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(54) Title: INHIBITORS OF THE SURFACE EXPRESSION OF THE VOLTAGE-GATED SODIUM ION CHANNEL 1.7 (NAV1.7) AND THEIR THERAPEUTIC USES

(57) Abstract: The disclosure provides compounds that indirectly interfere voltage-gated sodium ion channel 1.7 (Nav1.7) function by selectively modulating the trafficking of Nav1.7 to the plasma membrane of nociceptive neurons. Unlike direct blockers of Nav1.7 that bind to Nav1.7, the compounds of the disclosure do not affect the function of other voltage-gated sodium ion channels. The compounds can be used to treat a wide variety of pain and pain-associated disorders. Compared to opioids, the compounds have much less potential to cause addiction or physical dependence.



Inhibitors of the Surface Expression of the Voltage-Gated Sodium Ion Channel 1.7 (Nav1.7) and Their Therapeutic Uses

Cross-Reference to Related Applications

[0001] This application claims benefit of priority from U.S. Provisional Application No. 63/610,632, filed on December 15, 2023, which is incorporated by reference herein in its entirety.

Statement of Government Support

[0002] This invention was made in part with government support from the US Department of Health and Human Services, National Institutes of Health. The government has certain rights in the invention.

Background of the Disclosure

[0003] The voltage-gated sodium ion channel 1.7 (Nav1.7) plays an important role in the generation and conduction of action potentials by most excitable cells. Nav1.7 is usually expressed at high levels at the endings of pain-sensing neurons (nociceptors) whose cell bodies are located in the dorsal root ganglia (DRG) or the trigeminal ganglia, and in sympathetic ganglia neurons of the autonomic nervous system. Stimulation of nociceptor nerve endings produces a “generator potential” that is amplified by Nav1.7. When the membrane potential difference reaches a certain threshold, the nociceptive neurons fire. Therefore, Nav1.7 plays a critical role in the transmission of acute pain and chronic pain.

[0004] For example, chemotherapy and nerve injury often induce chronic peripheral neuropathy. The neuropathic pain develops along dermatomes innervated by peripheral nerves whose cell bodies are located in the DRG. Nav1.7 is expressed at high levels in peripheral nerve tissues and plays a critical role in the transmission of acute and chronic neuropathic pain.

[0005] Because Nav1.7 is not present in heart tissue or the central nervous system, a selective blocker of Nav1.7 can potentially be safely used systemically for pain relief without affecting cardiac electrical activity and without causing addiction or physical dependence. However, direct blockers of Nav1.7 that bind to Nav1.7 have not succeeded in clinical trials to date, in part because many of them also block other voltage-gated sodium ion channels and thus have significant side effects.

Summary of the Disclosure

[0006] The present disclosure describes compounds that indirectly inhibit Nav1.7 by selectively inhibiting the expression of Nav1.7 on the surface of nociceptive neurons. The compounds selectively inhibit conjugation of the protein small ubiquitin-like modifier 2 (SUMO2) to the cytosolic collapsin response mediator protein 2 (CRMP2) by the E2 SUMO-conjugating enzyme Ubc9. CRMP2 SUMOylation is essential for trafficking of Nav1.7 to the surface of nociceptive neurons. By selectively inhibiting CRMP2 SUMOylation and hence trafficking of Nav1.7 to the plasma membrane of nociceptive neurons, the compounds selectively inhibit Nav1.7 currents and thus pain signaling without affecting the function of other voltage-gated sodium ion channels including Nav1.1, Nav1.2, Nav1.3, Nav1.4, Nav1.5, Nav1.6, Nav1.8 and Nav1.9. The compounds can be used to treat a wide variety of pain and pain-associated disorders. Compared to opioids, the compounds described herein have much less potential to cause addiction or physical dependence.

Brief Description of the Drawings

[0007] A better understanding of features and advantages of the present disclosure will be obtained by reference to the following detailed description, which sets forth illustrative embodiments of the disclosure, and the accompanying drawings. The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon receipt and payment of the necessary fee.

