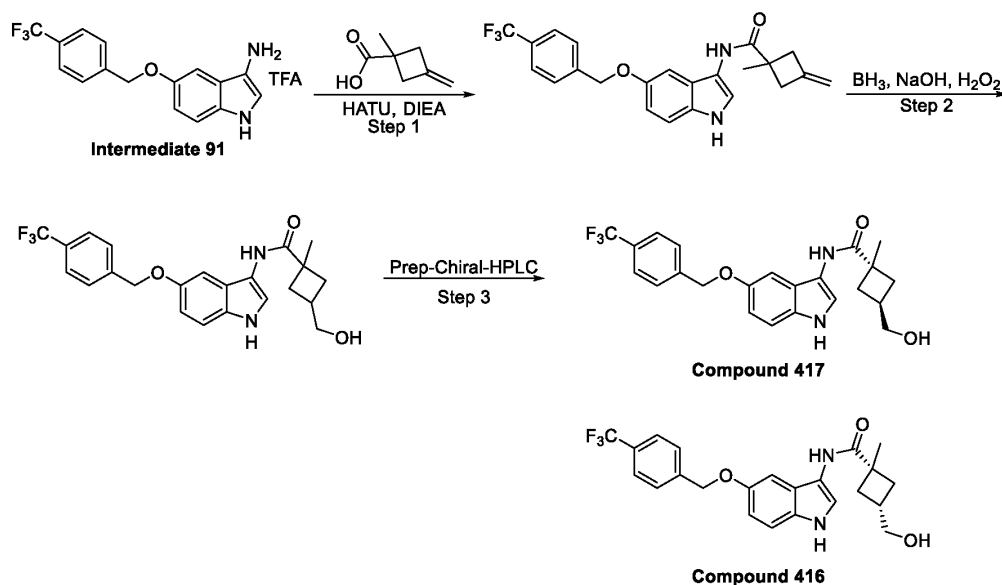
The analogs prepared in the following table were prepared using the same method described for Examples 221/222.

Example #	Compound #	Starting materials Used	Structure	LCMS data
223	419	 Intermediate 91		Method F: MS-ESI: 447.3[M+H] ⁺ .
224	418	 Intermediate 91		Method F: MS-ESI: 447.3 [M+H] ⁺ .

5 **Example 225/226:** *trans*-3-(hydroxymethyl)-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (compound 417) and *cis*-3-(hydroxymethyl)-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (compound 416)



10



Step 1: 1-methyl-3-methylene-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide

1-Methyl-3-methylenecyclobutane-1-carboxylic acid (350.1 mg, 2.8 mmol, 1.0 equiv.), 5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-amine TFA salt (850.0 mg, 2.8 mmol, 1.0 equiv.) and DIEA (2.3 mL, 13.9 mmol, 5.0 equiv.) were dissolved in DCM (10 mL), then HATU (1582.8 mg, 4.2 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for 2 hours at rt and then quenched by the addition of water. The resulting solution was extracted with dichloromethane, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with petroleum ether/EtOAc (1:1) to give 1-methyl-3-methylene-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide (660.0 mg) as a green solid. LCMS Method A: [M+H]⁺ = 415.2.

Step 2: 3-(hydroxymethyl)-1-methyl-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide

1-Methyl-3-methylene-N-(5-((4-(trifluoromethyl)benzyl)oxy)-1H-indol-3-yl)cyclobutane-1-carboxamide (600.0 mg, 1.4 mmol, 1.0 equiv.) was dissolved in THF (10 mL) and cooled to 0 °C, then BH₃-THF (5.8 mL, 1M, 5.8 mmol, 4.0 equiv.) was added

dropwise, maintaining the solution at 0 °C. The reaction mixture was stirred for 1 hour at 0 °C, then to the above mixture were added aqueous NaOH (30% wt., 3.0 mL, 6.7 mmol, 4.6 equiv,) and H₂O₂ (30% wt., 1.3 mL, 3.3 mmol, 2.3 equiv,) were added dropwise at 0 °C. The reaction mixture was stirred for additional 2 hours at rt and then quenched by the addition of saturated aqueous NH₄Cl. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with dichloromethane/methanol (10:1) to give the crude product, that was further purified by Prep-HPLC with the following conditions: Column: SunFire Prep C18 OBD Column, 19*150 mm, 5µm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 60% B to 80% B in 5.5 min; Wave Length: 210/254 nm; RT1: 5.30 min. This resulted in 3-(hydroxymethyl)-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (150 mg). LCMS Method A: [M+H]⁺ = 433.3.

Step 3: *trans*-3-(hydroxymethyl)-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (compound 417) and *cis*-3-(hydroxymethyl)-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (compound 416)

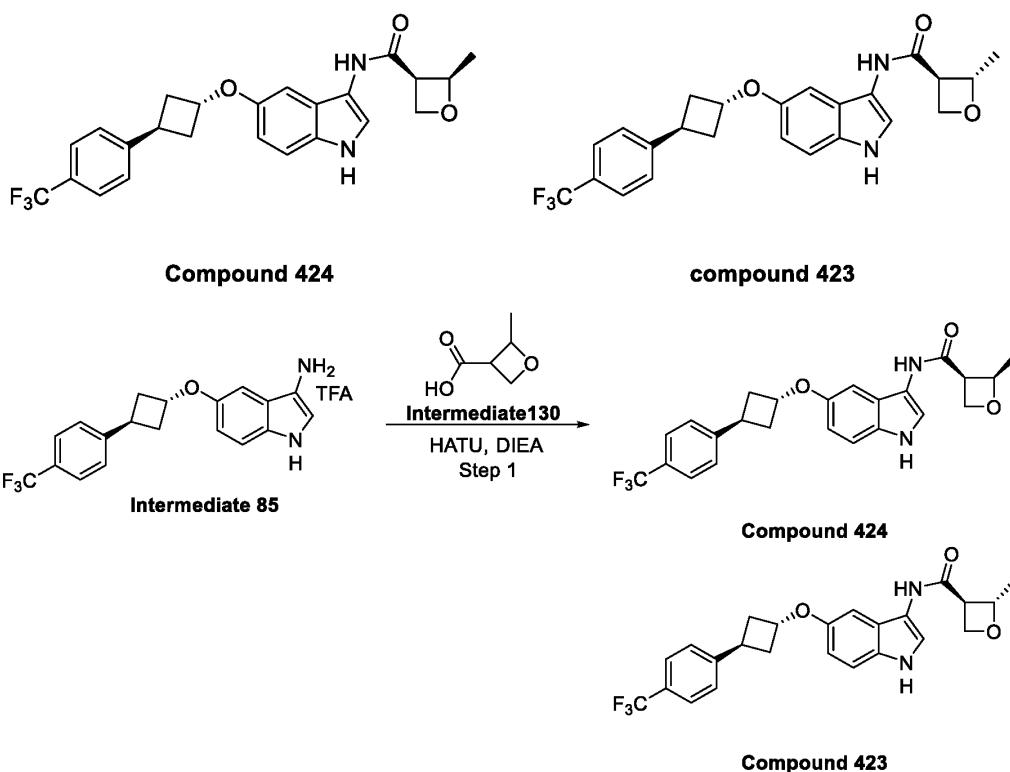
3-(Hydroxymethyl)-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl) cyclobutane-1-carboxamide (150 mg) was separated by Prep-CHIRAL-HPLC with the following conditions: Column: JW-CHIRALPAK IA-3, 4.6*50mm, 3µm; Mobile Phase A: Hex (0.1% DEA): IPA=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B. This resulted in *trans*-3-(hydroxymethyl)-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (compound 417, 98.2 mg) as a white solid and *cis*-3-(hydroxymethyl)-1-methyl-*N*-(5-((4-(trifluoromethyl)benzyl)oxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (compound 416), 38.3 mg) as a white solid.

compound 417: LCMS Method D: [M+H]⁺ = 433.3. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.66 (s, 1H), 9.19 (s, 1H), 7.78–7.71 (m, 4H), 7.61 (d, *J* = 2.4 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.86–6.83 (m, 1H), 5.21 (s, 2H), 4.49 (t, *J* = 5.6

Hz, 1H), 3.41–3.35 (m, 2H), 2.59–2.56 (m, 2H), 2.24–2.20 (m, 1H), 1.74–1.69 (m, 2H), 1.48 (s, 3H).

compound 416: LCMS Method D: $[M+H]^+ = 433.3$. ^1H NMR (400 MHz, DMSO- d_6): δ 10.65 (d, $J = 2.0$ Hz, 1H), 9.08 (s, 1H), 7.81–7.71 (m, 4H), 7.60 (d, $J = 2.4$ Hz, 1H), 7.37 (d, $J = 2.4$ Hz, 1H), 7.25 (d, $J = 8.8$ Hz, 1H), 6.86–6.84 (m, 1H), 5.21 (s, 2H), 4.58 (t, $J = 5.2$ Hz, 1H), 3.37–3.33 (m, 2H), 2.40–2.34 (m, 1H), 2.21–2.15 (m, 2H), 1.94–1.89 (m, 2H), 1.48 (s, 3H).

Example 227/228: (2R,3R)-2-methyl-N-(5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)oxetane-3-carboxamide (compound 424) and (2S,3R)-2-methyl-N-(5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)oxetane-3-carboxamide (compound 423)



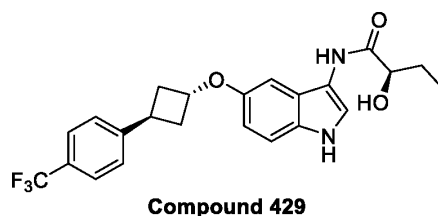
5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-amine TFA salt (100.0 mg, 0.3 mmol, 1.0 equiv.) and 2-methyloxetane-3-carboxylic acid (50.3 mg, 0.4

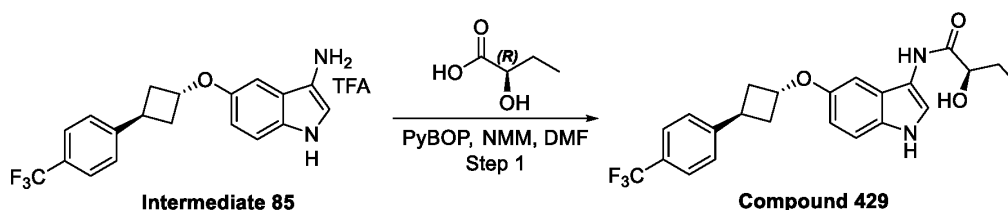
mmol, 1.5 equiv.) were dissolved in THF (5 mL), then HATU (164.7 mg, 0.4 mmol, 1.5 equiv.) and DIEA (0.15 mL, 0.9 mmol, 3.0 equiv.) were added. The reaction mixture was stirred for 1 hour at rt and then concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel;
5 mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 30% to 70% gradient in 30 min; detector, UV 254 nm. The crude product was further purified by Prep-HPLC with the following conditions: Column: SunFire Prep C18 OBD Column, 19*150 mm, 5 μm ; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 60% B to 90% B in 5.5 min; Wave Length: 210/254 nm; RT1: 5.1 min, RT2: 5.4 min. This
10 resulted in *cis*-2-methyl-N-(5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)oxetane-3-carboxamide (compound 424) (6.2 mg) as an off-white solid and *trans*-2-methyl-N-(5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)oxetane-3-carboxamide (compound 423) (5.6 mg) as an off-white solid.

compound 424: LCMS Method F: $[\text{M}+\text{H}]^+ = 445.3$. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 10.67 (d, $J = 2.4$ Hz, 1H), 9.62 (s, 1H), 7.73–7.70 (m, 3H), 7.61–7.59 (m, 2H),
15 7.24 (d, $J = 8.8$ Hz, 1H), 7.08 (d, $J = 2.0$ Hz, 1H), 6.76–6.73 (m, 1H), 5.15–5.10 (m, 1H), 4.94–4.89 (m, 1H), 4.74 (t, $J = 6.0$ Hz, 1H), 4.55–4.52 (m, 1H), 4.02–3.97 (m, 1H), 3.84–3.79 (m, 1H), 2.65–2.60 (m, 4H), 1.23 (d, $J = 7.2$ Hz, 3H).

compound 423: LCMS Method F: $[\text{M}+\text{H}]^+ = 445.1$. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 10.67 (d, $J = 1.2$ Hz, 1H), 9.71 (s, 1H), 7.76–7.71 (m, 3H), 7.60 (d, $J = 8.4$ Hz,
20 2H), 7.24 (d, $J = 8.4$ Hz, 1H), 7.12 (d, $J = 2.0$ Hz, 1H), 6.76–6.73 (m, 1H), 4.96–4.90 (m, 2H), 4.60–4.51 (m, 2H), 3.83–3.79 (m, 1H), 3.69–3.63 (m, 1H), 2.69–2.61 (m, 4H), 1.42 (d, $J = 6.0$ Hz, 3H).

Example 229: (R)-2-hydroxy-N-(5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1H-indol-3-yl)butanamide (compound 429)
25





5-[trans-3-[4-(trifluoromethyl) phenyl] cyclobutoxy]-1H-indol-3-amine TFA salt (120.0 mg, 0.3 mmol, 1.0 equiv.) was dissolved in DMF (5 mL), (R)-2-hydroxybutyric acid (72.1 mg, 0.7 mmol, 2.0 equiv.), NMM (210.3 mg, 2.1 mmol, 6.0 equiv.) and PyBOP (180.3 mg, 0.3 mmol, 1.0 equiv.) were added. The reaction mixture was stirred for 5 hours at rt and then concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 5% to 70% gradient in 25 min; detector, UV 254 nm. The resulting crude product was further purified by Prep-HPLC with the following conditions:

Column: SunFire Prep C18 OBD Column, 19*150 mm, 5 μ m; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 55% B to 80% B in 5.3 min; Wave Length: 210/254 nm; RT1: 5.3 min. This resulted in (2R)-2-hydroxy-N-{5-[trans-3-[4-(trifluoromethyl) phenyl] cyclobutoxy]-1H-indol-3-yl} butanamide (28.0 mg) as a white solid. LCMS Method E: [M+H]⁺ = 433.3. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.68 (d, *J* = 2.6 Hz, 1H), 9.38 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.64–7.58 (m, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 6.76–6.73 (m, 1H), 5.46 (d, *J* = 5.6 Hz, 1H), 4.94–4.91 (m, 1H), 4.06–4.02 (m, 1H), 3.83–3.79 (m, 1H), 2.67–2.62 (m, 4H), 1.77–1.72 (m, 1H), 1.66–1.59 (m, 1H), 0.92 (t, *J* = 7.6 Hz, 3H).

The analogs prepared in the following table were prepared using the same method described for Example 229.

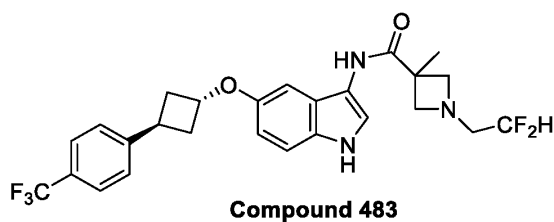
Example #	Compound #	Starting materials Used	Structure	condition	LCMS data

230	496	Intermediate 91 /Tetramethyloxetane-3-carboxylic acid		HATU, DIEA, DCM	Method E: MS-ESI: 4475.2[M-H] ⁺ .
231	464	Intermediate 107 /1-methylcyclopropane-1-carboxylic acid		T ₃ P, TEA, DMF	Method F: MS-ESI: 402.1[M+H] ⁺ .
232	455	Intermediate 106 /AcCl		TEA, DCM	Method F: MS-ESI: 390.1[M+H] ⁺ .
233	434	Intermediate 90 /2-(2,2,2-trifluoroethoxy)acetic acid		HATU, DIEA, DCM	Method F: MS-ESI: 508.2[M+H] ⁺ .
234	433	Intermediate 90 /4,4,4-trifluoro-3-hydroxybutanoic acid		HATU, DIEA, DCM	Method F: MS-ESI: 508.2[M+H] ⁺ .
235	431	Intermediate 33 /(R)-2-hydroxybutanoic acid		HATU, DIEA, DCM	Method F: MS-ESI: 407.2[M+H] ⁺ .

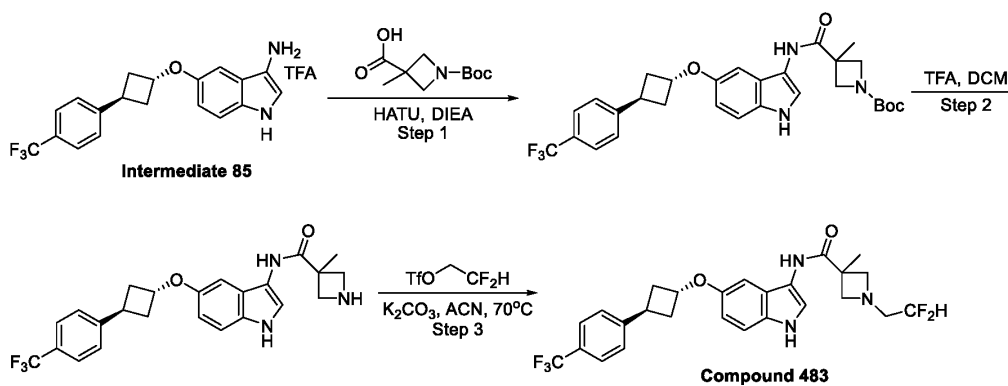
236	430	Intermediate 33 /(S)-2- hydroxybutanoic acid		HATU, DIEA, DCM	Method F: MS- ESI: 407.2[M +H]⁺.
237	428	Intermediate 90 /2,4- dimethyloxetane- 3-carboxylic acid		T ₃ P, TEA, ACN	Method E: MS- ESI: 419.2 [M+H]⁺.
238	422	Intermediate 86 /Intermediate 131		HATU, DIEA, DCM	Method F: MS- ESI: 502.2[M +H]⁺.
239	421	Intermediate 91 /Intermediate 132		HATU, DIEA, DCM	Method F: MS- ESI: 468.1 [M+H]⁺.
240	420	Intermediate 91 /1- (hydroxymethyl) cyclobutane-1- carboxylic acid		HATU, DIEA, DCM	Method F: MS- ESI: 459.2[M +H]⁺.
241	413	Intermediate 86 /Intermediate 133		T ₃ P, TEA, THF	Method F: MS- ESI: 500.2[M +H]⁺.

242	412	Intermediate 86 /Intermediate 134		T ₃ P, TEA, THF	Method F: MS- ESI: 500.2[M +H] ⁺ .
243	409	Intermediate 91 /2,2- dimethyloxetane- 3-carboxylic acid		HATU, DIEA, DCM	Method F: MS- ESI: 419.2[M +H] ⁺ .

Example 244: 1-(2,2-difluoroethyl)-3-methyl-N-(5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)azetidine-3-carboxamide (compound 483)



5



Step 1: *tert*-butyl 3-methyl-3-((5-(*trans*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)carbamoyl)azetidine-1-carboxylate

5 5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-amine (300.0 mg, 0.9 mmol, 1.0 equiv.) and 1-(*tert*-butoxycarbonyl)-3-methylazetidine-3-carboxylic acid (223.7 mg, 1.0 mmol, 1.2 equiv.) were dissolved in THF (15 mL), then HATU (395.2 mg, 1.0 mmol, 1.2 equiv.) and DIEA (0.3 mL, 1.7 mmol, 2.0 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred overnight at rt and then concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 30% to 90% gradient in 20 min; detector, UV 254 nm. This resulted in *tert*-butyl 3-methyl-3-((5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)carbamoyl)azetidine-1-carboxylate (274.0 mg) as a brown yellow oil.
10 LCMS Method A: [M+H]⁺ = 544.2.

Step 2: 3-methyl-*N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)azetidine-3-carboxamide

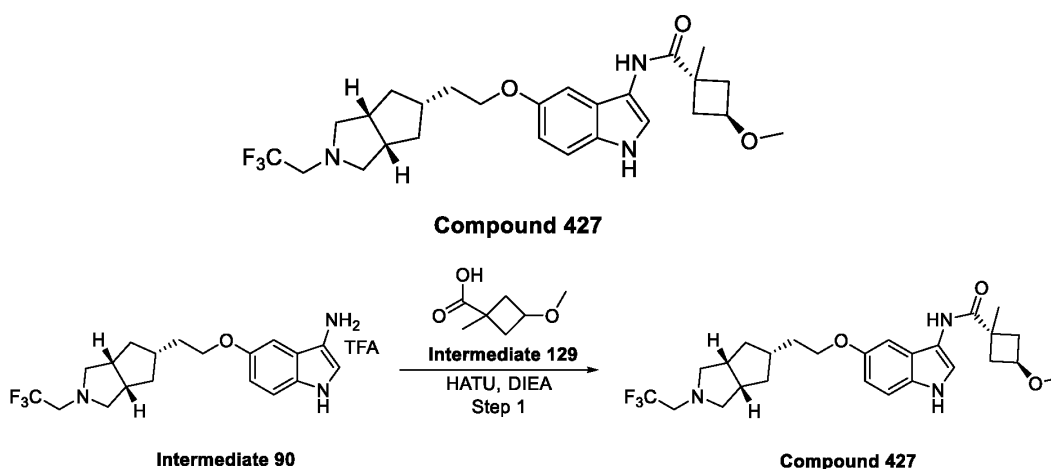
tert-Butyl 3-methyl-3-((5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)carbamoyl)azetidine-1-carboxylate (200.0 mg, 0.3 mmol, 1.0 equiv.) was
15 dissolved in DCM (4 mL), then TFA (1 mL) was added. The reaction mixture was stirred for 4 hours at rt and concentrated under vacuum to give the crude product, which was used in the next step directly without further purification. LCMS Method A: [M+H]⁺ = 444.2.

Step 3: 1-(2,2-difluoroethyl)-3-methyl-*N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)azetidine-3-carboxamide

3-Methyl-*N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)azetidine-3-carboxamide (100.0 mg, 0.2 mmol, 1.0 equiv.) and 2,2-difluoroethyl trifluoromethanesulfonate (72.4 mg, 0.3 mmol, 1.5 equiv.) were dissolved in ACN (5 mL), K₂CO₃ (62.3 mg, 0.5 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 4
25 hours at 80 °C, then cooled to rt and diluted with water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column, Xselect CSH C18 OBD Column 30*150mm 5um; mobile phase, Water (0.1% FA) and ACN (31% ACN up to 45% in 7 min). This resulted in 1-(2,2-difluoroethyl)-3-methyl-*N*-(5-(trans-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)azetidine-3-
30

carboxamide (33.0 mg) as a white solid. LCMS Method E: $[M+H]^+ = 508.2$. ^1H NMR (400 MHz, DMSO- d_6) δ 10.67 (d, $J = 1.6$ Hz, 1H), 9.36 (s, 1H), 8.15 (s, 1H), 7.70 (d, $J = 8.0$ Hz, 2H), 7.68 (d, $J = 8.4$ Hz, 3H), 7.26–7.23 (m, 1H), 7.10 (d, $J = 2.4$ Hz, 1H), 6.76–6.74 (m, 1H), 6.10–5.82 (m, 1H), 4.94–4.91 (m, 1H), 3.83–3.79 (m, 2H), 3.64–3.60 (m, 2H), 3.22 (d, $J = 7.2$ Hz, 2H), 2.86–2.81 (m, 2H), 2.65–2.61 (m, 4H), 1.53 (s, 3H).

Example 245: *trans*-3-methoxy-1-methyl-*N*-(5-(2-((3*a*R,5*r*,6*a*S)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[*c*]pyrrol-5-yl)ethoxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (compound 427)



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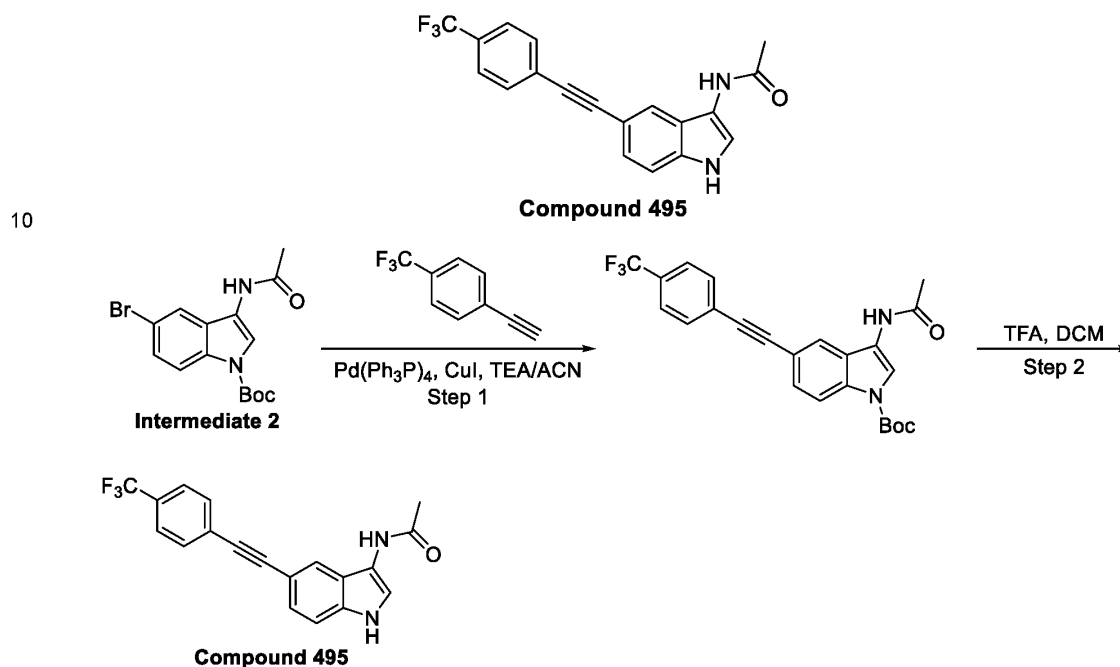
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20

3-Methoxy-1-methylcyclobutane-1-carboxylic acid (627.8 mg, 4.3 mmol, 2.0 equiv.) and DIEA (1.8 mL, 10.9 mmol, 5.0 equiv.) were dissolved in DCM (10 mL), then HATU (1241.9 mg, 3.3 mmol, 1.5 equiv.) and 5-(2-((3*a*R,5*r*,6*a*S)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[*c*]pyrrol-5-yl)ethoxy)-1*H*-indol-3-amine (800.0 mg, 2.2 mmol, 1.0 equiv.) were added. The reaction mixture was stirred for 2 hours at rt and then quenched by the addition of water. The resulting solution was extracted with dichloromethane, washed with brine, dried over anhyd. Na_2SO_4 and concentrated under vacuum. The residue was purified by Prep-TLC (petroleum ether/EtOAc = 1:1) to afford racemate, that was purified by Prep-CHIRAL-HPLC with the following conditions: Column: JW-CHIRALPAK-IF, 20*250mm, 5 μ m; Mobile Phase A: EtOH--HPLC, Mobile Phase B: Hex: DCM=3: 1 (0.1% FA)--HPLC; Flow rate: 20 mL/min; Gradient: 80% B to 80% B in 10 min; Wave Length: 220/254 nm; RT1(min): 5.6. This resulted in *trans*-3-

methoxy-1-methyl-*N*-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[*c*]pyrrol-5-yl)ethoxy)-1*H*-indol-3-yl)cyclobutane-1-carboxamide (87.3 mg) as a green solid. LCMS Method F: $[M+H]^+ = 494.2$. ^1H NMR (400 MHz, DMSO-*d*₆) δ 10.61 (s, 1H), 9.24 (s, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.74–6.71 (m, 1H), 3.97 (t, *J* = 6.0 Hz, 2H), 3.73–3.70 (m, 1H), 3.22–3.17 (m, 2H), 3.14 (s, 3H), 2.85–2.80 (m, 2H), 2.64 (d, *J* = 8.4 Hz, 2H), 2.44–2.40 (m, 4H), 2.10–2.06 (m, 2H), 1.95–1.76 (m, 5H), 1.51 (s, 3H), 0.98–0.95 (m, 2H).

Example 246: *N*-(5-((4-(trifluoromethyl)phenyl)ethynyl)-1*H*-indol-3-yl)acetamide (compound 495)



Step 1: *tert*-butyl 3-acetamido-5-((4-(trifluoromethyl)phenyl)ethynyl)-1*H*-indole-1-carboxylate

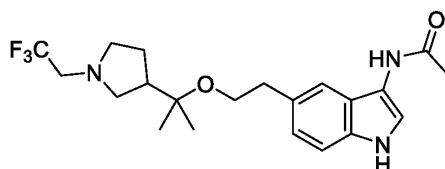
15 *tert*-Butyl 3-acetamido-5-bromo-1*H*-indole-1-carboxylate (500.0 mg, 1.4 mmol, 1.0 equiv.) and 1-ethynyl-4-(trifluoromethyl)benzene (289.0 mg, 1.6 mmol, 1.2 equiv.) were dissolved in TEA (4 mL) and ACN (4 mL), then $Pd(PPh_3)_4$ (327.1 mg, 0.2 mmol, 0.2 equiv.) and CuI (26.9 mg, 0.1 mmol, 0.1 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred for 16 hours at 90 °C, then cooled to rt and

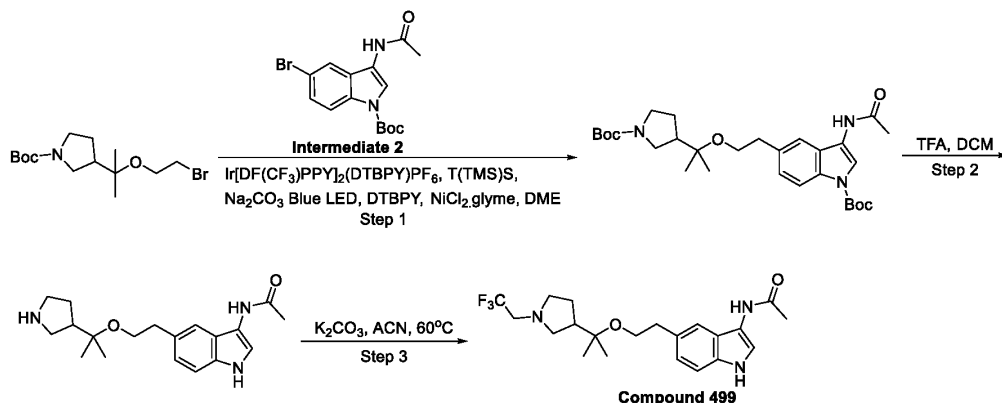
quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with petroleum ether/EtOAc (1:1) to give *tert*-butyl 3-acetamido-5-((4-(trifluoromethyl)phenyl)ethynyl)-1*H*-indole-1-carboxylate (700.0 mg) as a brown solid. LCMS Method A: $[\text{M}+\text{H}]^+ = 443.2$.

Step 2: *N*-(5-((4-(trifluoromethyl)phenyl)ethynyl)-1*H*-indol-3-yl)acetamide

tert-Butyl 3-acetamido-5-((4-(trifluoromethyl)phenyl)ethynyl)-1*H*-indole-1-carboxylate (600.0 mg, 1.3 mmol, 1.0 equiv.) was dissolved in DCM (4 mL), then TFA (2 mL) was added. The reaction mixture was stirred for 30 min at rt and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm ; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 44% B to 61% B in 8 min; Wave Length: 254 nm; RT1(min): 7.55. This resulted in *N*-(5-((4-(trifluoromethyl)phenyl)ethynyl)-1*H*-indol-3-yl)acetamide (35.7 mg) as a pale brown solid. LCMS Method E: $[\text{M}-\text{H}]^- = 341.1$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.08 (s, 1H), 9.92 (s, 1H), 8.16 (s, 1H), 7.80–7.74 (m, 5H), 7.39 (d, $J = 8.4$ Hz, 1H), 7.32–7.29 (m, 1H), 2.10 (s, 3H).

Example 247: *N*-(5-(2-((2-(1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)propan-2-yl)oxy)ethyl)-1*H*-indol-3-yl)acetamide (compound 499)





Step 1: *tert*-butyl 3-(2-(2-bromoethoxy)propan-2-yl)pyrrolidine-1-carboxylate

tert-Butyl 3-(2-(2-bromoethoxy)propan-2-yl)pyrrolidine-1-carboxylate (800.0 mg, 1.7 mmol, 1.0 equiv.) and 8-(2-bromoethoxy)-1,4-dioxaspiro[4.5]decane (900.8 mg, 3.4 mmol, 2.0 equiv.) were dissolved in DME (10 mL), then tris(trimethylsilyl)silane (633.6 mg, 2.5 mmol, 1.5 equiv.), Na₂CO₃ (360.1 mg, 3.4 mmol, 2.0 equiv.), Ir[DF(CF₃)PPY]₂(DTBPY)PF₆ (190.6 mg, 0.2 mmol, 0.1 equiv.), DTBPY (45.6 mg, 0.2 mmol, 0.1 equiv.) and 1,2-dimethoxyethane dihydrochloride nickel (37.3 mg, 0.2 mmol, 0.1 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred overnight at rt under nitrogen atmosphere and the Blue LED light. The resulting mixture was concentrated under vacuum and the residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10 mmol/L NH₄HCO₃), 30% to 70% gradient in 30 min; detector, UV 254 nm. This resulted in *tert*-butyl 3-acetamido-5-(2-((1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propan-2-yl)oxy)ethyl)-1*H*-indole-1-carboxylate (200.0 mg) as a brown oil. LCMS Method A: [M+H]⁺ = 530.2.

Step 2: *N*-(5-(2-((2-(pyrrolidin-3-yl)propan-2-yl)oxy)ethyl)-1*H*-indol-3-yl)acetamide

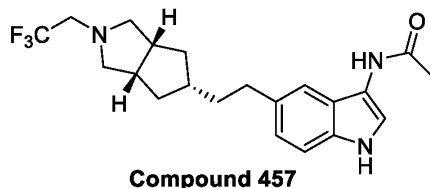
tert-Butyl 5-[2-({2-[1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl]propan-2-yl}oxy)ethyl]-3-acetamidindole-1-carboxylate (200.0 mg, 0.9 mmol, 1.0 equiv.) was dissolved in DCM (5 mL), then TFA (1 mL) was added at 0 °C. The reaction mixture was stirred overnight at rt and concentrated under vacuum to give crude *N*-(5-(2-((2-(pyrrolidin-3-yl)propan-2-yl)oxy)ethyl)-1*H*-indol-3-yl)acetamide.

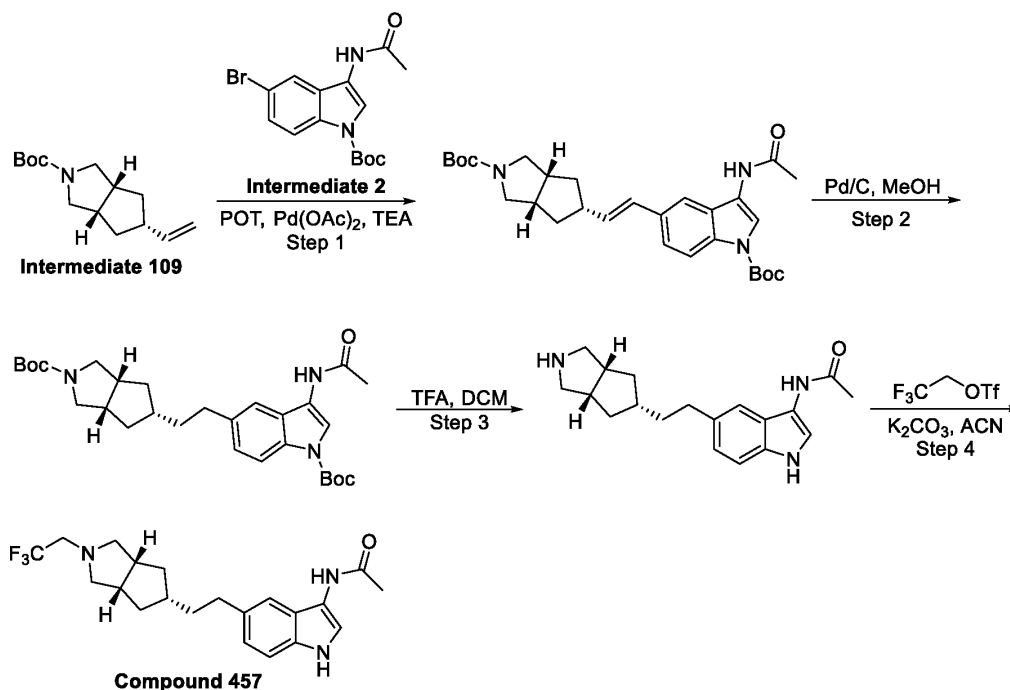
yl)propan-2-yl)oxy)ethyl)-1*H*-indol-3-yl)acetamide, that was used in the next step directly without further purification.

Step 3: *N*-(5-(2-((2-(1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)propan-2-yl)oxy)ethyl)-1*H*-indol-3-yl)acetamide

5 *N*-(5-(2-((2-(pyrrolidin-3-yl)propan-2-yl)oxy)ethyl)-1*H*-indol-3-yl)acetamide (60.0 mg, 0.2 mmol, 1.0 equiv.) was dissolved in ACN (2 mL), then K₂CO₃ (50.3 mg, 0.4 mmol, 2.0 equiv.) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (42.3 mg, 0.2 mmol, 1.0 equiv.) were added. The reaction mixture was stirred for 1 hour at 60 °C, then cooled to rt and concentrated under vacuum. The residue was purified by Prep-TLC
10 (dichloromethane/MeOH = 10:1) to give the crude product, that was further purified by Prep-HPLC with the following conditions: Column, Xselect CSH C18 OBD Column 30*150mm 5um; mobile phase, Water (0.1% FA) and ACN (15% ACN up to 30% in 7 min); Detector, UV 220/254 nm. This resulted in *N*-(5-(2-((2-(1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)propan-2-yl)oxy)ethyl)-1*H*-indol-3-yl)acetamide (12.6 mg)
15 as a white solid. LCMS Method F: [M+H]⁺ = 412.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.61 (s, 1H), 9.73 (s, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.59 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 3.51 (t, *J* = 7.2 Hz, 2H), 3.25–3.07 (m, 2H), 2.78 (t, *J* = 7.2 Hz, 2H), 2.73–2.63 (m, 2H), 2.58–2.54 (m, 2H), 2.33–2.25 (m, 1H), 2.08 (s, 3H), 1.64–1.51 (m, 2H), 1.04 (s, 6H).

20 **Example 248:** *N*-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[*c*]pyrrol-5-yl)ethyl)-1*H*-indol-3-yl)acetamide (compound 457)





Step 1: *tert*-butyl 3-acetamido-5-((E)-2-((3aR,5r,6aS)-2-(*tert*-butoxycarbonyl)octahydrocyclopenta[c]pyrrol-5-yl)vinyl)-1*H*-indole-1-carboxylate

tert-Butyl (3aR,5r,6aS)-5-vinylhexahydrocyclopenta[c]pyrrole-2(1*H*)-carboxylate (380.0 mg, 1.6 mmol, 1.0 equiv.) and *tert*-butyl 3-acetamido-5-bromo-1*H*-indole-1-carboxylate (735.2 mg, 2.1 mmol, 1.3 equiv.) were dissolved in ACN (5 mL), then Pd(OAc)₂ (71.9 mg, 0.3 mmol, 0.2 equiv.), P(o-Tol)₃ (194.9 mg, 0.6 mmol, 0.4 equiv.) and TEA (0.7 mL, 4.8 mmol, 3.0 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred for 16 hours at 80 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (15:1) to give *tert*-butyl 3-acetamido-5-((E)-2-((3aR,5r,6aS)-2-(*tert*-butoxycarbonyl)octahydrocyclopenta[c]pyrrol-5-yl)vinyl)-1*H*-indole-1-carboxylate (760.0 mg) as an orange solid. LCMS Method A: [M+H]⁺ = 510.2.

Step 2: *tert*-butyl 3-acetamido-5-(2-((3aR,5r,6aS)-2-(*tert*-butoxycarbonyl)octahydrocyclopenta [c]pyrrol-5-yl)ethyl)-1*H*-indole-1-carboxylate

tert-Butyl 3-acetamido-5-((E)-2-((3aR,5r,6aS)-2-(*tert*-butoxycarbonyl)octahydrocyclopenta[c] pyrrol-5-yl)vinyl)-1*H*-indole-1-carboxylate (660.0 mg, 1.3 mmol, 1.0 equiv.) was dissolved in MeOH (10 mL), then Pd/C (137.8 mg, 10%wt.) was added under an atmosphere of nitrogen. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 2 hours at rt. The solids were removed by filtration and the filtrate was concentrated under vacuum to give *tert*-butyl 3-acetamido-5-(2-((3aR,5r,6aS)-2-(*tert*-butoxycarbonyl)octahydrocyclopenta[c]pyrrol-5-yl)ethyl)-1*H*-indole-1-carboxylate (340.0 mg) as a white solid. LCMS Method A: $[M+H]^+ = 512$.

Step 3: *N*-(5-(2-((3aR,5r,6aS)-octahydrocyclopenta [c]pyrrol-5-yl)ethyl)-1*H*-indol-3-yl)acetamide

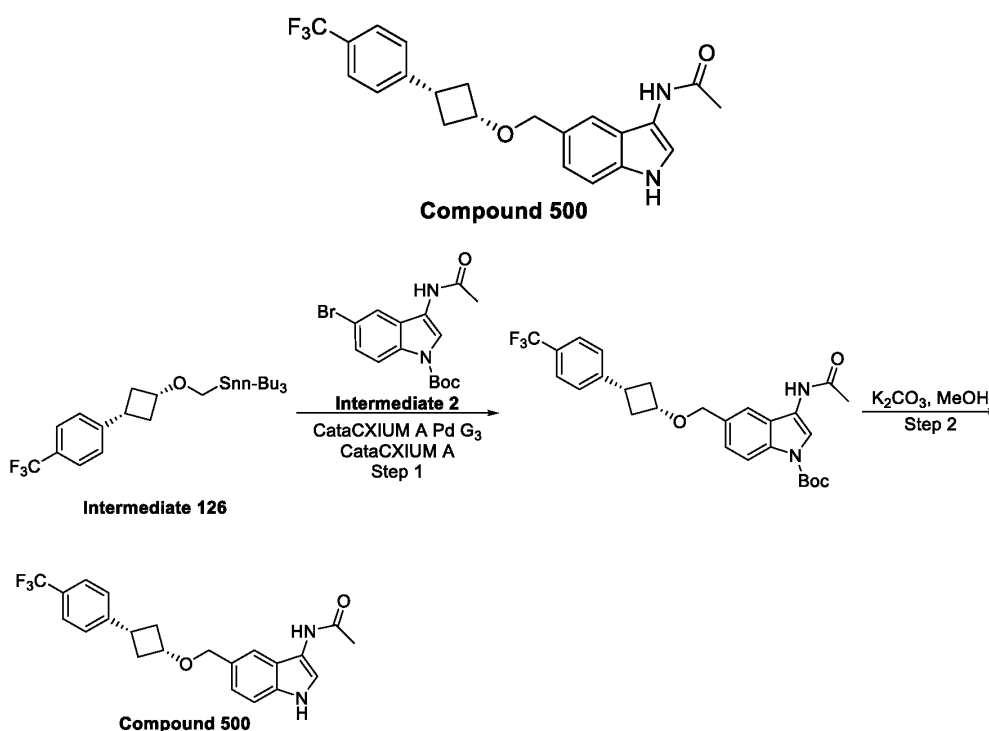
tert-Butyl 3-acetamido-5-(2-((3aR,5r,6aS)-2-(*tert*-butoxycarbonyl) octahydrocyclopenta[c]pyrrol-5-yl)ethyl)-1*H*-indole-1-carboxylate (300.0 mg, 0.6 mmol, 1.0 equiv.) was dissolved in DCM (5 mL), then TFA (5 mL) was added. The reaction mixture was stirred for 2 hours at rt and then concentrated under vacuum to give crude *N*-(5-(2-((3aR,5r,6aS)-octahydrocyclopenta[c]pyrrol-5-yl)ethyl)-1*H*-indol-3-yl)acetamide TFA salt (320.0 mg) as a grey solid. LCMS Method A: $[M+H]^+ = 512.1$.