[0008] **Figs. 1A-D** show that 10 mg/kg of intraperitoneally (i.p.) administered Compound **193** and Compound **215** markedly reduced both tactile allodynia (**Figs. 1A** and **B**) and cold allodynia (**Figs. 1C** and **D**) in 8 week-old, male C57BL/6J mice in a model of neuropathic pain. Compound **193** and Compound **215** reduced the tactile and cold allodynia in male neuropathic mice. **Fig. 1A**: Effect of the intraperitoneal administration of compounds on the tactile allodynia. **Fig. 1B**: Area under the curve of the antiallodynic effect induced by compounds. **Fig. 1C**: Effect of the intraperitoneal administration of compounds on the cold allodynia. **Fig. 1D**: Area under the curve of the antiallodynic effect induced by compounds. Data are presented as the mean $\pm$ SEM (n= 8 animals per group). In **Fig. 1B** and **Fig. 1D** ***P<0.001 vs vehicle group, as determined by one-way ANOVA followed by the Dunnett's test.

[0009] **Figs. 2A-D** show that 10 mg/kg of i.p. administered Compound **193** markedly reduced both tactile allodynia (**Figs. 2A** and **B**) and cold allodynia (**Figs. 2C** and **D**) in 8 week-old,

female C57BL/6J mice in the model of neuropathic pain. Compound **193** and Compound **215** reduced the tactile and cold allodynia in female neuropathic mice. **Fig. 2A**: Effect of the intraperitoneal administration of compounds on the tactile allodynia. **Fig. 2B**: Area under the curve of the antiallodynic effect induced by compounds. **Fig. 2C**: Effect of the intraperitoneal administration of compounds on the cold allodynia. **Fig. 2D**: Area under the curve of the antiallodynic effect induced by compounds. Data are presented as the mean $\pm$ SEM (n= 8 animals per group). In **Fig. 2B and Fig. 2D** ***P<0.001 vs vehicle group, as determined by one-way ANOVA followed by the Dunnett's test.

[0010] **Figs. 3A-D** show that i.p. administered Compound **193** reduced both tactile allodynia (**Figs. 3A and B**) and cold allodynia (**Figs. 3C and D**) in male mice in a dose-dependent manner. Compound **193** reduced the tactile and cold allodynia in a dose-dependent manner in male neuropathic mice. **Fig. 3A**: Effect of the intraperitoneal administration of Compound **193** on the tactile allodynia. **Fig. 3B**: Area under the curve of the antiallodynic effect induced by Compound **193**. **Fig. 3C**: Effect of the intraperitoneal administration of Compound **193** on the cold allodynia. **Fig. 3D**: Area under the curve of the antiallodynic effect induced by Compound **193**. Data are presented as the mean $\pm$ SEM (n= 8 animals per group). In **Fig. 3B and Fig. 3D** ***P<0.001 vs vehicle group, as determined by one-way ANOVA followed by the Dunnett's test.

[0011] **Figs. 4A and B** show that i.p. administered Compound **215** reduced cold allodynia (**Fig. 4B**) in male mice in a dose-dependent manner while its effect on tactile allodynia (**Fig. 4A**) was less dose-dependent.

[0012] **Figs. 5A-D** show that i.p. administered Compound **193** reduced both tactile allodynia (**Figs. 5A and B**) and cold allodynia (**Figs. 5C and D**) in female mice in a dose-dependent manner. Compound **193** reduced the tactile and cold allodynia in a dose-dependent manner in female neuropathic mice. **Fig. 5A**: Effect of the intraperitoneal administration of Compound **193** on the tactile allodynia. **Fig. 5B**: Area under the curve of the antiallodynic effect induced by Compound **193**. **Fig. 5C**: Effect of the intraperitoneal administration of Compound **193** on the cold allodynia. **Fig. 5D**: Area under the curve of the antiallodynic effect induced by Compound **193**. Data are presented as the mean $\pm$ SEM (n= 8 animals per group). In **Fig. 5B and Fig. 5D** ***P<0.001 vs vehicle group, as determined by one-way ANOVA followed by the Dunnett's test.