Step 4: *N*-(5-(2-((3aR,5r,6aS)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[c]pyrrol-5-yl)ethyl)-1*H*-indol-3-yl)acetamide

N-(5-(2-((3aR,5r,6aS)-octahydrocyclopenta[c]pyrrol-5-yl)ethyl)-1*H*-indol-3-yl)acetamide (250.0 mg, 0.8 mmol, 1.0 equiv.) and K₂CO₃ (443.8 mg, 3.2 mmol, 4.0 equiv.) were dissolved in ACN (5 mL), then 2,2,2-trifluoroethyl trifluoromethanesulfonate (242.2 mg, 1.0 mmol, 1.3 equiv.) was added. The reaction mixture was stirred for 1 hour at 70 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (1:1) to give the crude product, that was further purified by Prep-HPLC with the following conditions: Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 75% B in 7.5 min; Wave Length: 220

nm; RT1: 7.5 min. This resulted in *N*-(5-(2-((3*a*R,5*r*,6*a*S)-2-(2,2,2-trifluoroethyl)octahydrocyclopenta[*c*]pyrrol-5-yl)ethyl)-1*H*-indol-3-yl)acetamide (20.8 mg) as a white solid. LCMS Method D: $[M+H]^+ = 394.2$. ^1H NMR (400 MHz, DMSO- d_6) δ 10.60 (s, 1H), 9.74 (s, 1H), 7.63 (d, $J = 2.4$ Hz, 1H), 7.58 (s, 1H), 7.21 (d, $J = 8.4$ Hz, 1H), 6.93 (d, $J = 8.0$ Hz, 1H), 3.21–3.16 (m, 2H), 2.64–2.60 (m, 4H), 2.46–2.41 (m, 4H), 2.08–2.05 (m, 5H), 2.08 (s, 5H), 1.66–1.63 (m, 3H), 0.92–0.88 (m, 2H).

Example 249: *N*-(5-((*cis*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)methyl)-1*H*-indol-3-yl)acetamide (compound 500)



Step 1: *tert*-butyl 3-acetamido-5-((*cis*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)methyl)-1*H*-indole-1-carboxylate

tert-Butyl 5-bromo-3-acetamidoindole-1-carboxylate (431.0 mg, 1.2 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (5 mL), then bis(adamantan-1-yl)(butyl)phosphane (87.5 mg, 0.2 mmol, 0.2 equiv.), Chloro[(diadamantan-1-yl)(*n*-butyl)phosphino][2-aminao-1,1-biphenyl-2-yl]palladium(II) (81.6 mg, 0.1 mmol, 0.1 equiv.) and tributyl({[(1*s*,3*s*)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy)methyl})stannane (697.0 mg,

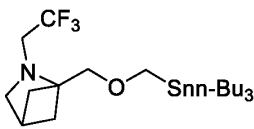
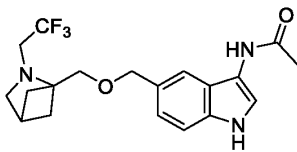
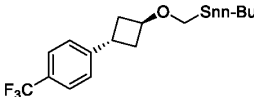
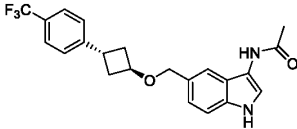
1.3 mmol, 1.1 equiv.) were added under an atmosphere of nitrogen. The reaction mixture was stirred for 2 hours at 100 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (1:1) to give *tert*-butyl 3-acetamido-5-((*cis*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)methyl)-1*H*-indole-1-carboxylate (190.0 mg) as a white solid. LCMS Method A: $[M+H]^+ = 503.2$.

Step 2: *N*-(5-((*cis*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)methyl)-1*H*-indol-3-yl)acetamide

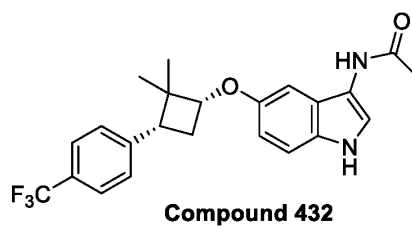
tert-Butyl 3-acetamido-5-((*cis*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)methyl)-1*H*-indole-1-carboxylate (170.0 mg, 0.3 mmol, 1.0 equiv.) was dissolved in MeOH (5 mL), then K₂CO₃ (93.5 mg, 0.7 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 1 hour at 70 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. sodium sulfate and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 43% B to 61% B in 8 min; Wave Length: 220 nm; RT1(min): 7.48. This resulted in *N*-(5-((*cis*-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)methyl)-1*H*-indol-3-yl)acetamide (61.9 mg) as a white solid. LCMS Method E: $[M-H]^- = 401.1$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.74 (s, 1H), 9.83 (s, 1H), 7.77 (s, 1H), 7.70–7.65 (m, 3H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.09–7.07 (m, 1H), 4.49 (s, 2H), 4.09–4.02 (m, 1H), 3.14–3.10 (m, 1H), 2.71–2.65 (m, 2H), 2.09 (s, 3H), 2.01–1.93 (m, 2H).

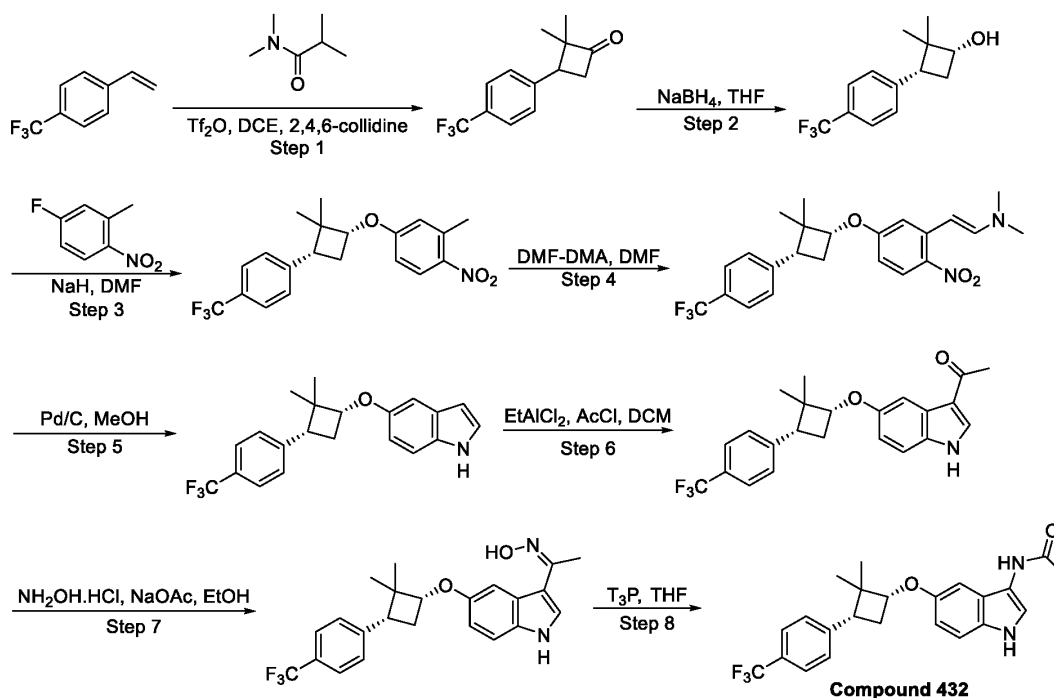
The analogs prepared in the following table were prepared using the same method described for Examples 249.

Exempl e #	Compound #	Starting materials Used	Structure	LCMS data
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250	492	 Intermediate 128		Method F: MS-ESI: 382.1 [M+H] ⁺ .
251	482	 Intermediate 127		Method F: MS-ESI: 401.1 [M-H] ⁺ .

Example 252: *N*-(5-(*cis*-2,2-dimethyl-3-(4-(trifluoromethyl) phenyl)cyclobutoxy)-1*H*-indol-3-yl)acetamide (compound 432)





Step 1: 2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-one

N,N-dimethylisobutyramide (1.6 g, 13.9 mmol, 1.2 equiv.) was dissolved in DCE (20 mL) and cooled to 0 °C, Ti_2O (4.6 g, 16.3 mmol, 1.4 equiv.) was added under an atmosphere of nitrogen. The reaction mixture was stirred for 30 min at 0 °C, then to the above mixture were added 1-(trifluoromethyl)-4-vinylbenzene (2.0 g, 11.6 mmol, 1.0 equiv.) and 2,4,6-trimethylpyridine (2.0 g, 16.3 mmol, 1.4 equiv.) dropwise, maintaining the solution at 0 °C. The resulting mixture was stirred for additional 2 hours at 80 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with dichloromethane, washed with brine, dried over anhyd. sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with petroleum ether/EtOAc (10:1) to give 2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-one (1.9 g) as a yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 3.69 (dd, J = 17.2, 8.4 Hz, 1H), 3.55 (t, J = 8.8 Hz, 1H), 3.30 (dd, J = 17.2, 8.4 Hz, 1H), 1.28 (s, 3H), 0.68 (s, 3H).

Step 2: cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol

2,2-Dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-one (1.9 g, 7.9 mmol, 1.0 equiv.) was dissolved in THF (30 mL) and cooled to 0 °C, then NaBH₄ (299.8 mg, 7.9 mmol, 1.0 equiv.) was added. The reaction mixture was stirred for 30 min at 0 °C and then quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with petroleum ether/EtOAc (2:1) to give cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol (1.5 g) as a yellow oil. ¹H NMR (400 MHz, CDCl₃-d₁) δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.02 (dd, *J* = 8.4, 7.2 Hz, 1H), 2.88 (dd, *J* = 11.2, 7.6 Hz, 1H), 2.60–2.56 (m, 1H), 2.20–2.16 (m, 1H), 1.30 (s, 3H), 0.68 (s, 3H).

Step 3: 4-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-2-methyl-1-nitrobenzene

cis-2,2-Dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol (1.5 g, 6.1 mmol, 1.0 equiv.) was dissolved in DMF (20 mL) and cooled to 0 °C, then NaH (60%wt., 368.4 mg, 9.2 mmol, 1.5 equiv.) was added under an atmosphere of nitrogen. After stirred for 30 min, 4-fluoro-2-methyl-1-nitrobenzene (1.4 g, 9.2 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for additional 2 hours at rt and then quenched by the addition of water at 0 °C. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. reduced pressure. The residue was purified by silica gel column chromatography, eluting with petroleum ether/EtOAc (5:1) to give 4-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-2-methyl-1-nitrobenzene (1.0 g) as a yellow oil. LCMS Method A: [M+H]⁺ = 380.2.

Step 4: (E)-2-(5-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-2-nitrophenyl)-N,N-dimethylethen-1-amine

4-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-2-methyl-1-nitrobenzene (1.2 g, 3.2 mmol, 1.0 equiv.) and DMF-DMA (1.9 g, 16.0 mmol, 5.0 equiv.) were dissolved in DMF (15 mL). The reaction mixture was heated to 120 °C for 16 hours, then cooled to rt and concentrated under vacuum to give (E)-2-(5-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-2-nitrophenyl)-N,N-dimethylethen-1-amine (1.4 g, crude) as a red oil. LCMS Method A: [M+H]⁺ = 435.2.

Step 5: 5-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indole

(E)-2-(5-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-2-nitrophenyl)-*N,N*-dimethylethen-1-amine (1.4 g, 3.2 mmol, 1.0 equiv.) was dissolved in MeOH (15 mL), then Pd/C (685.8 mg, 10%wt.) was added under an atmosphere of nitrogen. The mixture was sparged with nitrogen, placed under an atmosphere of hydrogen gas (balloon), then stirred for 16 hours at rt. The solids were removed by filtration and the filter cake was washed with MeOH. The combined filtrate was concentrated under vacuum to give 5-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indole (605.0 mg) as a yellow solide. LCMS Method A: $[M+H]^+ = 360.1$. ^1H NMR (400 MHz, DMSO- d_6) δ 10.94 (s, 1H), 7.69 (d, $J = 7.6$ Hz, 2H), 7.43 (d, $J = 7.6$ Hz, 2H), 7.31–7.29 (m, 2H), 7.06 (s, 1H), 6.75 (d, $J = 8.8$ Hz, 1H), 6.34 (s, 1H), 4.52 (t, $J = 8.0$ Hz, 1H), 3.07 (t, $J = 9.6$ Hz, 1H), 2.70–2.63 (m, 1H), 2.45–2.37 (m, 1H), 1.38 (s, 3H), 0.68 (s, 3H).

Step 6: 1-(5-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy) -1*H*-indol-3-yl)ethan-1-one

5-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indole (450.0 mg, 1.2 mmol, 1.0 equiv.) was dissolved in DCM (10 mL) and cooled to -30 °C, then Et₂AlCl (1M in DCM, 1.9 mL, 1.9 mmol, 1.5 equiv.) and acetyl chloride (147.4 mg, 1.9 mmol, 1.5 equiv.) were added dropwise, maintaining the solution at -30 °C under an atmosphere of nitrogen. The reaction mixture was stirred for 2 hours at -30 °C and then quenched by the addition of ice-water. The resulting solution was extracted with dichloromethane, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with petroleum ether/EtOAc (1:1) to give 1-(5-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy) -1*H*-indol-3-yl)ethan-1-one (428.0 mg) as a brown solid. LCMS Method A: $[M+H]^+ = 402.2$. ^1H NMR (400 MHz, DMSO- d_6) δ 11.82 (s, 1H), 8.25 (d, $J = 3.2$ Hz, 1H), 7.76 (d, $J = 2.8$ Hz, 1H), 7.68 (d, $J = 8.0$ Hz, 2H), 7.44 (d, $J = 7.6$ Hz, 2H), 7.36 (d, $J = 8.8$ Hz, 1H), 6.86–6.83 (m, 1H), 4.54 (t, $J = 7.6$ Hz, 1H), 3.14–3.10 (m, 1H), 2.68–2.58 (m, 1H), 2.45–2.41 (m, 1H), 2.43 (s, 3H), 1.43 (s, 3H), 0.66 (s, 3H).

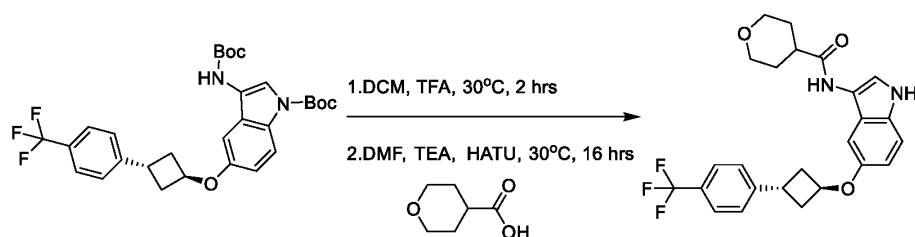
Step 7: (Z)-1-(5-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)ethan-1-one oxime

1-(5-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)ethan-1-one (428.0 mg, 1.1 mmol, 1.0 equiv.) and NaOAc (174.9 mg, 2.1 mmol, 2.0 equiv.) were dissolved in EtOH (5 mL), then NH₂OH.HCl (111.1 mg, 1.6 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for 4 hours at 60 °C, then cooled to rt and quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with petroleum ether/EtOAc (1:1) to give (Z)-1-(5-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)ethan-1-one oxime (340.0 mg) as a brown solid. LCMS Method A: [M+H]⁺ = 417.0.

Step 8: *N*-(5-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)acetamide

(Z)-1-(5-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)ethan-1-one oxime (200.0 mg, 0.5 mmol, 1.0 equiv.) was dissolved in THF (4 mL), then T₃P (305.6 mg, 0.9 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 1 hour at 70 °C and then quenched by the addition of water. The resulting solution was extracted with EtOAc, washed with brine, dried over anhyd. Na₂SO₄ and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 19*250 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 65% B to 77% B in 6 min; Wave Length: 254 nm; RT1(min): 5.78. This resulted in *N*-(5-(cis-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclobutoxy)-1*H*-indol-3-yl)acetamide (74.7 mg) as a white solid. LCMS Method F: [M+H]⁺ = 417.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.60 (s, 1H), 9.71 (s, 1H), 7.69–7.65 (m, 3H), 7.43 (d, *J* = 6.0 Hz, 2H), 7.32 (s, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 4.48 (t, *J* = 7.2 Hz, 1H), 3.12–3.08 (s, 1H), 2.74–2.67 (m, 1H), 2.42–2.37 (m, 1H), 2.09 (s, 3H), 1.36 (s, 3H), 0.72 (s, 3H).

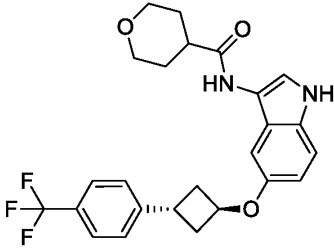
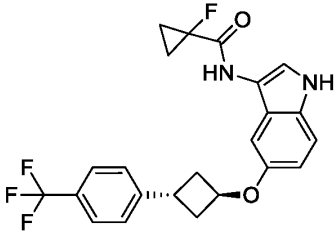
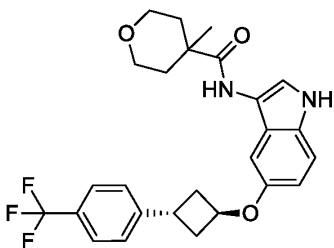
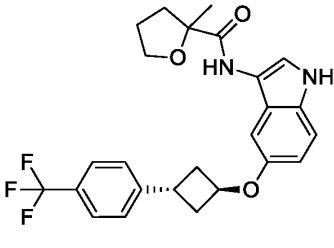
Example 253: Synthesis of *N*-{5-[(1*R*,3*R*)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1*H*-indol-3-yl}oxane-4-carboxamide (compound 493)



tert-butyl 3-[[[(tert-butoxy)carbonyl]amino]-5-[(1R,3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indole-1-carboxylate (98.3 mg, 0.18 mmol, 1.0 equiv.) was dissolved in DCM (3 mL), then TFA (1 mL) was added to the solution. The mixture was heated at 30 °C for 2 hours. The reaction mixture was concentrated by Speedvac to give a residue. Then the residue and oxane-4-carboxylic acid (46.8 mg, 0.36 mmol, 2.0 equiv.) were dissolved in DMF (2 mL), then TEA (130 µl, 0.9 mmol, 5.0 equiv.) and HATU (71.8 mg, 0.189 mmol, 1.05 equiv.) were added. The mixture was heated at 30 °C for 16 hours. The reaction mixture was concentrated by Speedvac to give a residue that was purified by prep HPLC-1-1 to give **N-{5-[(1R,3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}oxane-4-carboxamide** (24.7 mg, 0.054 mmol) as a powder. MS-ESI, 459.3 [M+H⁺]. ¹H NMR (400 MHz, DMSO-d₆), δ ppm 10.89 (br s, 1 H), 9.01 (s, 1 H), 7.68 (br d, *J*=8.1 Hz, 2 H), 7.58 (br d, *J*=8.00 Hz, 2 H), 7.28–7.12 (m, 3 H), 6.73 (dd, *J*=8.70 Hz, 1 H), 4.19 (t, *J*=6.60 Hz, 2 H), 3.22–3.09 (m, 2 H), 2.92 (q, *J*=7.40 Hz, 2 H), 1.22 (t, *J*=7.30 Hz, 3 H).

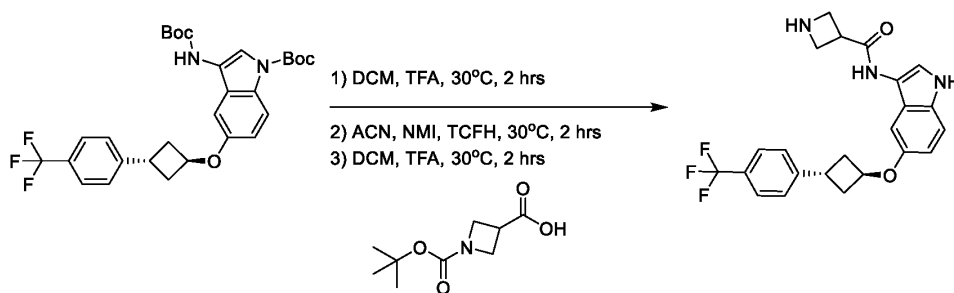
The compounds in the following table were prepared using the above procedures (example 253) with the appropriate starting material.

Example #	Compound #	Structure	IUPAC Name	LC-MS, MS-ESI, - [M+H ⁺].
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253	493		N-{5-[(1R,3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}oxane-4-carboxamide	459.3
254	489		1-fluoro-N-{5-[(1R,3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}cyclopropane-1-carboxamide	433.2
255	488		4-methyl-N-{5-[(1R,3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}oxane-4-carboxamide	473.4
256	487		2-methyl-N-{5-[(1R,3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}oxolane-2-carboxamide	459.3

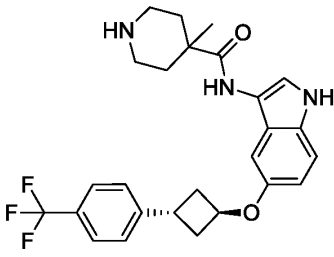
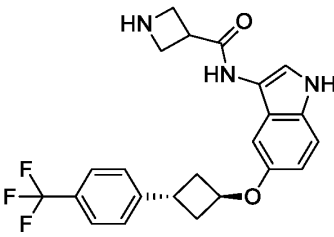
257	469		3-fluoro-3-methyl-N-{5-[(1R,3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}cyclobutane-1-carboxamide	461.3
258	468		1-(methoxymethyl)-N-{5-[(1R,3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}cyclopropane-1-carboxamide	459.3
259	467		2-cyano-N-{5-[(1R,3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}cyclobutane-1-carboxamide	454.3
260	486		2-(2-methoxyethoxy)-N-{5-[(1R,3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}acetamide	463.3

Example 261: Synthesis of N-{5-[(1R, 3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}azetidine-3-carboxamide (compound 459)



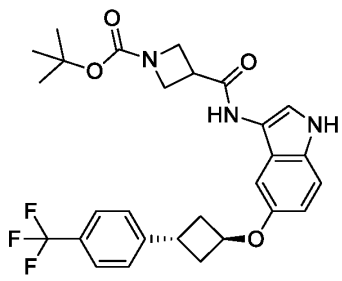
tert-butyl 3-[[[(tert-butoxy)carbonyl]amino]-5-[(1R,3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indole-1-carboxylate (136.5 mg, 0.25 mmol, 1.0 equiv.) was dissolved in DCM (3 mL), then TFA (1 mL) was added to the solution. The mixture was heated at 30 °C for 2 hours. The reaction mixture was concentrated by Speedvac to give a residue. Then the residue and 1-[(tert-butoxy)carbonyl] azetidine-3-carboxylic acid (100.5 mg, 0.5 mmol, 2.0 equiv.) were dissolved in ACN (1.5 mL), then NMI (500 µl) and TCFH (78.4 mg, 0.28 mmol, 1.1 equiv.) were added. The mixture was heated at 30 °C for 16 hours. The reaction mixture was concentrated by Speedvac to give a residue. The residue was diluted with H₂O (1 mL) and extracted with 3*1 mL EtOAc. The combined organic layers were washed with H₂O (1 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. After that DCM (3 mL) was added dropwise and TFA (1mL) at 30 °C for 2hrs. The reaction mixture was concentrated by Speedvac to give a residue that was purified by prep HPLC-1 to give N-{5-[(1R, 3R)-3-[4-(trifluoromethyl) phenyl] cyclobutoxy]-1H-indol-3-yl} azetidine-3-carboxamide (4.82 mg, 0.011 mmol) as a powder. MS-ESI, 430.3 [M+H⁺]. ¹H NMR (400 MHz, DMSO-*d*₆), δ ppm 11.03–10.95 (m, 1 H), 9.07 (s, 1 H), 7.63 (d, *J*=8.8 Hz, 2 H), 7.55 (s, 1 H), 7.29 (d, *J*=8.3 Hz, 1 H), 7.24 (d, *J*=2.5 Hz, 1 H), 7.14–7.06 (m, 3 H), 4.27 (t, *J*=6.8 Hz, 2 H), 3.17–3.07 (m, 2 H), 2.93 (q, *J*=7.4 Hz, 2 H), 1.23 (t, *J*=7.4 Hz, 3 H).

The compounds in the following table were prepared using the above procedure (example 261) with the appropriate starting material.

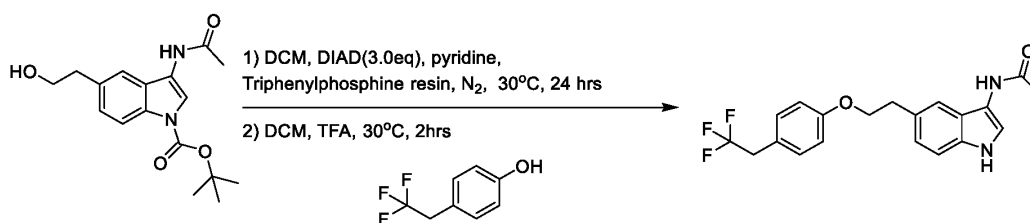
Example #	Compound #	Final compound	IUPAC Name	LC-MS, MS-ESI, - [M+H].
262	460		4-methyl-N-{5-[(1R,3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}piperidine-4-carboxamide	472.3
263	459		N-{5-[(1R,3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl}azetidine-3-carboxamide	430.3

5 The compound in the following table was prepared using steps 1) and 2) of the above procedure (example 261) with the appropriate starting material.

Example #	Compound #	Final compound	IUPAC Name	LC-MS, MS-ESI, - [M+H].
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264	466		tert-butyl 3-({5-[(1R,3R)-3-[4-(trifluoromethyl)phenyl]cyclobutoxy]-1H-indol-3-yl} carbamoyl)azetidine-1-carboxylate	529.3
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Example 265: Synthesis of N-(5-{2-[4-(2, 2, 2-trifluoroethyl)phenoxy]ethyl}-1H-indol-3-yl)acetamide (compound 442)

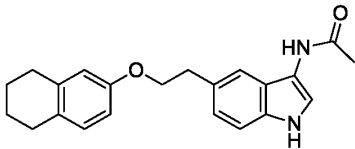
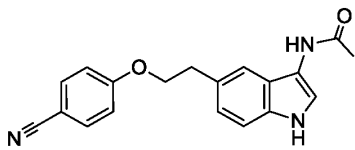
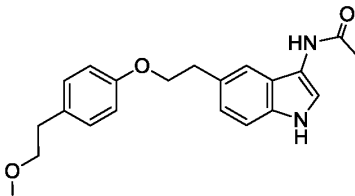
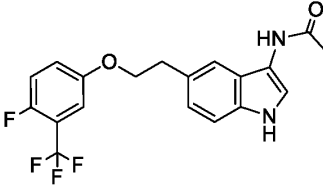


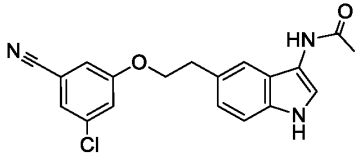
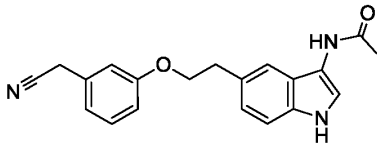
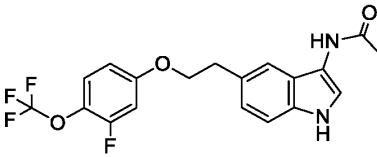
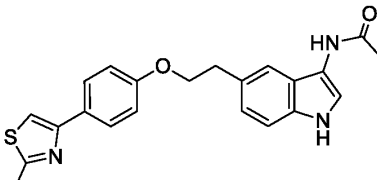
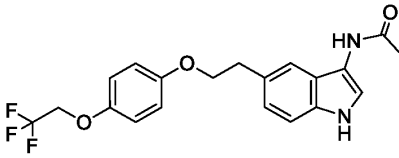
5

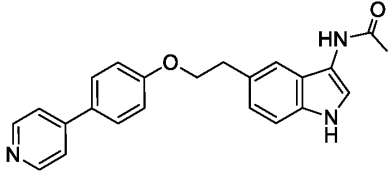
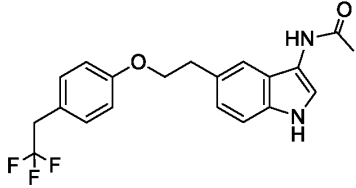
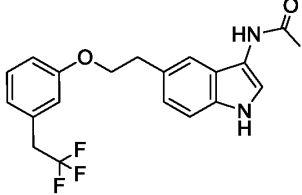
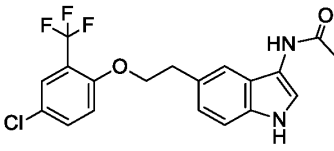
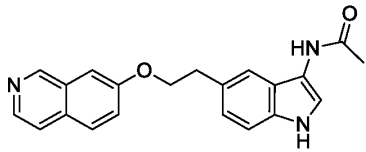
tert-butyl 3-acetamido-5-(2-hydroxyethyl)-1H-indole-1-carboxylate (66.8 mg, 0.21 mmol, 1.0 equiv.) and 4-(2,2,2-trifluoroethyl)phenol (73.9 mg, 0.42 mmol, 2.0 equiv.) were dissolved in DCM (2 mL), DIAD (127.3 mg, 0.63 mmol, 3.0 equiv.), pyridine (210 μ l) and Triphenylphosphine resin (350 mg, 3.0 g/mol, 1.05 mmol, 5.0 equiv.) were added under N₂ atmosphere. The mixture was heated at 30 °C for 24 hours under N₂ atmosphere. The mixture was diluted with 3*1 mL DCM and extracted with H₂O (1 mL). The combined organic layers were washed with H₂O (1 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. After that the residue were dissolved in DCM (2 mL), then TFA (500 μ l) was added. The mixture was heated at 30 °C for 2 hours. The reaction mixture was concentrated by Speedvac to give a residue that was purified by prep HPLC-1 to give N-(5-{2-[4-(2, 2, 2-trifluoroethyl)phenoxy]ethyl}-1H-indol-3-yl) acetamide (16.24 mg, 0.041 mmol) as a powder. MS-ESI, 400.3 [M+H⁺]. ¹H

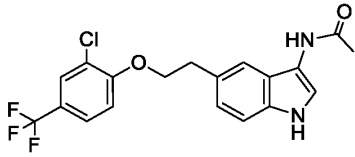
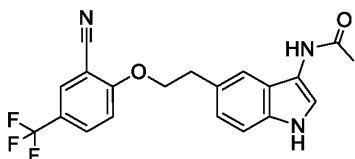
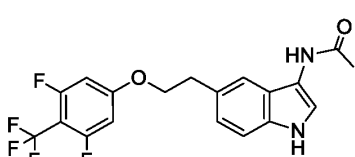
NMR (400 MHz, DMSO-*d*₆), δ ppm 10.67 (br s, 1 H), 9.77 (s, 1 H), 7.65 (d, *J*=9.88 Hz, 2 H), 7.29–7.22 (m, 3 H), 7.10–7.05 (m, 1 H), 6.98–6.92 (m, 2 H), 4.20 (t, *J*=7.03 Hz, 2 H), 3.62–3.46 (m, 2 H), 3.12–3.06 (m, 2 H), 2.08 (s, 3 H).

The compounds in the following table were prepared using the above procedure (example 265) with the appropriate starting material.

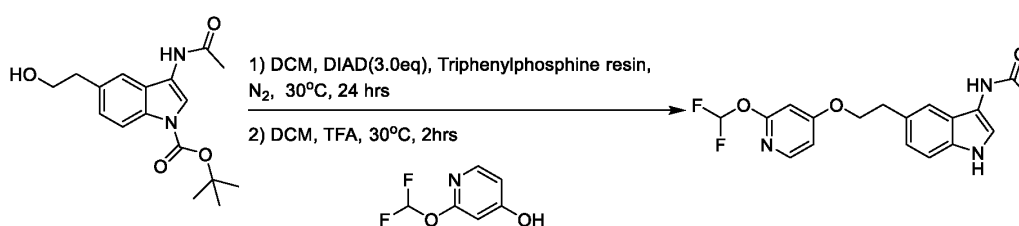
Example #	Example #	Final compound	IUPAC Name	LC-MS, MS-ESI, - [M+H+].
266	490		N-{5-[2-(5,6,7,8-tetrahydronaphthalen-2-yloxy)ethyl]-1H-indol-3-yl}acetamide	349.3
267	462		N-{5-[2-(4-cyanophenoxy)ethyl]-1H-indol-3-yl}acetamide	320.2
268	461		N-(5-{2-[4-(2-methoxyethyl)phenoxy]ethyl}-1H-indol-3-yl)acetamide	353.3
269	470		N-(5-{2-[4-(trifluoromethyl)phenoxy]ethyl}-1H-indol-3-yl)acetamide	381.2

270	476		N-{5-[2-(3-chloro-5-cyanophenoxy)ethyl]-1H-indol-3-yl}acetamide	354.2
271	453		N-(5-{2-[3-(cyanomethyl)phenoxy]ethyl}-1H-indol-3-yl)acetamide	334.3
272	438		N-(5-{2-[3-(trifluoromethoxy)phenoxy]ethyl}-1H-indol-3-yl)acetamide	397.3
273	475		N-(5-{2-[4-(2-methyl-1,3-thiazol-4-yl)phenoxy]ethyl}-1H-indol-3-yl)acetamide	392.2
274	452		N-(5-{2-[4-(2,2,2-trifluoroethoxy)phenoxy]ethyl}-1H-indol-3-yl)acetamide	393.2

275	451		N-(5-{2-[4-(pyridin-4-yl)phenoxy]ethyl}-1H-indol-3-yl)acetamide	372.2
276	442		N-(5-{2-[4-(2,2,2-trifluoroethyl)phenoxy]ethyl}-1H-indol-3-yl)acetamide	400.3
277	441		N-(5-{2-[3-(2,2,2-trifluoroethyl)phenoxy]ethyl}-1H-indol-3-yl)acetamide	452.3
278	450		N-(5-{2-[4-(2-chloro-2-(trifluoromethyl)phenoxy]ethyl}-1H-indol-3-yl)acetamide	397.2
279	449		N-{5-[2-(isoquinolin-7-yloxy)ethyl]-1H-indol-3-yl}acetamide	346.2

280	411		N-(5-{2-[2-chloro-4-(trifluoromethyl)phenoxy]ethyl}-1H-indol-3-yl)acetamide	397.1
281	440		N-(5-{2-[2-cyano-4-(trifluoromethyl)phenoxy]ethyl}-1H-indol-3-yl)acetamide	412.3
282	410		N-(5-{2-[3,5-difluoro-4-(trifluoromethyl)phenoxy]ethyl}-1H-indol-3-yl)acetamide	399.2

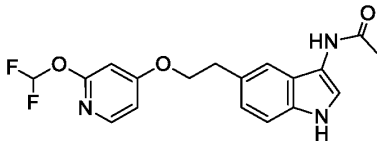
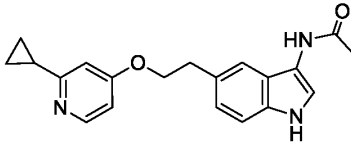
Example 283: Synthesis of N-[5-(2-{[2-(difluoromethoxy)pyridin-4-yl]oxy}ethyl)-1H-indol-3-yl]acetamide (compound 491)

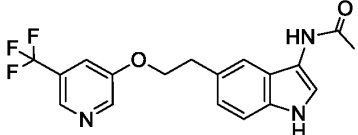
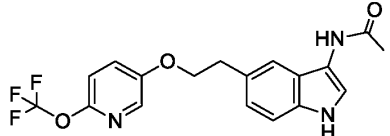
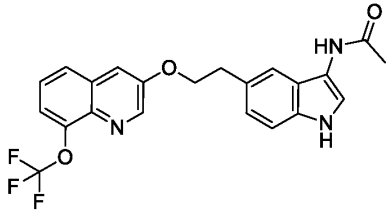
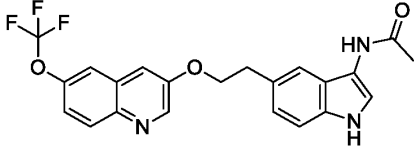


5 tert-butyl 3-acetamido-5-(2-hydroxyethyl)-1H-indole-1-carboxylate(66.8 mg, 0.21 mmol, 1.0 equiv.) and 2-(difluoromethoxy)pyridin-4-ol (67.6 mg, 0.42 mmol, 2.0 equiv.) were dissolved in DCM (2 mL), DIAD (127.3 mg, 0.63 mmol, 3.0 equiv.) and Triphenylphosphine resin (350 mg, 3.0 g/mol, 1.05 mmol, 5.0 equiv.) were added under

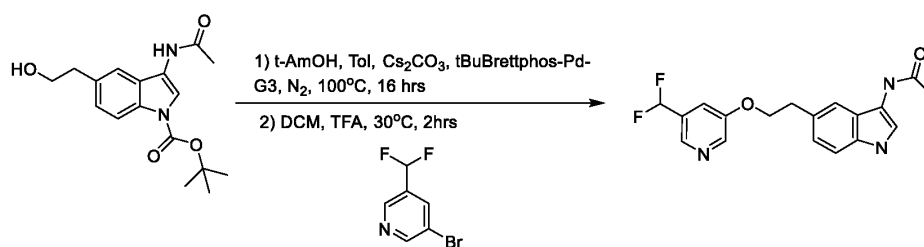
N₂ atmosphere. The mixture was heated at 30 °C for 24 hours under N₂ atmosphere. The mixture was diluted with 3*1 mL DCM and extracted with H₂O (1 mL). The combined organic layers were washed with H₂O (1 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. After that the residue were dissolved in DCM (2 mL), then TFA (500 µl) was added. The mixture was heated at 30 °C for 2 hours. The reaction mixture was concentrated by Speedvac to give a residue that was purified by prep HPLC-1 to give **N-[5-(2-{[2-(difluoromethoxy)pyridin-4-yl]oxy}ethyl)-1H-indol-3-yl]acetamide** (20.03 mg, 0.055 mmol) as a powder. MS-ESI, 362.2 [M+H⁺]. ¹H NMR (400 MHz, DMSO-*d*₆), δ ppm 10.69 (s, 1 H), 9.78 (s, 1 H), 8.04 (d, *J*=5.77 Hz, 1 H), 7.86 (s, 1 H), 7.69–7.65 (m, 1 H), 7.50 (s, 1 H), 7.91–7.48 (m, 1 H), 7.26 (d, *J*=8.53 Hz, 1 H), 7.06 (dd, *J*=8.28, 1.25 Hz, 1 H), 6.85 (dd, *J*=5.90, 2.13 Hz, 1 H), 6.66 (d, *J*=2.01 Hz, 1 H), 4.34 (t, *J*=6.90 Hz, 2 H), 3.11 (t, *J*=6.90 Hz, 2 H), 2.08 (s, 3 H).

The compounds in the following table were prepared using the above procedures (example 283) with the appropriate starting material.

Example #	Compound #	Final compound	IUPAC Name	LC-MS, MS-ESI, -- [M+H ⁺].
283	491		N-[5-(2-{[2-(difluoromethoxy)pyridin-4-yl]oxy}ethyl)-1H-indol-3-yl]acetamide	362.2
284	463		N-(5-{2-[(2-cyclopropylpyridin-4-yl)oxy]ethyl}-1H-indol-3-yl)acetamide	336.3

285	481		N-[5-(2-{[5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1H-indol-3-yl]acetamide	364.2
286	471		N-[5-(2-{[6-(trifluoromethoxy)pyridin-3-yl]oxy}ethyl)-1H-indol-3-yl]acetamide	380.2
287	477		N-[5-(2-{[8-(trifluoromethoxy)quinolin-3-yl]oxy}ethyl)-1H-indol-3-yl]acetamide	430.3
288	480		N-[5-(2-{[6-(trifluoromethoxy)quinolin-3-yl]oxy}ethyl)-1H-indol-3-yl]acetamide	430.3

Example 289: Synthesis of N-[5-(2-{[5-(difluoromethyl)pyridin-3-yl]oxy}ethyl)-1H-indol-3-yl]acetamide (compound 439)

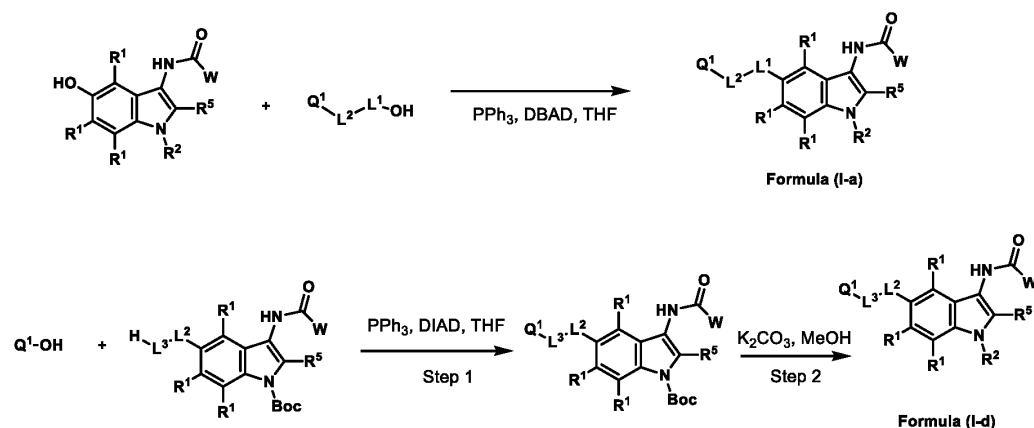


tert-butyl 3-acetamido-5-(2-hydroxyethyl)-1H-indole-1-carboxylate (66.8 mg, 0.21 mmol, 1.0 equiv.) and 3-bromo-5-(difluoromethyl)pyridine (86.5 mg, 0.42 mmol, 2.0 equiv.) were dissolved in t-AmOH (1 mL) and Tol (1 mL), Cs₂CO₃ (204.8 mg, 0.63 mmol, 3.0 equiv.) and tBuBrettphos-Pd-G3 (89.7 mg, 0.105 mmol, 0.5 equiv.) were added under N₂ atmosphere. The mixture was heated at 100 °C for 16 hours under N₂ atmosphere. The reaction mixture was concentrated by Speedvac to give a residue. The residue was diluted with H₂O (1 mL) and extracted with 3*1 mL DCM. The combined organic layers were washed with H₂O (1 mL), dried over anhydrous sodium sulfate anhydrous, filtered and concentrated under reduced pressure to give a residue. After that the residue were dissolved in DCM (2 mL), then TFA (500 µl) was added. The mixture was heated at 30 °C for 2 hours. The reaction mixture was concentrated by Speedvac to give a residue that was purified by prep HPLC-1 to give N-[5-(2-{[5-(difluoromethyl)pyridin-3-yl]oxy}ethyl)-1H-indol-3-yl]acetamide (13.71 mg, 0.040 mmol) as a powder. MS-ESI, 346.2 [M+H⁺].

The compounds in the following table were prepared using the above procedures (example 289) with the appropriate starting material.

Example #	Compound #	Final compound	IUPAC Name	LC-MS, MS-ESI, -- [M+H ⁺].
289	439		N-[5-(2-{[5-(difluoromethyl)pyridin-3-yl]oxy}ethyl)-1H-indol-3-yl]acetamide	346.2

Example 290. General methods for the synthesis of compounds of formula (I-a) and formula (I-d)



5 Biological Assays

STING pathway activation by the compounds described herein was measured using THP1-Dual™ cells (KO-IFNAR2).

THP1-Dual™ KO-IFNAR2 Cells (obtained from InvivoGen) were maintained in RPMI, 10% FCS, 5 ml P/S, 2mM L-glut, 10mM Hepes, and 1 mM sodium pyruvate. Compounds were spotted in empty 384 well tissue culture plates (Greiner 781182) by Echo for a final concentration of 0.0017 - 100 μ M. Cells were plated into the TC plates at 40 μ L per well, 2 $\times$ 10E6 cells/mL. For activation with STING ligand, 2'3'cGAMP (MW 718.38, obtained from Invivogen), was prepared in Optimem media.

The following solutions were prepared for each 1 $\times$ 384 plate:

- Solution A: 2 mL Optimem with one of the following stimuli:
 - 60 μ L of 10 mM 2'3'cGAMP $\rightarrow$ 150 μ M stock
- Solution B: 2 mL Optimem with 60 μ L Lipofectamine 2000 $\rightarrow$ Incubate 5 min at RT

2 mL of solution A and 2 mL Solution B was mixed and incubated for 20 min at room temperature (RT). 20 μ L of transfection solution (A+B) was added on top of the plated cells, with a final 2'3'cGAMP concentration of 15 μ M. The plates were then centrifuged immediately at 340 g for 1 minute, after which they were incubated at 37 °C,

5% CO₂, >98% humidity for 24h. Luciferase reporter activity was then measured. EC₅₀ values were calculated by using standard methods known in the art.