[0013] **Figs. 6A-D** show that representative compounds reduced the tactile and cold allodynia in male neuropathic mice. **Fig. 6A**: Effect of the intraperitoneal administration of compounds on the tactile allodynia. **Fig. 6B**: Area under the curve of the antiallodynic effect induced by compounds. **Fig. 6C**: Effect of the intraperitoneal administration of compounds on the cold allodynia. **Fig. 6D**: Area under the curve of the antiallodynic effect induced by compounds. Data are presented as the mean $\pm$ SEM (n= 8 animals per group). In **Fig. 6B and Fig. 6D** ***P<0.001 vs vehicle group, as determined by one-way ANOVA followed by the Dunnett's test.

[0014] **Figs. 7A-D** show that Compound **193** and Compound **261** reduced the tactile and cold allodynia in a comparison with Gabapentin (30 mg/kg) in male neuropathic mice. **Fig. 7A**: Effect of the intraperitoneal administration of compounds on the tactile allodynia **Fig. 7B** Area under the curve of the antiallodynic effect induced by compounds. **Fig. 7C**: Effect of the intraperitoneal administration of compounds on the cold allodynia. **Fig. 7D**: Area under the curve of the antiallodynic effect induced by compounds. Data are presented as the mean $\pm$ SEM (n= 8 animals per group). In **Figs. 7B and 7D** ***P<0.001 vs vehicle group, as determined by one-way ANOVA followed by the Dunnett's test.

Detailed Description of the Disclosure

General Disclosure

[0015] While various embodiments of the present disclosure are described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous modifications and changes to, and variations and substitutions of, the embodiments described herein will be apparent to those skilled in the art without departing from the disclosure. It is understood that various alternatives to the embodiments described herein can be employed in practicing the disclosure. It is also understood that every embodiment of the disclosure can optionally be combined with any one or more of the other embodiments described herein which are consistent with that embodiment.

[0016] Where a combination is disclosed, it is understood that each possible subcombination of the elements of that combination is also disclosed. Conversely, where different elements or groups of elements are individually disclosed, combinations thereof are also disclosed.

[0017] Where elements are presented in list format or as alternative members of a group (e.g., a Markush group), it is understood that each possible subgroup of the elements is also disclosed, and any one or more elements can be removed from the list or group.

[0018] Where a range of numerical values is recited, it is understood that the endpoints and each intervening integer value and each fraction thereof, as well as each subrange, between the recited endpoints (upper and lower limits) of that range are specifically disclosed. The endpoints of all ranges are included within the range and are independently combinable. Where a value has an inherent limit, that inherent limit is specifically disclosed. Where a value is explicitly recited, it is understood that values which are about the same as the recited value are specifically disclosed.

[0019] It is also understood that, unless clearly indicated to the contrary, in any method described or claimed herein that includes more than one act or step, the order of the acts or steps of the method is not necessarily limited to the order in which the acts or steps of the method are recited, but the disclosure encompasses embodiments in which the order is so limited.

[0020] It is further understood that, in general, where an embodiment in the description or the claims is referred to as comprising one or more features, the disclosure also encompasses embodiments that consist of, or consist essentially of, such feature(s).

[0021] It is also understood that any embodiment of the disclosure, e.g., any embodiment or compound found within the prior art, can be explicitly excluded from the claims, regardless of whether or not the specific exclusion is recited in the specification.

[0022] In addition, it is understood that any functional language used in any claims shall not be construed as “means-plus-function” language under 35 U.S.C. §112(f), unless specifically expressed as such by use of the term “means for” or “step(s) for” in a claim.

[0023] It is further understood that the present disclosure encompasses analogs, derivatives, prodrugs, metabolites, salts, solvates, hydrates, clathrates, isotopes, or isotopic forms including deuterated and tritiated forms, and polymorphs of all the compounds/substances disclosed herein, as appropriate. The specific recitation of “analogs”, “derivatives”, “prodrugs”, “metabolites”, “salts”, “solvates”, “hydrates”, “clathrates” or “polymorphs” with respect to a compound/substance or a group of compounds/substances in certain instances of the disclosure shall not be interpreted as an intended omission of any of these forms in other instances of the disclosure where the compound/substance or the group of compounds/substances is mentioned or shown without recitation of any of these forms, unless stated otherwise or the context clearly indicates otherwise.