Luciferase reporter assay: 10 µL of supernatant from the assay was transferred to white 384-plate with flat bottom and squared wells. One pouch of QUANTI-LucTM Plus was dissolved in 25 mL of water. 100 µL of QLC Stabilizer per 25 mL of QUANTI-LucTM Plus solution was added. 50 µL of QUANTI-LucTM Plus/QLC solution per well was then added. Luminescence was measured on a Platereader (e.g., Spectramax I3X (Molecular Devices GF3637001)).

Luciferase reporter activity was then measured. EC₅₀ values were calculated by using standard methods known in the art.

Table BA shows the activity of compounds in STING reporter assay: <0.008 µM = “+++++”; ≥0.008 and <0.04 µM = “++++”; ≥0.04 and <0.2 µM = “+++”; ≥0.2 and <1 µM = “++”; ≥1 and <5 µM = “+”; ≥5 and <100 µM = “-”.

Table BA

Compound No.	Pharmaron, THP1_IFNAR2 STING 24h Luci Normalized: GeoMean EC ₅₀ (µM)
101	+++
102	++++
103	++++
104	+++
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106	+++
107	++++
108	+
109	++++
110	+++
111	++++
112	+
113	++
114	+++
115	++++

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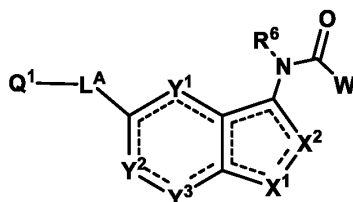
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Numbered Clauses

The compounds, compositions, methods, and other subject matter described herein are further described in the following numbered clauses:

- 5 1. A compound of Formula (I):



Formula I

or a pharmaceutically acceptable salt thereof or a tautomer thereof, wherein:

- 10 L^A is $-(L^1)_{a1}-(L^2)_{a2}-(L^3)_{a3}-(L^4)_{a4}-(L^5)_{a5}-*$, wherein * represents the point of attachment to Q^1 ;

$a1$, $a2$, $a3$, $a4$, and $a5$ are each independently 0 or 1,
provided that $a1 + a2 + a3 + a4 + a5 \geq 1$, and

each of L^1 , L^3 , and L^5 is independently selected from the group consisting of: -O-, -N(H)-, -N(R^d)-, S(O)₀₋₂, and -C(=O)-;

provided that when one or both of $a2$ and $a4$ is 0, then the combinations of L^1 , L^3 , and L^5 cannot form O-O, N-O, N-N, O-S, S-S, or N-S(O)₀ bonds, and

each of L^2 and L^4 is independently selected from the group consisting of:

- straight-chain C₁₋₆ alkylene, straight-chain C₂₋₆ alkenylene, or straight-chain C₂₋₆ alkynylene, each of which is optionally substituted with 1-6 R^b ;
- C₃₋₁₀ cycloalkylene or C₃₋₁₀ cycloalkenylene, each of which is optionally substituted with 1-3 R^c ; and
- heterocyclylene or heterocycloalkenylene, each having 4-10 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), N(R^d), O, and S(O)₀₋₂, wherein the heterocyclylene or heterocycloalkenylene is optionally substituted with 1-3 R^c ;

Q^1 is $-R^g$;

Y^1 , Y^2 , and Y^3 are each independently selected from the group consisting of CR¹, C(=O), N, and NR²;

X^1 is selected from the group consisting of O, S, N, NR², and CR¹;

X^2 is selected from the group consisting of O, S, N, NR⁴, and CR⁵;

each $\equiv$ is independently a single bond or a double bond, provided that the five-membered ring comprising X^1 and X^2 is heteroaryl, and that the six-membered ring comprising Y^1 , Y^2 , and Y^3 is aryl or heteroaryl;

further provided that L^A cannot include a cyclic group directly attached to the 6-membered ring containing Y^1 , Y^2 , and Y^3 ;

each occurrence of R^1 and R^5 is independently selected from the group consisting of: H; R^c ; R^g ; and $-(L^g)_{bg}-R^g$;

each occurrence of R^2 and R^4 is independently selected from the group consisting of: H; R^d ; R^g ; and $-(L^g)_{bg}-R^g$;

R^6 is selected from the group consisting of: H; R^d ; and R^g ;

5

W is selected from the group consisting of:

- H;
 - C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl, each of which is optionally substituted with 1-6 R^{a2} , wherein one or more of the internal optionally substituted methylene group can be replaced by one or more heteroatom selected from O or S, wherein when W is alkenyl or alkynyl, the heteroatom is not directly connected to the sp^2 or sp carbon;
 - monocyclic C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c ; and
 - monocyclic heterocyclyl or heterocycloalkenyl of 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c ;
- provided that when W is heterocyclyl or heterocycloalkenyl, it is attached to the C(=O)NR⁶ group via a ring carbon atom;

20

each occurrence of R^a and R^{a2} is independently selected from the group consisting of: -OH; -halo; -NR^cR^f; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)O(C_{1-4} alkyl); -C(=O)(C_{1-4} alkyl); -C(=O)OH; -CONR'R''; -S(O)₁₋₂NR'R''; -S(O)₁₋₂(C_{1-4} alkyl); and cyano;

25

each occurrence of R^b and R^c is independently selected from the group consisting of: halo; cyano; C_{1-10} alkyl which is optionally substituted with 1-6 independently selected R^a ; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -S(O)₁₋₂(C_{1-4} alkyl); -S(O)(=NH)(C_{1-4} alkyl); -NR^cR^f; -OH; -S(O)₁₋₂NR'R''; C_{1-4} thioalkoxy; -NO₂; -

30

$C(=O)(C_{1-10} \text{ alkyl})$; $-C(=O)O(C_{1-4} \text{ alkyl})$; $-C(=O)OH$; $-C(=O)NR'R''$; $-NR'C(=O)(C_{1-4} \text{ alkyl})$ and $-SF_5$;

each occurrence of R^d is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with 1-3 independently selected R^a ; $-C(O)(C_{1-4} \text{ alkyl})$; $-C(O)O(C_{1-4} \text{ alkyl})$; $-CONR'R''$; $-S(O)_{1-2}NR'R''$; $-S(O)_{1-2}(C_{1-4} \text{ alkyl})$; $-OH$; and C_{1-4} alkoxy;

each occurrence of R^e and R^f is independently selected from the group consisting of: H; C_{1-6} alkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of $NR'R''$, $-OH$, halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; $-C(O)(C_{1-4} \text{ alkyl})$; $-C(O)O(C_{1-4} \text{ alkyl})$; $-CONR'R''$; $-S(O)_{1-2}NR'R''$; $-S(O)_{1-2}(C_{1-4} \text{ alkyl})$; $-OH$; and C_{1-4} alkoxy;

each occurrence of R^g is independently selected from the group consisting of:

- C_{3-12} cycloalkyl or C_{3-12} cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, R^e , and R^h ;
- heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, R^e , and R^h ;
- heteroaryl of 5-12 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, R^e , and R^h ; and
- C_{6-10} aryl optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, R^e , and R^h ;

each occurrence of R^h is independently selected from the group consisting of:

- C₃₋₁₂ cycloalkyl or C₃₋₁₂ cycloalkenyl, each of which is optionally substituted with 1-4 **Rⁱ**;
- heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 **Rⁱ**;
- heteroaryl of 5-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heteroaryl is optionally substituted with 1-4 **Rⁱ**; and
- C₆₋₁₀ aryl optionally substituted with 1-4 **Rⁱ**;

each occurrence of **Rⁱ** is independently selected from the group consisting of: C₁₋₆ alkyl; C₁₋₄ haloalkyl; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; and halo;

- each occurrence of **L^g** is independently selected from the group consisting of: -O-, -NH-, -N**R^d**, -S(O)₀₋₂, C(O), and C₁₋₃ alkylene optionally substituted with 1-3 **R^a**;
- each occurrence of **bg** is independently 1, 2, or 3; and

- each occurrence of **R[']** and **R^{''}** is independently selected from the group consisting of: H; -OH; and C₁₋₄ alkyl.

2. The compound of clause 1, wherein **a2** is 1.

3. The compound of clauses 1 or 2, wherein **L²** is straight-chain C₁₋₆ alkylene, straight-chain C₂₋₆ alkenylene, or straight-chain C₂₋₆ alkynylene, each of which is optionally substituted with 1-6 **R^b**.

4. The compound of any one of clauses 1-3, wherein **L²** is straight-chain C₁₋₆ alkylene, which is optionally substituted with 1-6 **R^b**.

5. The compound of any one of clauses 1-4, wherein L^2 is straight-chain C_{1-3} alkylene, which is optionally substituted with 1-3 R^b .

6. The compound of any one of clauses 1-5, wherein L^2 is selected from the group consisting of: $-CH_2-$, $-CHR^b-$, and $-C(R^b)_2-$.

7. The compound of any one of clauses 1-6, wherein L^2 is $-CH_2-$.

8. The compound of any one of clauses 1-4, wherein L^2 is straight-chain C_{2-3} alkylene which is optionally substituted with 1-3 R^b .

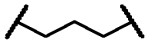
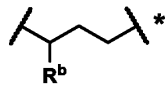
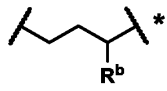
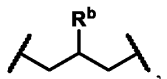
9. The compound of any one of clauses 1-4 or 8, wherein L^2 is straight-chain C_2 alkylene which is optionally substituted with 1-3 R^b .

10. The compound of any one of clauses 1-4 or 8-9, wherein L^2 is selected from the group consisting of: $-CH_2CH_2-$, $-CH_2CH(R^b)-*$, and $-CH_2C(R^b)_2-$, wherein the asterisk represents point of attachment to $-(L^3)_{a3}-$.

11. The compound of any one of clauses 1-4 or 8-10, wherein L^2 is $-CH_2CH_2-$.

12. The compound of any one of clauses 1-4 or 8, wherein L^2 is straight-chain C_3 alkylene which is optionally substituted with 1-3 R^b .

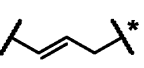
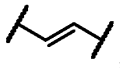
13. The compound of any one of clauses 1-4, 8, or 12, wherein L^2 is selected

from the group consisting of: , , , and , wherein the asterisk represents point of attachment to $-(L^3)_{a3}-$.

14. The compound of any one of clauses 1-3, wherein L^2 is straight-chain C_{2-6} alkenylene, which is optionally substituted with 1-6 R^b .

15. The compound of any one of clauses 1-3 or 14, wherein L^2 is straight-chain C_{2-4} alkenylene, which is optionally substituted with 1-3 R^b .

5 16. The compound of any one of clauses 1-3 or 14-15, wherein L^2 is selected

from the group consisting of:  and , wherein the asterisk represents the point of attachment to $-(L^3)_{a3}$.

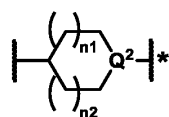
10 17. The compound of clauses 1 or 2, wherein L^2 is selected from the group consisting of:

- C_{3-10} cycloalkylene or C_{3-10} cycloalkenylene, each of which is optionally substituted with 1-3 R^c ; and
- heterocyclylene or heterocycloalkenylene, each having 4-10 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), $N(R^d)$, O, and $S(O)_{0-2}$, wherein the heterocyclylene or heterocycloalkenylene is optionally substituted with 1-3 R^c .

20 18. The compound of any one of clauses 1-2 or 17, wherein L^2 is selected from the group consisting of:

- C_{3-8} cycloalkylene, which is optionally substituted with 1-3 R^c ; and
- heterocyclylene having 4-8 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), $N(R^d)$, O, and $S(O)_{0-2}$, wherein the heterocyclylene is optionally substituted with 1-3 R^c .

25 19. The compound of any one of clauses 1-2 or 17-18, wherein L^2 is:



which is optionally substituted with 1-2 R^c , wherein $n1$ and $n2$ are independently 0, 1, or 2; Q^2 is CH, CR^c , or N; and the asterisk represents the point of attachment to $-(L^3)_{a3}$.

20. The compound of clause 19, wherein Q^2 is CH.
21. The compound of clauses 19 or 20, wherein $n1$ and $n2$ are each 0.
- 5 22. The compound of any one of clauses 1-2 or 17-21, wherein L^2 is
- *, wherein the asterisk represents the point of attachment to $-(L^3)_{a3}$.
23. The compound of clause 1, wherein $a2$ is 0.
- 10 24. The compound of any one of clauses 1-23, wherein $a1$ is 1.
25. The compound of any one of clauses 1-24, wherein L^1 is selected from the group consisting of: -O-, -N(H)-, -N(R^d)-, and -S-.
- 15 26. The compound of any one of clauses 1-25, wherein L^1 is -O-.
27. The compound of any one of clauses 1-23, wherein $a1$ is 0.
- 20 28. The compound of any one of clauses 1-27, wherein $a3$ is 1.
29. The compound of any one of clauses 1-28, wherein L^3 is selected from the group consisting of: -O-, -N(H)-, -N(R^d)-, and -S-.
- 25 30. The compound of any one of clauses 1-29, wherein L^3 is -O-.
31. The compound of any one of clauses 1-29, wherein L^3 is -N(H)- or -N(R^d)-, optionally -N(H)-.
- 30 32. The compound of any one of clauses 1-27, wherein $a3$ is 0.
33. The compound of any one of clauses 1-32, wherein $a4$ is 1.
34. The compound of any one of clauses 1-33, wherein L^4 is straight-chain C_{1-3} alkylene, which is optionally substituted with 1-3 R^b .
- 35

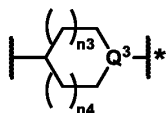
35. The compound of any one of clauses 1-34, wherein L^4 is $-CH_2-$.

36. The compound of any one of clauses 1-33, wherein L^4 is selected from the group consisting of:

- C_{3-8} cycloalkylene, which is optionally substituted with 1-3 R^c ; and
- heterocyclylene having 4-8 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), N(R^d), O, and S(O)₀₋₂, wherein the heterocyclylene is optionally substituted with 1-3 R^c .

10

37. The compound of any one of clauses 1-33 or 36, wherein L^4 is:



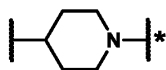
which is optionally substituted with 1-2 R^c , wherein $n3$ and $n4$ are independently 0, 1, or 2; Q^3 is CH, CR^c , or N; and the asterisk represents the point of attachment to $-(L^5)_{a5}-$.

15

38. The compound of clause 37, wherein $n3$ and $n4$ are each 1.

39. The compound of clauses 37 or 38, wherein Q^3 is N.

40. The compound of any one of clauses 1-33 or 36-39, wherein L^4 is



, wherein the asterisk represents the point of attachment to $-(L^5)_{a5}-$.

20

41. The compound of any one of clauses 1-32, wherein $a4$ is 0.

25

42. The compound of any one of clauses 1-41, wherein $a5$ is 0.

43. The compound of clause 1, wherein one of $a1$, $a3$, and $a5$ is 1, and the other two are 0.

44. The compound of clauses 1 or 43, wherein one of **a2** and **a4** is 1, and the other is 0 or 1.

5 45. The compound of any one of clauses 1 or 43-44, wherein **a1** and **a2** are each 1.

46. The compound of any one of clauses 1 or 43-45, wherein:
a1 and **a2** are each 1;
L¹ is -O-, -N(H)-, or -N(**R^d**)-;
10 **L²** is selected from the group consisting of:
• straight-chain C₁₋₃ alkylene, which is optionally substituted with 1-3 **R^b**;
• C₃₋₈ cycloalkylene, which is optionally substituted with 1-3 **R^c**; and
• heterocyclylene having 4-8 ring atoms wherein 1-3 ring atoms are ring
heteroatoms each independently selected from the group consisting of: N, N(H), N(**R^d**), O,
15 and S(O)₀₋₂, wherein the heterocyclylene is optionally substituted with 1-3 **R^c**.

47. The compound of any one of clauses 1 or 43-46, wherein:
a1 and **a2** are each 1;
L¹ is -O-; and
20 **L²** is straight-chain C₁₋₃ alkylene, which is optionally substituted with 1-3 **R^b**.

48. The compound of any one of clauses 1 or 43-47, wherein:
a1 and **a2** are each 1;
L¹ is -O-; and
25 **L²** is selected from the group consisting of: -CH₂-, -CH**R^b**-, and -C(**R^b**)₂-.

49. The compound of any one of clauses 1 or 43-47, wherein:
a1 and **a2** are each 1;
L¹ is -O-; and
30 **L²** is straight-chain C₂₋₃ alkylene which is optionally substituted with 1-3 **R^b**.

50. The compound of clause 49, wherein L^2 is straight-chain C_2 alkylene which is optionally substituted with 1-3 R^b .

51. The compound of clauses 49 or 50, wherein L^2 is selected from the group consisting of: $-CH_2CH_2-$, $-CH_2CH(R^b)-*$, and $-CH_2C(R^b)_2-*$, wherein the asterisk represents point of attachment to $-(L^3)_{a3}-$.

52. The compound of any one of clauses 49-51, wherein L^2 is $-CH_2CH_2-$.

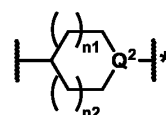
53. The compound of any one of clauses 1 or 43-46, wherein:

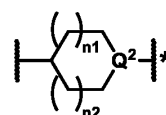
$a1$ and $a2$ are each 1;

L^1 is $-O-$;

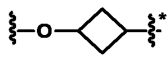
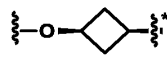
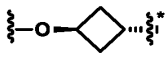
L^2 is selected from the group consisting of:

- C_{3-8} cycloalkylene, which is optionally substituted with 1-3 R^c ; and
- heterocyclylene having 4-8 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), N(R^d), O, and S(O)₀₋₂, wherein the heterocyclylene is optionally substituted with 1-3 R^c .



54. The compound of clause 53, wherein L^2 is:  which is optionally substituted with 1-2 R^c , wherein $n1$ and $n2$ are independently 0, 1, or 2; Q^2 is CH, CR^c , or N; and the asterisk represents the point of attachment to $-(L^3)_{a3}-$.

55. The compound of clause 54, wherein $n1$ and $n2$ are independently 0 or 1, optionally 0; and Q^2 is CH; optionally wherein $n1$ and $n2$ are 0 and Q^2 is CH; optionally wherein L^2 is cyclobutane-diyl optionally substituted with 1-2 R^c ; ; optionally wherein L^2 is cyclobutane-1,3-diyl optionally substituted with 1-2 R^c ; ; optionally wherein L^2 is unsubstituted cyclobutane-diyl; optionally wherein L^2 is unsubstituted cyclobutane-1,3-diyl.

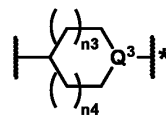
56. The compound of any one of clauses 43-55, wherein **a3**, **a4**, and **a5** are each 0, optionally wherein **L^A** is $\text{-O-CH}_2\text{CH}_2\text{-}^*$, or  (such as  or ) , wherein * represents the point of attachment to **Q¹**.

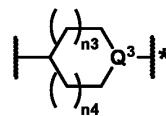
57. The compound of any one of clauses 43-55, wherein **a3** and **a5** are 0; and **a4** is 1.

58. The compound of clause 57, wherein **L⁴** is selected from the group consisting of:

- C₃₋₈ cycloalkylene, which is optionally substituted with 1-3 **R^c**; and
- heterocyclylene having 4-8 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), N(**R^d**), O, and S(O)₀₋₂, wherein the heterocyclylene is optionally substituted with 1-3 **R^c**.

15



59. The compound of clauses 57 or 58, wherein **L⁴** is:  which is optionally substituted with 1-2 **R^c**, wherein **n3** and **n4** are independently 0, 1, or 2; **Q³** is CH, **CR^c**, or N; and the asterisk represents the point of attachment to $-(L^5)_{a5}$.

60. The compound of clause 59, wherein **n3** and **n4** are independently 0 or 1; and **Q³** is N.

61. The compound of any one of clauses 1 or 43-44, wherein: **a1** is 0; and **a2** is 1.

25

62. The compound of any one of clauses 1, 43-44, or 61, wherein **a1** is 0; **a2** is 1; and **L²** is straight-chain C₁₋₆ alkylene, which is optionally substituted with 1-6 **R^b**.

63. The compound of clauses 61 or 62, wherein **L²** is straight-chain C₁₋₃ alkylene, which is optionally substituted with 1-3 **R^b**.

30

64. The compound of any one of clauses 61-63, wherein L^2 is selected from the group consisting of: $-CH_2-$, $-CHR^b-$, and $-C(R^b)_2-$.

5 65. The compound of any one of clauses 61-64, wherein L^2 is $-CH_2-$.

66. The compound of any one of clauses 61-63, wherein L^2 is straight-chain C_{2-3} alkylene which is optionally substituted with 1-3 R^b .

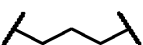
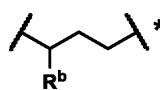
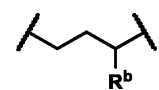
10 67. The compound of any one of clauses 61-63 or 66, wherein L^2 is straight-chain C_2 alkylene, which is optionally substituted with 1-3 R^b .

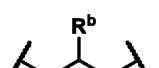
68. The compound of any one of clauses 61-63 or 66-67, wherein L^2 is selected from the group consisting of: $-CH_2CH_2-$, $-CH_2CH(R^b)-*$, and $-CH_2C(R^b)_2-$, wherein the
15 asterisk represents point of attachment to $-(L^3)_{a3}$.

69. The compound of any one of clauses 61-63 or 66-68, wherein L^2 is $-CH_2CH_2-$.

20 70. The compound of any one of clauses 61-63 or 66, wherein L^2 is straight-chain C_3 alkylene, which is optionally substituted with 1-3 R^b .

71. The compound of any one of clauses 61-63, 66, or 70, wherein L^2 is selected

from the group consisting of: , , , and

25 , wherein the asterisk represents point of attachment to $-(L^3)_{a3}$.

72. The compound of any one of clauses 61-71, wherein $a3$ is 0; $a4$ is 0; and $a5$ is 0.

30 73. The compound of any one of clauses 61-71, wherein $a3$ is 1.

74. The compound of clause 73, wherein **a3** is 1; and **L³** is selected from the group consisting of: is -O-, -N(H)-, and -N(**R^d**)-.

75. The compound of clauses 73 or 74, wherein **a3** is 1; and **L³** is -O-.

5

76. The compound of any one of clauses 61-71 or 73-74, wherein **a3** is 1; and **L³** is -N(H)- or -N(**R^d**)-, optionally -N(H)-.

77. The compounds of any one of clauses 61-71 or 73-76, wherein **a4** is 1; and **L⁴** is straight-chain C₁₋₃ alkylene, which is optionally substituted with 1-3 **R^b**.

10

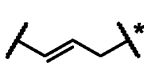
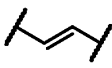
78. The compound of any one of clauses 61-71 or 73-77, wherein **a4** is 1; and **L⁴** is -CH₂-.

15

79. The compound of any one of clauses 61-71 or 73-77, wherein **a4** is 0; and **a5** is 0, optionally wherein **L^A** is -CH₂CH₂-O-*, wherein * represents to point of attachment to **Q¹**.

80. The compound of clause 1, wherein **a1** is 0; **a2** is 1; **L²** is straight-chain C₂₋₄ alkenylene, which is optionally substituted with 1-3 **R^b**.

20

81. The compound of clause 80, wherein **L²** is selected from the group consisting of:  and , wherein the asterisk represents the point of attachment to -(**L³**)_{a3}-.

25

82. The compound of clauses 80 or 81, wherein **a3** is 0; **a4** is 0; and **a5** is 0.

83. The compound of any one of clauses 1-82, wherein **Q¹** is selected from the group consisting of:

30

- heteroaryl of 5-12 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heteroaryl is optionally substituted with 1-4 **R^c**; and

- C₆₋₁₀ aryl optionally substituted with 1-4 R^c.

84. The compound of any one of clauses 1-82, wherein Q¹ is selected from the group consisting of:

- heteroaryl of 5-6 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heteroaryl is optionally substituted with 1-3 R^c; and
- phenyl optionally substituted with 1-3 R^c.

10

85. The compound of any one of clauses 1-82, wherein Q¹ is selected from the group consisting of:

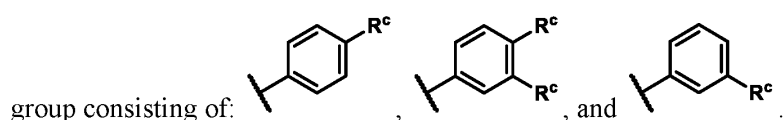
- heteroaryl of 6 ring atoms, wherein 1-2 ring atoms are ring nitrogen atoms, and wherein the heteroaryl is optionally substituted with 1-3 R^c; and
- phenyl optionally substituted with 1-3 R^c.

15

86. The compound of any one of clauses 1-85, wherein Q¹ is phenyl optionally substituted with 1-3 R^c.

20

87. The compound of any one of clauses 1-86, wherein Q¹ is selected from the

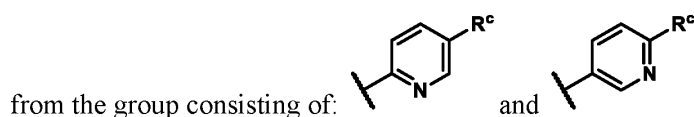


25

88. The compound of any one of clauses 1-85, wherein Q¹ is heteroaryl of 6 ring atoms, wherein 1-2 ring atoms are ring nitrogen atoms, and wherein the heteroaryl is optionally substituted with 1-3 R^c.

89. The compound of any one of clauses 1-85 or 88, wherein Q¹ is pyridyl, which is optionally substituted with 1-3 R^c.

90. The compound of any one of clauses 1-85 or 88-89, wherein Q^1 is selected



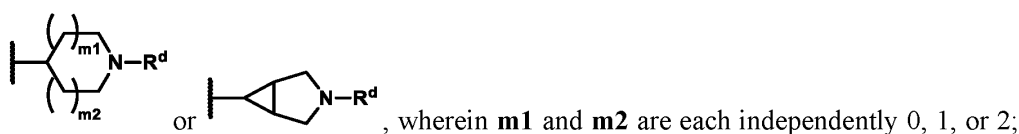
91. The compound of any one of clauses 1-82, wherein Q^1 is heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c .

92. The compound of any one of clauses 1-82 or 91, wherein Q^1 is heterocyclyl of 4-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heterocyclyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c .

93. The compound of any one of clauses 1-82 or 91-92, wherein Q^1 is heterocyclyl of 4-8 ring atoms, wherein 1-2 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, provided that one ring atom is N(R^d),

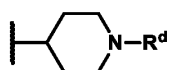
and wherein the heterocyclyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c .

94. The compound of any one of clauses 1-82 or 91-93, wherein Q^1 is



and wherein Q^1 is optionally substituted with 1-2 R^c .

95. The compound of any one of clauses 1-82 or 91-94, wherein Q^1 is



96. The compound of any one of clauses 1-82 or 91-94, wherein Q^1 is



5

97. The compound any one of clauses 91-96, wherein each R^d present in Q^1 is independently selected from the group consisting of: $-C(O)O(C_{1-4} \text{ alkyl})$; and C_{1-6} alkyl optionally substituted with 1-3 independently selected R^a .

10 98. The compound of any one of clauses 91-97, wherein each R^d present in Q^1 is C_{1-6} alkyl optionally substituted with 1-3 independently selected halo.

99. The compound of any one of clauses 91-98, wherein each R^d present in Q^1 is:

- 15
- i. C_{1-4} alkyl substituted with 1-3 $-F$;
 - ii. C_{2-3} alkyl substituted with 1-3 $-F$; or
 - iii. $-CH_2CF_3$.

20 100. The compound of any one of clauses 83-99, wherein each R^c present in Q^1 is independently selected from the group consisting of: halo; cyano; C_{1-4} alkoxy; C_{1-4} haloalkoxy; and C_{1-10} alkyl which is optionally substituted with 1-6 independently selected R^a .

25 101. The compound of any one of clauses 83-100, wherein each R^c present in Q^1 is independently selected from the group consisting of: halo; cyano; C_{1-4} alkoxy; C_{1-4} haloalkoxy; and C_{1-6} alkyl which is optionally substituted with 1-6 independently selected halo.

102. The compound of any one of clauses 83-101, wherein each R^c present in Q^1 is independently selected from the group consisting of: halo and C_{1-3} alkyl which is optionally substituted with 1-6 independently selected halo.

5 **103.** The compound of any one of clauses 83-102, wherein each R^c present in Q^1 is:

- i. C_{1-3} alkyl which is optionally substituted with 1-6 $-F$; or
- ii. CF_3 .

10 **104.** The compound of any one of clauses 83-102, wherein each R^c present in Q^1 is an independently selected halo, optionally $-F$ or $-Cl$.

105. The compound of any one of clauses 1-104, wherein Y^1 is CR^1 .

15 **106.** The compound of any one of clauses 1-105, wherein Y^2 is CR^1 .

107. The compound of any one of clauses 1-106, wherein Y^3 is CR^1 .

20 **108.** The compound of any one of clauses 1-107, wherein each occurrence of R^1 is independently H or R^c .

109. The compound of any one of clauses 1-108, wherein each occurrence of R^1 is H.

25 **110.** The compound of any one of clauses 1-108, wherein 1-2 occurrence of R^1 is R^c ; and each remaining occurrence of R^1 is H.

111. The compound of any one of clauses 1-108 or 110, wherein one occurrence of R^1 is halo, optionally $-F$ or $-Cl$; and each remaining occurrence of R^1 is H.

30 **112.** The compound of any one of clauses 1-111, wherein Y^1 , Y^2 , and Y^3 are each independently selected CR^1 .

113. The compound of any one of clauses 1-107 or 112, wherein $\mathbf{Y}^1$, $\mathbf{Y}^2$, and $\mathbf{Y}^3$ are each CH.

114. The compound of any one of clauses 1-107 or 112, wherein one of $\mathbf{Y}^1$, $\mathbf{Y}^2$,
5 and $\mathbf{Y}^3$ is $\mathbf{CR}^c$, optionally C-halo; and each of the remaining two $\mathbf{Y}^1$, $\mathbf{Y}^2$, and $\mathbf{Y}^3$ is CH.

115. The compound of any one of clauses 1-114, wherein $\mathbf{X}^1$ is $\mathbf{NR}^2$.

116. The compound of any one of clauses 1-115, wherein $\mathbf{X}^1$ is NH.

10

117. The compound of any one of clauses 1-116, wherein $\mathbf{X}^2$ is $\mathbf{CR}^5$.

118. The compound of any one of clauses 1-117, wherein $\mathbf{X}^2$ is CH.

15

119. The compound of any one of clauses 1-114, wherein $\mathbf{X}^1$ is $\mathbf{NR}^2$; and $\mathbf{X}^2$ is $\mathbf{CR}^5$.

120. The compound of any one of clauses 1-114 or 119, wherein $\mathbf{X}^1$ is NH; and $\mathbf{X}^2$ is CH.

20

121. The compound of any one of clauses 1-104, wherein $\mathbf{Y}^1$, $\mathbf{Y}^2$, and $\mathbf{Y}^3$ are each an independently selected $\mathbf{CR}^1$; $\mathbf{X}^1$ is $\mathbf{NR}^2$; and $\mathbf{X}^2$ is $\mathbf{CR}^5$.

122. The compound of any one of clauses 1-104 or 121, wherein $\mathbf{Y}^1$, $\mathbf{Y}^2$, and $\mathbf{Y}^3$
25 are each CH; $\mathbf{X}^1$ is NH; and $\mathbf{X}^2$ is CH.

123. The compound of any one of clauses 1-122, wherein $\mathbf{R}^6$ is H.

124. The compound of any one of clauses 1-123, wherein $\mathbf{W}$ is C_{1-10} alkyl, C_{2-10}
30 alkenyl, or C_{2-10} alkenyl, each of which is optionally substituted with 1-6 $\mathbf{R}^{a2}$.

125. The compound of any one of clauses 1-124, wherein $\mathbf{W}$ is C_{1-10} alkyl, which is optionally substituted with 1-6 $\mathbf{R}^{a2}$.

126. The compound of any one of clauses 1-125, wherein **W** is C₁₋₆ alkyl, which is optionally substituted with 1-6 **R^{a2}**.

127. The compound of any one of clauses 1-126, wherein **W** is C₁₋₄ alkyl, which is optionally substituted with 1-6 **R^{a2}**.

128. The compound of any one of clauses 1-127, wherein **W** is unsubstituted C₁₋₄ alkyl.

129. The compound of any one of clauses 1-128, wherein **W** is selected from the group consisting of: methyl, ethyl, n-propyl, isopropyl, and isobutyl

130. The compound of any one of clauses 1-129, wherein **W** is methyl or ethyl.

131. The compound of any one of clauses 1-126, wherein **W** is C₁₋₄ alkyl, which is substituted with 1-6 **R^{a2}**.

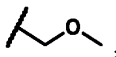
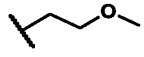
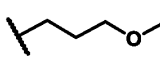
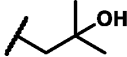
132. The compound of any one of clauses 1-126 or 131, wherein each **R^{a2}** is independently selected from the group consisting of:

i. -OH; -halo; -**NR^eR^f**; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -C(=O)O(C₁₋₄ alkyl); -C(=O)(C₁₋₄ alkyl); and cyano; or

ii. halo; -OH; C₁₋₄ alkoxy; and C₁₋₄ haloalkoxy.

133. The compound of any one of clauses 1-126 or 131-132, wherein **W**:

i. C₁₋₄ alkyl which is substituted with 1-3 substituents each independently selected from the group consisting of: halo; -OH; C₁₋₄ alkoxy; and C₁₋₄ haloalkoxy; or

ii. selected from the group consisting of: **W** is , , , and .

134. The compound of any one of clauses 1-123, wherein **W** is selected from the group consisting of:

- monocyclic C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c; and

- monocyclic heterocyclyl or heterocycloalkenyl of from 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c.

10 **135.** The compound of any one of clauses 1-123 or 134, wherein **W** is monocyclic C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c.

15 **136.** The compound of any one of clauses 1-123 or 134-135, wherein **W** is monocyclic C₃₋₈ cycloalkyl, which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c.

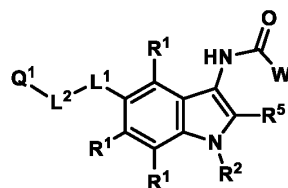
20 **137.** The compound of any one of clauses 1-123 or 134-136, wherein **W** is unsubstituted C₃₋₈ cycloalkyl.

138. The compound of any one of clauses 1-123 or 134-137, wherein **W** is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

25 **139.** The compound of any one of clauses 1-123 or 134-138, wherein **W** is cyclobutyl.

140. The compound of any one of clauses 1-123, wherein **W** is H.

30 **141.** The compound of clause 1, wherein the compound is a compound of Formula **(I-a)**:



Formula (I-a)

or a pharmaceutically acceptable salt thereof, wherein:

L¹ is selected from the group consisting of: -O-, -N(H)-, and -N(R^d)-;

5 L² is selected from the group consisting of:

- straight-chain C₁₋₃ alkylene, which is optionally substituted with 1-3 R^b;
- C₃₋₈ cycloalkylene, which is optionally substituted with 1-3 R^c; and
- heterocyclylene having 4-8 ring atoms wherein 1-3 ring atoms are ring

heteroatoms each independently selected from the group consisting of: N, N(H), N(R^d), O,
10 and S(O)₀₋₂, wherein the heterocyclylene is optionally substituted with 1-3 R^c;

Q¹ is -R^g;

each occurrence of R¹ and R⁵ is independently selected from the group consisting
of: H; R^c; R^g; and -(L^g)_{hg}-R^g;

15 each occurrence of R² is independently selected from the group consisting of: H;
R^d; R^g; and -(L^g)_{hg}-R^g;

W is selected from the group consisting of:

- H;
- 20 • C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl, each of which is optionally substituted with 1-6 R^{a2}, wherein one or more of the internal optionally substituted methylene group can be replaced by one or more heteroatom selected from O or S, wherein when W is alkenyl or alkynyl, the heteroatom is not directed connected to the *sp*² or *sp* carbon;
- 25 • monocyclic C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c; and

• monocyclic heterocyclyl or heterocycloalkenyl of 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**,

provided that when **W** is heterocyclyl or heterocycloalkenyl, it is attached to the C(=O)NR⁶ group via a ring carbon atom.

142. The compound of clause 141, wherein **L¹** is -O-.

143. The compound of clauses 141 or 142, wherein **L²** is straight-chain C₁₋₃ alkylene, which is optionally substituted with 1-3 **R^b**.

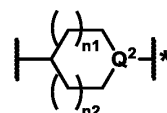
144. The compound of any one of clauses 141-143, wherein **L²** is selected from the group consisting of: -CH₂-, -CHR^b-, and -C(**R^b**)₂-, optionally wherein **L²** is -CH₂-.

145. The compound of any one of clauses 141-143 wherein **L²** is straight-chain C₂ alkylene which is optionally substituted with 1-3 **R^b**.

146. The compound of any one of clauses 141-143 or 145, wherein **L²** is selected from the group consisting of: -CH₂CH₂-, -CH₂CH(**R^b**)-*, and -CH₂C(**R^b**)₂-, wherein the asterisk represents point of attachment to -**Q¹**.

147. The compound of clause 146, wherein **L²** is -CH₂CH₂-.

148. The compound of any one of clauses 141-143, wherein **L²** is straight-chain C₃ alkylene which is optionally substituted with 1-3 **R^b**.



149. The compound of clauses 141 or 142, wherein **L²** is: which is optionally substituted with 1-2 **R^c**, wherein **n1** and **n2** are independently 0, 1, or 2; **Q²** is CH, CR^c, or N; and the asterisk represents the point of attachment to **Q¹**;

150. The compound of clause 149, wherein **n1** and **n2** are independently 0 or 1, optionally 0; and **Q²** is CH; optionally wherein **n1** and **n2** are 0 and **Q²** is CH; optionally wherein **L²** is cyclobutane-diyl optionally substituted with 1-2 **R^c**; optionally wherein **L²** is cyclobutane-1,3-diyl optionally substituted with 1-2 **R^c**; optionally wherein **L²** is cyclobutane-diyl optionally substituted with 1-2 **R^c**; optionally wherein **L²** is unsubstituted cyclobutane-diyl; optionally wherein **L²** is unsubstituted cyclobutane-1,3-diyl.

151. The compound of clause 141, wherein **L¹** is -O-; and **L²** is straight-chain C₂₋₃ alkylene which is optionally substituted with 1-3 **R^b**.

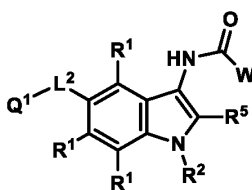
152. The compound of clause 151, wherein **L²** is:

- i. straight-chain C₂ alkylene which is optionally substituted with 1-3 **R^b**;
- ii. selected from the group consisting of: -CH₂CH₂-, -CH₂CH(**R^b**)-*, and -CH₂C(**R^b**)₂-*, wherein the asterisk represents point of attachment to -**Q¹**; or
- iii. -CH₂CH₂-.

153. The compound of clause 141, wherein **L¹** is -O-; and **L²** is:

- i. selected from the group consisting of: -CH₂-, -CH(**R^b**)-, and -C(**R^b**)₂; or
- ii. -CH₂-.

154. The compound of clause 1, wherein the compound is a compound of Formula (**I-b**):



Formula (**I-b**)

or a pharmaceutically acceptable salt thereof, wherein:

L² is straight-chain C₁₋₆ alkylene or straight-chain C₂₋₆ alkenylene, each of which is optionally substituted with 1-6 **R^b**;

Q¹ is -**R^g**;

each occurrence of $\mathbf{R}^1$ and $\mathbf{R}^5$ is independently selected from the group consisting of: H; $\mathbf{R}^c$; $\mathbf{R}^g$; and $-(\mathbf{L}^g)_{hg}-\mathbf{R}^g$;

each occurrence of $\mathbf{R}^2$ is independently selected from the group consisting of: H;
 5 $\mathbf{R}^d$; $\mathbf{R}^g$; and $-(\mathbf{L}^g)_{hg}-\mathbf{R}^g$; and

$\mathbf{W}$ is selected from the group consisting of:

- H;
- C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl, each of which is optionally
 10 substituted with 1-6 $\mathbf{R}^{a2}$, wherein one or more of the internal optionally substituted methylene group can be replaced by one or more heteroatom selected from O or S, wherein when $\mathbf{W}$ is alkenyl or alkynyl, the heteroatom is not directed connected to the sp^2 or sp carbon;
- monocyclic C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl, each of which is optionally
 15 substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R}^c$; and
- monocyclic heterocyclyl or heterocycloalkenyl of 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^d$), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is
 20 optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R}^c$,

provided that when $\mathbf{W}$ is heterocyclyl or heterocycloalkenyl, it is attached to the C(=O)NR⁶ group via a ring carbon atom.

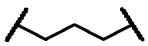
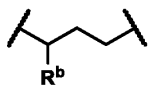
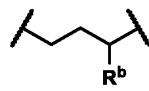
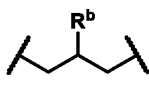
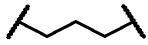
25 **155.** The compound of clause 154, wherein $\mathbf{L}^2$ is straight-chain C_{2-3} alkylene which is optionally substituted with 1-3 $\mathbf{R}^b$.

156. The compound of clauses 154 or 155, wherein $\mathbf{L}^2$ is straight-chain C_2 alkylene which is optionally substituted with 1-3 $\mathbf{R}^b$.

30

157. The compound of any one of clauses 154-156, wherein L^2 is selected from the group consisting of: $-CH_2CH_2-$, $-CH_2CH(R^b)-*$, and $-CH_2C(R^b)_2-$, wherein the asterisk represents point of attachment to $-Q^1$, optionally wherein L^2 is $-CH_2CH_2-$.

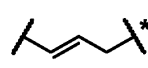
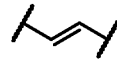
5 158. The compound of clauses 154-155, wherein L^2 is straight-chain C_3 alkylene which is optionally substituted with 1-3 R^b .

159. The compound of any one of clauses 154-155 or 158, wherein L^2 is selected from the group consisting of: , , , and , wherein the asterisk represents point of attachment to $-Q^1$, optionally wherein L^2 is .

10

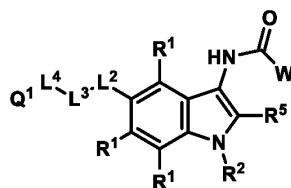
160. The compound of clause 154, wherein L^2 is straight-chain C_{2-4} alkenylene, which is optionally substituted with 1-3 R^b .

15

161. The compound of clauses 154 or 160, wherein L^2 is selected from the group consisting of:  and , wherein the asterisk represents the point of attachment to $-Q^1$.

20

162. The compound of clause 1, wherein the compound is a compound of Formula (I-c):



Formula (I-c)

or a pharmaceutically acceptable salt thereof, wherein:

25 L^2 and L^4 are independently selected straight-chain C_{1-3} alkylene which is optionally substituted with 1-6 R^b ;

L^3 is selected from the group consisting of: -O-, -N(H)-, and -N(R^d)-;

Q^1 is $-R^g$;

each occurrence of R^1 and R^5 is independently selected from the group consisting of: H; R^c ; R^g ; and $-(L^g)_{bg}-R^g$;

each occurrence of R^2 is independently selected from the group consisting of: H; R^d ; R^g ; and $-(L^g)_{bg}-R^g$; and

W is selected from the group consisting of:

- H;
 - C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl, each of which is optionally substituted with 1-6 R^{a2} , wherein one or more of the internal optionally substituted methylene group can be replaced by one or more heteroatom selected from O or S, wherein when W is alkenyl or alkynyl, the heteroatom is not directed connected to the sp^2 or sp carbon;
 - monocyclic C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c ; and
 - monocyclic heterocyclyl or heterocycloalkenyl of 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c ;
- provided that when W is heterocyclyl or heterocycloalkenyl, it is attached to the C(=O)NR⁶ group via a ring carbon atom.

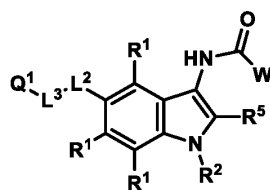
163. The compound of clause 162, wherein L^2 and L^4 are independently selected from the group consisting of: $-CH_2-$, $-CHR^b-$, and $-C(R^b)_2$.

164. The compound of clauses 162 or 163, wherein L^2 and L^4 are each $-CH_2-$.

165. The compound of any one of clauses 162-164, wherein L^3 is $-O-$.

166. The compound of any one of clauses 162-164, wherein L^3 is $-N(H)-$ or $-N(R^d)-$, optionally $-N(H)-$.

167. The compound of clause 1, wherein the compound is a compound of Formula (I-d):



Formula (I-d)

or a pharmaceutically acceptable salt thereof, wherein:

L^2 is straight-chain C_{1-3} alkylene which is optionally substituted with 1-6 R^b ; and

L^3 is selected from the group consisting of: $-O-$, $-N(H)-$, and $-N(R^d)-$;

Q^1 is $-R^g$;

each occurrence of R^1 and R^5 is independently selected from the group consisting of: H; R^c ; R^g ; and $-(L^g)_{hg}-R^g$;

each occurrence of R^2 is independently selected from the group consisting of: H; R^d ; R^g ; and $-(L^g)_{hg}-R^g$; and

W is selected from the group consisting of:

- H;
- C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl, each of which is optionally substituted with 1-6 R^{a2} , wherein one or more of the internal optionally substituted methylene group can be replaced by one or more heteroatom selected from O or S, wherein when W is alkenyl or alkynyl, the heteroatom is not directed connected to the sp^2 or sp carbon;

- monocyclic C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c; and

- monocyclic heterocyclyl or heterocycloalkenyl of 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c,

provided that when W is heterocyclyl or heterocycloalkenyl, it is attached to the C(=O)NR⁶ group via a ring carbon atom.

168. The compound of clause 167, wherein L² is selected from the group consisting of: -CH₂-, -CHR^b-, and -C(R^b)₂.

169. The compound of clause 167, wherein L² is straight-chain C₂ alkylene which is optionally substituted with 1-3 R^b.

170. The compound of clauses 167 or 169, wherein L² is selected from the group consisting of: -CH₂CH₂-, -CH₂CH(R^b)-*, and -CH₂C(R^b)₂-, wherein the asterisk represents point of attachment to -L³, optionally wherein L² is -CH₂CH₂-.

171. The compound of any one of clauses 167-170, wherein L³ is -O-.

172. The compound of any one of clauses 167-170, wherein L³ is -N(H)- or -N(R^d)-, optionally -N(H)-.

173. The compound of any one of clauses 141-172, wherein Q¹ is selected from the group consisting of:

- heteroaryl of 5-6 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heteroaryl is optionally substituted with 1-3 R^c; and

- phenyl optionally substituted with 1-3 R^c.

5

174. The compound of any one of clauses 141-173, wherein Q¹ is selected from the group consisting of:

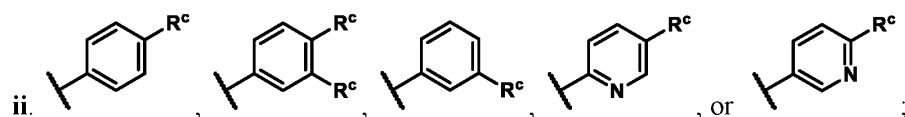
- heteroaryl of 6 ring atoms, wherein 1-2 ring atoms are ring nitrogen atoms, and wherein the heteroaryl is optionally substituted with 1-3 R^c; and

10

- phenyl optionally substituted with 1-3 R^c.

175. The compound of any one of clauses 141-174, wherein Q¹ is:

i. phenyl or pyridyl, each optionally substituted with 1-3 R^c;



15

iii. any groups of i or ii, wherein each R^c present in Q¹ is independently selected from the group consisting of: halo and C₁₋₃ alkyl which is optionally substituted with 1-6 independently selected halo; or

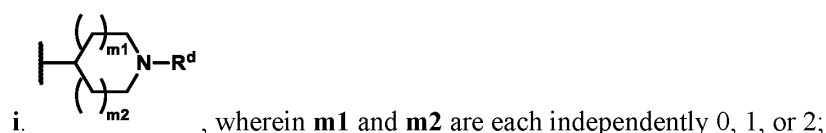
iv. any groups of i or ii, wherein each R^c present in Q¹ is independently selected from the group consisting of: -F, -Cl, and -CF₃.

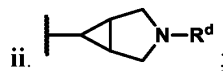
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176. The compound of any one of clauses 141-172, wherein Q¹ is heterocyclyl of 4-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heterocyclyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c.

25

177. The compound of any one of clauses 141-172 or 176, wherein Q¹ is:





iii any groups of i or ii, wherein the R^d present in Q^1 is selected from the group consisting of: $-C(O)O(C_{1-4} \text{ alkyl})$; and C_{1-6} alkyl optionally substituted with 1-3 independently selected R^a ; or

5 iv. any groups of i or ii, wherein the R^d present in Q^1 is C_{2-3} alkyl substituted with 1-3 $-F$.

178. The compound of any one of clauses 141-177, wherein each R^1 is H.

10 179. The compound of any one of clauses 141-177, wherein one occurrence of R^1 is R^c ; and each remaining R^1 is H.

180. The compound of any one of clauses 141-179, wherein R^2 is H; and R^5 is H.

15 181. The compound of any one of clauses 141-180, wherein W is C_{1-6} alkyl, which is optionally substituted with 1-6 R^{a2} .

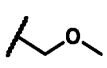
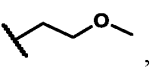
20 182. The compound of any one of clauses 141-181, wherein W is unsubstituted C_{1-4} alkyl.

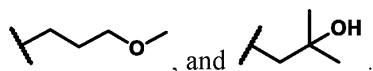
183. The compound of any one of clauses 141-182, wherein W is methyl or ethyl.

25 184. The compound of any one of clauses 141-181, wherein W is C_{1-4} alkyl, which is substituted with 1-6 R^{a2} .

185. The compound of any one of clauses 141-181 or 184, wherein W :

i. C_{1-4} alkyl which is substituted with 1-3 substituents each independently selected from the group consisting of: halo; $-OH$; C_{1-4} alkoxy; and C_{1-4} haloalkoxy; or

30 ii. selected from the group consisting of: W is , ,



186. The compound of any one of clauses 141-181, wherein **W** is selected from the group consisting of:

- monocyclic C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**; and
- monocyclic heterocyclyl or heterocycloalkenyl of from 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**.

187. The compound of any one of clauses 141-181 or 186, wherein **W** is monocyclic C₃₋₈ cycloalkyl, which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**.

188. The compound of any one of clauses 141-181 or 186-187, wherein **W** is:

- i. unsubstituted C₃₋₈ cycloalkyl; or
- ii. cyclobutyl.

189. The compound of clause 1, wherein the compound is selected from the group consisting of compounds delineated in **Table C1**, and a pharmaceutically acceptable salt thereof, optionally wherein the compound is compound 101-147; or 148-408; or 409-596.

190. A pharmaceutical composition comprising a compound of clauses 1-189 and one or more pharmaceutically acceptable excipients.

191. A method for inhibiting STING activity, the method comprising contacting STING with a compound or a pharmaceutically acceptable salt thereof as defined in any one of clauses 1-189; or a pharmaceutical composition as defined in clause 190.

192. The method of clause 191, wherein the inhibiting comprises antagonizing STING.

193. The method of any one of clauses 191-192, which is carried out *in vitro*.

5

194. The method of clauses 193, wherein the method comprises contacting a sample comprising one or more cells comprising STING with the compound.

195. The method of clauses 193 or 194, wherein the one or more cells are one or more cancer cells.

10

196. The method of clauses 194 or 195, wherein the sample further comprises one or more cancer cells, wherein the cancer is selected from the group consisting of melanoma, cervical cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, urothelial carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal carcinoma, colorectal cancer, pancreatic cancer, kidney cancer, hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia syndrome, multiple myeloma, transitional cell carcinoma, neuroblastoma, plasma cell neoplasms, Wilm's tumor, or hepatocellular carcinoma.

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197. The method of clauses 191 or 192, which is carried out *in vivo*.

198. The method of clause 197, wherein the method comprises administering the compound to a subject having a disease in which increased (e.g., excessive) STING signaling contributes to the pathology and/or symptoms and/or progression of the disease.

25

199. The method of clause 198, wherein the subject is a human.

200. The method of clause 199, wherein the disease is cancer.

30

201. The method of clause 200, wherein the cancer is selected from the group consisting of melanoma, cervical cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, urothelial carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal carcinoma, colorectal cancer, pancreatic cancer, kidney cancer, hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia syndrome, multiple myeloma, transitional cell carcinoma, neuroblastoma, plasma cell neoplasms, Wilm's tumor, or hepatocellular carcinoma.

202. The method of clauses 200 or 201, wherein the cancer is a refractory cancer.

203. The method of clause 198, wherein the compound is administered in combination with one or more additional cancer therapies.

204. The method of clause 203, wherein the one or more additional cancer therapies comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy, or a combination thereof.

205. The method of clause 204, wherein chemotherapy comprises administering one or more additional chemotherapeutic agents.

206. The method of clause 205, wherein the one or more additional chemotherapeutic agents is selected from an alkylating agent (e.g., cisplatin, carboplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide and/or oxaliplatin); an anti-metabolite (e.g., azathioprine and/or mercaptopurine); a terpenoid (e.g., a vinca alkaloid and/or a taxane; e.g., Vincristine, Vinblastine, Vinorelbine and/or Vindesine, Taxol, Paclitaxel and/or Docetaxel); a topoisomerase (e.g., a type I topoisomerase and/or a type 2 topoisomerase; e.g., camptothecins, such as irinotecan and/or topotecan; amsacrine, etoposide, etoposide phosphate and/or teniposide); a cytotoxic antibiotic (e.g., actinomycin, anthracyclines, doxorubicin, daunorubicin, valrubicin, idarubicin, epirubicin, bleomycin, plicamycin and/or mitomycin); a hormone (e.g., a luteinizing hormone releasing

hormone agonist; e.g., leuprolidine, goserelin, triptorelin, histrelin, bicalutamide, flutamide and/or nilutamide); an antibody (e.g., Abciximab, Adalimumab, Alemtuzumab, Atlizumab, Basiliximab, Belimumab, Bevacizumab, Bretuximab vedotin, Canakinumab, Cetuximab, Ceertolizumab pegol, Daclizumab, Denosumab, Eculizumab, Efalizumab, 5 Gemtuzumab, Golimumab, Golimumab, Ibritumomab tiuxetan, Infliximab, Ipilimumab, Muromonab-CD3, Natalizumab, Ofatumumab, Omalizumab, Palivizumab, Panitumab, Ranibizumab, Rituximab, Tocilizumab, Tositumomab and/or Trastuzumab); an anti-angiogenic agent; a cytokine; a thrombotic agent; a growth inhibitory agent; an anti-helminthic agent; and an immune checkpoint inhibitor that targets an immune checkpoint

10 receptor selected from the group consisting of CTLA-4, PD-1, PD-L1, PD-1 – PD-L1, PD-1 – PD-L2, interleukin-2 (IL-2), indoleamine 2,3-dioxygenase (IDO), IL-10, transforming growth factor- β (TGF β), T cell immunoglobulin and mucin 3 (TIM3 or HAVCR2), Galectin 9 – TIM3, Phosphatidylserine – TIM3, lymphocyte activation gene 3 protein (LAG3), MHC class II – LAG3, 4-1BB–4-1BB ligand, OX40–OX40 ligand, GITR, GITR

15 ligand – GITR, CD27, CD70–CD27, TNFRSF25, TNFRSF25–TL1A, CD40L, CD40–CD40 ligand, HVEM–LIGHT–LTA, HVEM, HVEM – BTLA, HVEM – CD160, HVEM – LIGHT, HVEM–BTLA–CD160, CD80, CD80 – PDL-1, PDL2 – CD80, CD244, CD48 – CD244, CD244, ICOS, ICOS–ICOS ligand, B7-H3, B7-H4, VISTA, TMIGD2, HHLA2–TMIGD2, Butyrophilins, including BTNL2, Siglec family, TIGIT and PVR

20 family members, KIRs, ILTs and LIRs, NKG2D and NKG2A, MICA and MICB, CD244, CD28, CD86 – CD28, CD86 – CTLA, CD80 – CD28, CD39, CD73 Adenosine–CD39–CD73, CXCR4–CXCL12, Phosphatidylserine, TIM3, Phosphatidylserine – TIM3, SIRPA–CD47, VEGF, Neuropilin, CD160, CD30, and CD155 (e.g., CTLA-4 or PD1 or PD-L1).

25

207. The method of any one of clauses 198-206, wherein the compound is administered intratumorally.

208. A method of treating cancer, comprising administering to a subject in need of such treatment an effective amount of a compound as defined in any one of clauses 1-189, or a pharmaceutical composition as defined in clause 190.

5 **209.** The method of clause 208, wherein the cancer is selected from the group consisting of melanoma, cervical cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, urothelial carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal carcinoma, colorectal cancer, pancreatic cancer, kidney cancer,
10 hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia syndrome, multiple myeloma, transitional cell carcinoma, neuroblastoma, plasma cell neoplasms, Wilm's tumor, or hepatocellular carcinoma.

210. The method of clause 208 or 209, wherein the cancer is a refractory cancer.
15

211. The method of clause 208, wherein the compound is administered in combination with one or more additional cancer therapies.

212. The method of clause 211, wherein the one or more additional cancer
20 therapies comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy, or a combination thereof.

213. The method of clause 212, wherein chemotherapy comprises administering one or more additional chemotherapeutic agents.
25

214. The method of clause 212, wherein the one or more additional chemotherapeutic agents is selected from an alkylating agent (e.g., cisplatin, carboplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide and/or oxaliplatin); an anti-metabolite (e.g., azathioprine and/or mercaptopurine); a terpenoid (e.g., a vinca
30 alkaloid and/or a taxane; e.g., Vincristine, Vinblastine, Vinorelbine and/or Vindesine Taxol, Paclitaxel and/or Docetaxel); a topoisomerase (e.g., a type I topoisomerase and/or

a type 2 topoisomerase; e.g., camptothecins, such as irinotecan and/or topotecan; amsacrine, etoposide, etoposide phosphate and/or teniposide); a cytotoxic antibiotic (e.g., actinomycin, anthracyclines, doxorubicin, daunorubicin, valrubicin, idarubicin, epirubicin, bleomycin, plicamycin and/or mitomycin); a hormone (e.g., a lutenizing hormone releasing hormone agonist; e.g., leuprolidine, goserelin, triptorelin, histrelin, bicalutamide, flutamide and/or nilutamide); an antibody (e.g., Abciximab, Adalimumab, Alemtuzumab, Atlizumab, Basiliximab, Belimumab, Bevacizumab, Bretuximab vedotin, Canakinumab, Cetuximab, Ceertolizumab pegol, Daclizumab, Denosumab, Eculizumab, Efalizumab, Gemtuzumab, Golimumab, Golimumab, Ibritumomab tiuxetan, Infliximab, Ipilimumab, Muromonab-CD3, Natalizumab, Ofatumumab, Omalizumab, Palivizumab, Panitumab, Ranibizumab, Rituximab, Tocilizumab, Tositumomab and/or Trastuzumab); an anti-angiogenic agent; a cytokine; a thrombotic agent; a growth inhibitory agent; an anti-helminthic agent; and an immune checkpoint inhibitor that targets an immune checkpoint receptor selected from the group consisting of CTLA-4, PD-1, PD-L1, PD-1 – PD-L1, PD-1 – PD-L2, interleukin-2 (IL-2), indoleamine 2,3-dioxygenase (IDO), IL-10, transforming growth factor- β (TGF β), T cell immunoglobulin and mucin 3 (TIM3 or HAVCR2), Galectin 9 – TIM3, Phosphatidylserine – TIM3, lymphocyte activation gene 3 protein (LAG3), MHC class II – LAG3, 4-1BB–4-1BB ligand, OX40–OX40 ligand, GITR, GITR ligand – GITR, CD27, CD70–CD27, TNFRSF25, TNFRSF25–TL1A, CD40L, CD40–CD40 ligand, HVEM–LIGHT–LTA, HVEM, HVEM – BTLA, HVEM – CD160, HVEM – LIGHT, HVEM–BTLA–CD160, CD80, CD80 – PDL-1, PDL2 – CD80, CD244, CD48 – CD244, CD244, ICOS, ICOS–ICOS ligand, B7-H3, B7-H4, VISTA, TMIGD2, HHLA2–TMIGD2, Butyrophilins, including BTNL2, Siglec family, TIGIT and PVR family members, KIRs, ILTs and LIRs, NKG2D and NKG2A, MICA and MICB, CD244, CD28, CD86 – CD28, CD86 – CTLA, CD80 – CD28, CD39, CD73 Adenosine–CD39–CD73, CXCR4–CXCL12, Phosphatidylserine, TIM3, Phosphatidylserine – TIM3, SIRPA–CD47, VEGF, Neuropilin, CD160, CD30, and CD155 (e.g., CTLA-4 or PD1 or PD-L1).

215. The method of any one of clauses 208-214, wherein the compound is administered intratumorally.

5 **216.** A method of inducing an immune response in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound as defined in any one of clauses 1-189, or a pharmaceutical composition as defined in clause 190.

10 **217.** The method of clause 216, wherein the subject has cancer.

218. The method of clause 217, wherein the subject has undergone and/or is undergoing and/or will undergo one or more cancer therapies.

15 **219.** The method of clause 217, wherein the cancer selected from the group consisting of melanoma, cervical cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, urothelial carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal carcinoma, colorectal cancer, pancreatic cancer, kidney cancer, hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia
20 syndrome, multiple myeloma, transitional cell carcinoma, neuroblastoma, plasma cell neoplasms, Wilm's tumor, or hepatocellular carcinoma.

220. The method of clause any one of clauses 217-219, wherein the cancer is a refractory cancer.

25 **221.** The method of clause 219, wherein the immune response is an innate immune response.

222. The method of clause 221, wherein the at least one or more cancer therapies
30 comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy, or a combination thereof.

223. The method of clause 222, wherein chemotherapy comprises administering one or more additional chemotherapeutic agents.

224. The method of clause 223, wherein the one or more additional chemotherapeutic agents is selected from alkylating agent (e.g., cisplatin, carboplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide and/or oxaliplatin); an anti-metabolite (e.g., azathioprine and/or mercaptopurine); a terpenoid (e.g., a vinca alkaloid and/or a taxane; e.g., Vincristine, Vinblastine, Vinorelbine and/or Vindesine
 5 Taxol, Paclitaxel and/or Docetaxel); a topoisomerase (e.g., a type I topoisomerase and/or a type 2 topoisomerase; e.g., camptothecins, such as irinotecan and/or topotecan; amsacrine, etoposide, etoposide phosphate and/or teniposide); a cytotoxic antibiotic (e.g., actinomycin, anthracyclines, doxorubicin, daunorubicin, valrubicin, idarubicin, epirubicin, bleomycin, plicamycin and/or mitomycin); a hormone (e.g., a lutenizing hormone releasing
 10 hormone agonist; e.g., leuprolidine, goserelin, triptorelin, histrelin, bicalutamide, flutamide and/or nilutamide); an antibody (e.g., Abciximab, Adalimumab, Alemtuzumab, Atlizumab, Basiliximab, Belimumab, Bevacizumab, Bretuximab vedotin, Canakinumab, Cetuximab, Ceertolizumab pegol, Daclizumab, Denosumab, Eculizumab, Efalizumab, Gemtuzumab, Golimumab, Golimumab, Ibritumomab tiuxetan, Infliximab, Ipilimumab, Muromonab-CD3, Natalizumab, Ofatumumab, Omalizumab, Palivizumab, Panitumab,
 20 Ranibizumab, Rituximab, Tocilizumab, Tositumomab and/or Trastuzumab); an anti-angiogenic agent; a cytokine; a thrombotic agent; a growth inhibitory agent; an anti-helminthic agent; and an immune checkpoint inhibitor that targets an immune checkpoint receptor selected from the group consisting of CTLA-4, PD-1, PD-L1, PD-1 – PD-L1, PD-1 – PD-L2, interleukin-2 (IL-2), indoleamine 2,3-dioxygenase (IDO), IL-10, transforming
 25 growth factor- β (TGF β), T cell immunoglobulin and mucin 3 (TIM3 or HAVCR2), Galectin 9 – TIM3, Phosphatidylserine – TIM3, lymphocyte activation gene 3 protein (LAG3), MHC class II – LAG3, 4-1BB–4-1BB ligand, OX40–OX40 ligand, GITR, GITR ligand – GITR, CD27, CD70–CD27, TNFRSF25, TNFRSF25–TL1A, CD40L, CD40–
 30 CD40 ligand, HVEM–LIGHT–LTA, HVEM, HVEM – BTLA, HVEM – CD160, HVEM

– LIGHT, HVEM–BTLA–CD160, CD80, CD80 – PDL-1, PDL2 – CD80, CD244, CD48
– CD244, CD244, ICOS, ICOS–ICOS ligand, B7-H3, B7-H4, VISTA, TMIGD2,
HHLA2–TMIGD2, Butyrophilins, including BTNL2, Siglec family, TIGIT and PVR
family members, KIRs, ILTs and LIRs, NKG2D and NKG2A, MICA and MICB, CD244,
5 CD28, CD86 – CD28, CD86 – CTLA, CD80 – CD28, CD39, CD73 Adenosine–CD39–
CD73, CXCR4–CXCL12, Phosphatidylserine, TIM3, Phosphatidylserine – TIM3,
SIRPA–CD47, VEGF, Neuropilin, CD160, CD30, and CD155 (e.g., CTLA-4 or PD1 or
PD-L1).

10 **225.** A method of treatment of a disease in which increased (e.g., excessive)
STING signaling contributes to the pathology and/or symptoms and/or progression of the
disease, comprising administering to a subject in need of such treatment an effective
amount of a compound as defined in any one of clauses 1-189, or a pharmaceutical
composition as defined in clause 190.

15 **226.** A method of treatment comprising administering to a subject having a
disease in which increased (e.g., excessive) STING signaling contributes to the pathology
and/or symptoms and/or progression of the disease an effective amount of a compound as
defined in any one of clauses 1-189, or a pharmaceutical composition as defined in clause
20 190.

227. A method of treatment comprising administering to a subject a compound
as defined in any one of clauses 1-189, or a pharmaceutical composition as defined in
clause 190, wherein the compound or composition is administered in an amount effective
25 to treat a disease in which increased (e.g., excessive) STING signaling contributes to the
pathology and/or symptoms and/or progression of the disease, thereby treating the disease.

228. The method of any one of clauses 225-227, wherein the disease is cancer.

30 **229.** The method of clause 228, wherein the cancer is selected from the group
consisting of melanoma, cervical cancer, breast cancer, ovarian cancer, prostate cancer,

testicular cancer, urothelial carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal carcinoma, colorectal cancer, pancreatic cancer, kidney cancer, hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia
5 syndrome, multiple myeloma, transitional cell carcinoma, neuroblastoma, plasma cell neoplasms, Wilm's tumor, or hepatocellular carcinoma.

230. The method of clause 228 or 229, wherein the cancer is a refractory cancer.

10 **231.** The method of any one of clauses 228-230, wherein the compound is administered in combination with one or more additional cancer therapies.

232. The method of clause 231, wherein the one or more additional cancer therapies comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy,
15 cryotherapy or gene therapy, or a combination thereof.

233. The method of clause 232, wherein chemotherapy comprises administering one or more additional chemotherapeutic agents.

20 **234.** The method of clause 233, wherein the one or more additional chemotherapeutic agents is selected from an alkylating agent (e.g., cisplatin, carboplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide and/or oxaliplatin); an anti-metabolite (e.g., azathioprine and/or mercaptopurine); a terpenoid (e.g., a vinca alkaloid and/or a taxane; e.g., Vincristine, Vinblastine, Vinorelbine and/or Vindesine
25 Taxol, Paclitaxel and/or Docetaxel); a topoisomerase (e.g., a type I topoisomerase and/or a type 2 topoisomerase; e.g., camptothecins, such as irinotecan and/or topotecan; amsacrine, etoposide, etoposide phosphate and/or teniposide); a cytotoxic antibiotic (e.g., actinomycin, anthracyclines, doxorubicin, daunorubicin, valrubicin, idarubicin, epirubicin, bleomycin, plicamycin and/or mitomycin); a hormone (e.g., a lutenizing hormone releasing
30 hormone agonist; e.g., leuprolidine, goserelin, triptorelin, histrelin, bicalutamide, flutamide and/or nilutamide); an antibody (e.g., Abciximab, Adalimumab, Alemtuzumab,

Atlizumab, Basiliximab, Belimumab, Bevacizumab, Bretuximab vedotin, Canakinumab, Cetuximab, Ceertolizumab pegol, Daclizumab, Denosumab, Eculizumab, Efalizumab, Gemtuzumab, Golimumab, Golimumab, Ibritumomab tiuxetan, Infliximab, Ipilimumab, Muromonab-CD3, Natalizumab, Ofatumumab, Omalizumab, Palivizumab, Panitumumab,
 5 Ranibizumab, Rituximab, Tocilizumab, Tositumomab and/or Trastuzumab); an anti-angiogenic agent; a cytokine; a thrombotic agent; a growth inhibitory agent; an anti-helminthic agent; and an immune checkpoint inhibitor that targets an immune checkpoint receptor selected from the group consisting of CTLA-4, PD-1, PD-L1, PD-1 – PD-L1, PD-1 – PD-L2, interleukin-2 (IL-2), indoleamine 2,3-dioxygenase (IDO), IL-10, transforming
 10 growth factor- β (TGF β), T cell immunoglobulin and mucin 3 (TIM3 or HAVCR2), Galectin 9 – TIM3, Phosphatidylserine – TIM3, lymphocyte activation gene 3 protein (LAG3), MHC class II – LAG3, 4-1BB–4-1BB ligand, OX40–OX40 ligand, GITR, GITR ligand – GITR, CD27, CD70–CD27, TNFRSF25, TNFRSF25–TL1A, CD40L, CD40–CD40 ligand, HVEM–LIGHT–LTA, HVEM, HVEM – BTLA, HVEM – CD160, HVEM
 15 – LIGHT, HVEM–BTLA–CD160, CD80, CD80 – PDL-1, PDL2 – CD80, CD244, CD48 – CD244, CD244, ICOS, ICOS–ICOS ligand, B7-H3, B7-H4, VISTA, TMIGD2, HHLA2–TMIGD2, Butyrophilins, including BTNL2, Siglec family, TIGIT and PVR family members, KIRs, ILTs and LIRs, NKG2D and NKG2A, MICA and MICB, CD244, CD28, CD86 – CD28, CD86 – CTLA, CD80 – CD28, CD39, CD73 Adenosine–CD39–
 20 CD73, CXCR4–CXCL12, Phosphatidylserine, TIM3, Phosphatidylserine – TIM3, SIRPA–CD47, VEGF, Neuropilin, CD160, CD30, and CD155 (e.g., CTLA-4 or PD1 or PD-L1).

235. The method of any one of clauses 225-234, wherein the compound is administered intratumorally.
 25

236. A method of treatment of a disease, disorder, or condition associated with STING, comprising administering to a subject in need of such treatment an effective

amount of a compound as defined in any one of clauses 1-189, or a pharmaceutical composition as defined in clause 190.

5 **237.** The method of clause 236, wherein the disease, disorder, or condition is selected from type I interferonopathies, Aicardi-Goutières Syndrome (AGS), genetic forms of lupus, inflammation-associated disorders, and rheumatoid arthritis.

10 **238.** The method of clause 237, wherein the disease, disorder, or condition is a type I interferonopathy (e.g., STING-associated vasculopathy with onset in infancy (SAVI)).

239. The method of clause 238, wherein the type I interferonopathy is STING-associated vasculopathy with onset in infancy (SAVI).

15 **240.** The method of clause 237, wherein the disease, disorder, or condition is Aicardi-Goutières Syndrome (AGS).

20 **241.** The method of clause 237, wherein the disease, disorder, or condition is a genetic form of lupus.

242. The method of clause 237, wherein the disease, disorder, or condition is inflammation-associated disorder.

25 **243.** The method of clause 242, wherein the inflammation-associated disorder is systemic lupus erythematosus.

244. The method of any one of clauses 191-243, wherein the method further comprises identifying the subject.

245. A combination comprising a compounds defined in any one of clauses 1 to 189 or a pharmaceutically acceptable salt or tautomer thereof, and one or more therapeutically active agents.

5 **246.** A compound defined in any one of clauses 1-189 or a pharmaceutically acceptable salt or tautomer thereof, or a pharmaceutical composition defined in clause 190, for use as a medicament.

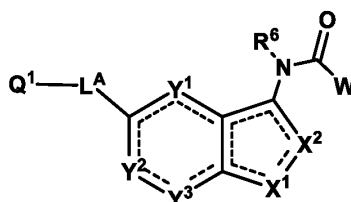
10 **247.** A compound defined in any one of clauses 1-189 or a pharmaceutically acceptable salt or tautomer thereof, or a pharmaceutical composition defined in clause 190, for use in the treatment of a disease, condition or disorder modulated by STING inhibition.

15 **248.** A compound defined in any one of clauses 1-189 or a pharmaceutically acceptable salt or tautomer thereof, or the pharmaceutical composition defined in clause 190, for use in the treatment of a disease mentioned in any one of clauses 191-244.

20 **249.** Use of a compound defined in any one of clauses 1-189 or a pharmaceutically acceptable salt or tautomer thereof, or a pharmaceutical composition defined in clause 190, in the manufacture of a medicament for the treatment of a disease mentioned in in any one of clauses 191-244.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



Formula I

5 or a pharmaceutically acceptable salt thereof or a tautomer thereof, wherein:

L^A is $-(L^1)_{a1}-(L^2)_{a2}-(L^3)_{a3}-(L^4)_{a4}-(L^5)_{a5-*}$, wherein * represents the point of attachment to Q^1 ;

$a1$, $a2$, $a3$, $a4$, and $a5$ are each independently 0 or 1,

provided that $a1 + a2 + a3 + a4 + a5 \geq 1$, and

10

each of L^1 , L^3 , and L^5 is independently selected from the group consisting of: $-O-$, $-N(H)-$, $-N(R^d)-$, $S(O)_{0-2}$, and $-C(=O)-$;

provided that when one or both of $a2$ and $a4$ is 0, then the combinations of L^1 , L^3 , and L^5 cannot form $O-O$, $N-O$, $N-N$, $O-S$, $S-S$, or $N-S(O)_0$ bonds, and

15

each of L^2 and L^4 is independently selected from the group consisting of:

- straight-chain C_{1-6} alkylene, straight-chain C_{2-6} alkenylene, or straight-chain C_{2-6} alkynylene, each of which is optionally substituted with 1-6 R^b ;
 - C_{3-10} cycloalkylene or C_{3-10} cycloalkenylene, each of which is optionally substituted with 1-3 R^c provided the C_{3-10} cycloalkylene or C_{3-10} cycloalkenylene is not directly connected to the 6-membered ring containing Y^1 , Y^2 , and Y^3 ; and
 - heterocyclylene or heterocycloalkenylene, each having 4-10 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, $N(H)$, $N(R^d)$, O, and $S(O)_{0-2}$, wherein the heterocyclylene or heterocycloalkenylene is optionally substituted with 1-3 R^c , provided the heterocyclylene or heterocycloalkenylene is not directly connected to the 6-membered ring containing Y^1 , Y^2 , and Y^3 ;
- 20
- 25

Q^1 is $-R^g$;

Y^1 , Y^2 , and Y^3 are each independently selected from the group consisting of CR^1 ,
 5 C(=O), N, and NR^2 ;

X^1 is selected from the group consisting of O, S, N, NR^2 , and CR^1 ;

X^2 is selected from the group consisting of O, S, N, NR^4 , and CR^5 ;

each $\equiv$ is independently a single bond or a double bond, provided that the five-
 membered ring comprising X^1 and X^2 is heteroaryl, and that the six-membered ring
 10 comprising Y^1 , Y^2 , and Y^3 is aryl or heteroaryl;

further provided that L^A cannot include a cyclic group directly attached to the 6-
 membered ring containing Y^1 , Y^2 , and Y^3 ;

each occurrence of R^1 and R^5 is independently selected from the group consisting
 15 of: H; R^c ; R^g ; and $-(L^g)_{hg}-R^g$;

each occurrence of R^2 and R^4 is independently selected from the group consisting
 of: H; R^d ; R^g ; and $-(L^g)_{hg}-R^g$;

R^6 is selected from the group consisting of: H; R^d ; and R^g ;

20

W is selected from the group consisting of:

- H;
- C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl, each of which is optionally
 25 substituted with 1-6 R^{a2} , wherein one or more of the internal optionally substituted
 methylene group can be replaced by one or more heteroatom selected from O or S, wherein
 when W is alkenyl or alkynyl, the heteroatom is not directed connected to the sp^2 or sp
 carbon;
- monocyclic C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl, each of which is optionally
 30 substituted with 1-4 substituents independently selected from the group consisting of oxo
 and R^c ; and

- monocyclic heterocyclyl or heterocycloalkenyl of 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**,

provided that when **W** is heterocyclyl or heterocycloalkenyl, it is attached to the C(=O)NR⁶ group via a ring carbon atom;

- each occurrence of **R^a** and **R^{a2}** is independently selected from the group consisting of: -OH; -halo; -NR^eR^f; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -C(=O)O(C₁₋₄ alkyl); -C(=O)(C₁₋₄ alkyl); -C(=O)OH; -CONR'R''; -S(O)₁₋₂NR'R''; -S(O)₁₋₂(C₁₋₄ alkyl); and cyano;

- each occurrence of **R^b** and **R^c** is independently selected from the group consisting of: halo; cyano; C₁₋₁₀ alkyl which is optionally substituted with 1-6 independently selected **R^a**; C₂₋₆ alkenyl; C₂₋₆ alkynyl; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -S(O)₁₋₂(C₁₋₄ alkyl); -S(O)(=NH)(C₁₋₄ alkyl); -NR^eR^f; -OH; -S(O)₁₋₂NR'R''; -C₁₋₄ thioalkoxy; -NO₂; -C(=O)(C₁₋₁₀ alkyl); -C(=O)O(C₁₋₄ alkyl); -C(=O)OH; -C(=O)NR'R''; -NR'C(=O)(C₁₋₄ alkyl) and -SF₅;

- each occurrence of **R^d** is independently selected from the group consisting of: C₁₋₆ alkyl optionally substituted with 1-3 independently selected **R^a**; -C(O)(C₁₋₄ alkyl); -C(O)O(C₁₋₄ alkyl); -CONR'R''; -S(O)₁₋₂NR'R''; -S(O)₁₋₂(C₁₋₄ alkyl); -OH; and C₁₋₄ alkoxy;

- each occurrence of **R^e** and **R^f** is independently selected from the group consisting of: H; C₁₋₆ alkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of NR'R'', -OH, halo, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy; -C(O)(C₁₋₄ alkyl); -C(O)O(C₁₋₄ alkyl); -CONR'R''; -S(O)₁₋₂NR'R''; -S(O)₁₋₂(C₁₋₄ alkyl); -OH; and C₁₋₄ alkoxy;

each occurrence of **R^g** is independently selected from the group consisting of:

- C₃₋₁₂ cycloalkyl or C₃₋₁₂ cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, **R^c**, and **R^h**;

- heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, **R^c**, and **R^h**;

- heteroaryl of 5-12 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, **R^c**, and **R^h**; and

- C₆₋₁₀ aryl optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, **R^c**, and **R^h**;

each occurrence of **R^h** is independently selected from the group consisting of:

- C₃₋₁₂ cycloalkyl or C₃₋₁₂ cycloalkenyl, each of which is optionally substituted with 1-4 **Rⁱ**;
- heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 **Rⁱ**;
- heteroaryl of 5-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S(O)₀₋₂, and wherein the heteroaryl is optionally substituted with 1-4 **Rⁱ**; and
- C₆₋₁₀ aryl optionally substituted with 1-4 **Rⁱ**;

each occurrence of **Rⁱ** is independently selected from the group consisting of: C₁₋₆ alkyl; C₁₋₄ haloalkyl; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; and halo;

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each occurrence of L^g is independently selected from the group consisting of: -O-, -NH-, $-NR^d$, $-S(O)_{0-2}$, C(O), and C_{1-3} alkylene optionally substituted with 1-3 R^a ;

each occurrence of bg is independently 1, 2, or 3; and

5 each occurrence of R' and R'' is independently selected from the group consisting of: H; -OH; and C_{1-4} alkyl.

2. The compound of claim 1, wherein $a2$ is 1.

10 3. The compound of claims 1 or 2, wherein L^2 is straight-chain C_{1-6} alkylene, straight-chain C_{2-6} alkenylene, or straight-chain C_{2-6} alkynylene, each of which is optionally substituted with 1-6 R^b ,

optionally wherein L^2 is straight-chain C_{1-6} alkylene, which is optionally substituted with 1-6 R^b ;

15 optionally wherein L^2 is straight-chain C_{1-3} alkylene, which is optionally substituted with 1-3 R^b .

4. The compound of claims 1 or 2, wherein L^2 is selected from the group consisting of:

• C_{3-10} cycloalkylene or C_{3-10} cycloalkenylene, each of which is optionally substituted with 1-3 R^c ; and

• heterocyclylene or heterocycloalkenylene, each having 4-10 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), $N(R^d)$, O, and $S(O)_{0-2}$, wherein the heterocyclylene or heterocycloalkenylene is optionally substituted with 1-3 R^c .

5. The compound of any one of claims 1-4, wherein $a1$ is 1.

30 6. The compound of any one of claims 1-5, wherein L^1 is selected from the group consisting of: -O-, -N(H)-, $-N(R^d)$ -, and -S-,

optionally wherein L^1 is $-O-$.

7. The compound of any one of claims 1-3, wherein $a1$ is 0.

5 8. The compound of any one of claims 1-7, wherein $a3$ is 1.

9. The compound of any one of claims 1-8, wherein L^3 is selected from the group consisting of: $-O-$, $-N(H)-$, $-N(R^d)-$, and $-S-$,
optionally wherein L^3 is $-O-$.

10

10. The compound of any one of claims 1-7, wherein $a3$ is 0.

11. The compound of any one of claims 1-10, wherein $a4$ is 1.

15

12. The compound of claim 1, wherein:
 $a1$ and $a2$ are each 1;

optionally, wherein:

$a1$ and $a2$ are each 1;

20

L^1 is $-O-$, $-N(H)-$, or $-N(R^d)-$; and

L^2 is selected from the group consisting of:

- straight-chain C_{1-3} alkylene, which is optionally substituted with 1-3 R^b ;
- C_{3-8} cycloalkylene, which is optionally substituted with 1-3 R^c ; and
- heterocyclylene having 4-8 ring atoms wherein 1-3 ring atoms are ring

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heteroatoms each independently selected from the group consisting of: N, N(H), $N(R^d)$, O, and $S(O)_{0-2}$, wherein the heterocyclylene is optionally substituted with 1-3 R^c ;

optionally wherein:

$a1$ and $a2$ are each 1;

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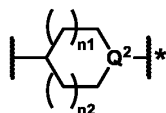
L^1 is $-O-$; and

L^2 is straight-chain C_{1-3} alkylene, which is optionally substituted with 1-3 R^b ;

optionally wherein:

a1 and **a2** are each 1;

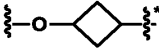
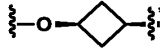
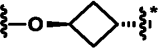
L¹ is -O-; and **L²** is C₃₋₈ cycloalkylene, which is optionally substituted with 1-3 **R^c**;



optionally wherein **L²** is: which is optionally substituted with 1-2 **R^c**, wherein **n1** and **n2** are independently 0, 1, or 2; **Q²** is CH, CR^c, or N; and the asterisk represents the point of attachment to -(L³)_{a3}-;

optionally wherein **n1** and **n2** are independently 0 or 1, optionally 0; and **Q²** is CH; optionally wherein **n1** and **n2** are 0 and **Q²** is CH; optionally wherein **L²** is cyclobutane-diyl optionally substituted with 1-2 **R^c**; optionally wherein **L²** is cyclobutane-1,3-diyl optionally substituted with 1-2 **R^c**; optionally wherein **L²** is unsubstituted cyclobutane-diyl; optionally wherein **L²** is unsubstituted cyclobutane-1,3-diyl.

13. The compound of claim 12, wherein **a3**, **a4**, and **a5** are each 0, optionally

wherein **L^A** is -O-CH₂CH₂-, or  (such as  or ), wherein * represents the point of attachment to **Q¹**.

14. The compound of claim 1, wherein **a1** is 0; **a2** is 1; optionally wherein **L²** is straight-chain C₁₋₆ alkylene, which is optionally substituted with 1-6 **R^b**,

optionally wherein **L²** is straight-chain C₁₋₃ alkylene, which is optionally substituted with 1-3 **R^b**.

15. The compound of claim 14, wherein **a3** is 1; optionally, wherein **L³** is selected from the group consisting of: is -O-, -N(H)-, and -N(**R^d**)-, optionally wherein **L³** is -O-.

16. The compound of claims 14 or 15, wherein **a4** is 0; and **a5** is 0.

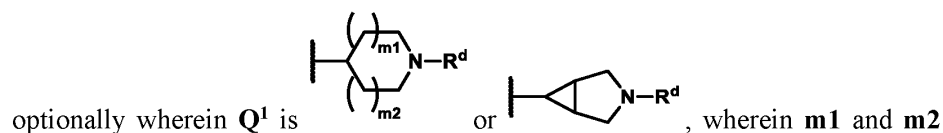
17. The compound of any one of claims 1-16, wherein **Q¹** is selected from the group consisting of:

- heteroaryl of 5-6 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heteroaryl is optionally substituted with 1-3 R^c; and
- phenyl optionally substituted with 1-3 R^c.

5

18. The compound of any one of claims 1-16, wherein Q¹ is heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)₀₋₂, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c;

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optionally wherein each R^d present in Q¹ is independently selected from the group consisting of: -C(O)O(C₁₋₄ alkyl); and C₁₋₆ alkyl optionally substituted with 1-3 independently selected R^a.

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19. The compound of any one of claims 1-18, wherein Y¹ is CR¹; Y² is CR¹; and/or Y³ is CR¹.

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20. The compound of any one of claims 1-19, wherein Y¹, Y², and Y³ are each CH.

21. The compound of any one of claims 1-20, wherein X¹ is NR²; and X² is CR⁵; optionally wherein X¹ is NH; and X² is CH.

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22. The compound of any one of claims 1-21, wherein R⁶ is H.

23. The compound of any one of claims 1-22, wherein W is:

(i) C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkenyl, each of which is optionally substituted with 1-6 R^{a2}, wherein one or more of the internal optionally substituted methylene group can be replaced by one or more heteroatom selected from O or S, wherein when **W** is alkenyl or alkynyl, the heteroatom is not directed connected to the *sp*² or *sp* carbon;

optionally C₁₋₁₀ alkyl, which is optionally substituted with 1-6 R^{a2}; optionally C₁₋₄ alkyl, which is optionally substituted with 1-6 R^{a2}.

24. The compound of any one of claims 1-22, wherein **W** is:

(i) monocyclic C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c;

optionally monocyclic C₃₋₈ cycloalkyl, which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and R^c.

25. The compound of claim 1, wherein the compound is selected from the group consisting of the compounds delineated in **Table C1** or a pharmaceutically acceptable salt thereof.

26. A pharmaceutical composition comprising a compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

27. A method for inhibiting STING activity, the method comprising contacting STING with a compound as claimed in any one of claims 1-25, or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition as claimed in claim 26.

28. A method of inducing an immune response in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound as claimed in any one of claims 1-25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as claimed in claim 26.

29. A method of treatment of disease, disorder, or condition associated with STING, such as a disease, disorder, or condition, in which increased STING signaling, such as excessive STING signaling, contributes to the pathology and/or symptoms and/or progression of the disease, such as cancer, comprising administering to a subject in need
5 of such treatment an effective amount of a compound as claimed in any one of claims 1-24, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as claimed in claim 25.

30. A combination comprising a compounds defined in any one of claims 1-25
10 or a pharmaceutically acceptable salt or tautomer thereof, and one or more therapeutically active agents.

31. A compound defined in any one of claims 1-25 or a pharmaceutically acceptable salt or tautomer thereof, or a pharmaceutical composition defined in claim 26,
15 for use as a medicament.

32. A compound defined in any one of clauses 1-25 or a pharmaceutically acceptable salt or tautomer thereof, or a pharmaceutical composition defined in claim 26,
20 for use in the treatment of a disease, condition or disorder modulated by STING inhibition.