[0024] It is also understood that the present disclosure encompasses all possible tautomers, all possible regioisomers, and all possible stereoisomers, including both enantiomers and all

possible diastereomers in substantially pure form and mixtures of both enantiomers in any ratio (including a racemic mixture of enantiomers) and mixtures of two or more diastereomers in any ratio, of the compounds/substances described herein as appropriate, and not only the specific tautomers, regioisomers and stereoisomers as indicated by drawn structure or nomenclature. Some embodiments of the disclosure relate to the specific tautomers, regioisomers and stereoisomers indicated by drawn structure or nomenclature. The specific recitation of the phrase “or tautomers thereof”, “or regioisomers thereof”, “or stereoisomers thereof” or the like with respect to a compound/substance or a group of compounds/substances in certain instances of the disclosure shall not be interpreted as an intended omission of any of the other possible tautomers, regioisomers and stereoisomers of the compound/substance or the group of compounds/substances in other instances of the disclosure where the term “compound” or the like is used, or where the compound/substance or the group of compounds/substances is mentioned or shown, without recitation of the phrase “or tautomers thereof”, “or regioisomers thereof”, “or stereoisomers thereof” or the like, unless stated otherwise or the context clearly indicates otherwise.

[0025] Headings are included herein for reference and to aid in locating certain sections. Headings are not intended to limit the scope of the embodiments and concepts described in the sections under those headings, and those embodiments and concepts may have applicability in other sections throughout the entire disclosure.

[0026] All patent literature and all non-patent literature cited herein are incorporated herein by reference in their entirety to the same extent as if each patent literature or non-patent literature were specifically and individually indicated to be incorporated herein by reference in its entirety.

Definitions

[0027] Unless defined otherwise or clearly indicated otherwise by their use herein, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which this application belongs.

[0028] As used in the specification and the claims, the indefinite articles “a” and “an” and the definite article “the” can include plural referents as well as singular referents unless specifically stated otherwise or the context clearly indicates otherwise.

[0029] The terms “or/and” and “and/or” mean “either ... or ..., or both ... and ...” when referring to two elements, and mean “either ..., ... or ..., or any combination or all thereof”

when referring to three or more elements. As an example, the phrase “A or/and B” means “either A or B, or both A and B”, and the phrase “A, B or/and C” means “either A, B or C, or any combination or all thereof”.

[0030] As used in the specification and the claims, all transitional terms such as “comprising”, “containing”, “having”, “including”, “possessing”, “holding”, “carrying”, “bearing”, “composed of”, “characterized by” and the like are open-ended and inclusive, that is, mean including but not limited to and do not exclude additional, unrecited element(s) or method step(s). Only the transitional term “consisting of” is closed, that is, excludes any additional, unrecited element or method step, and the transitional term “consisting essentially of” is semi-closed, that is, only allows inclusion of additional, unrecited element(s) or method step(s) that do not materially affect the basic and novel characteristic(s) of that particular embodiment.

[0031] The term “exemplary” as used herein means “serving as an example, instance or illustration”. Any embodiment or feature characterized herein as “exemplary” should not be construed as preferred or advantageous over other embodiments or features.

[0032] The term “about” or “approximately” means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term “about” or “approximately” means within one standard deviation. In some embodiments, when no particular margin of error (e.g., a standard deviation to a mean value given in a chart or table of data) is recited, the term “about” or “approximately” means that range which would encompass the recited value and the range which would be included by rounding up or down to the recited value as well, taking into account significant figures. In certain embodiments, the term “about” or “approximately” means within $\pm 10\%$ or 5% of the specified value. Whenever the term “about” or “approximately” precedes the first numerical value in a series of two or more numerical values or in a series of two or more ranges of numerical values, the term “about” or “approximately” applies to each one of the numerical values in that series of numerical values or in that series of ranges of numerical values.

[0033] In some embodiments, the term “substantially all” means at least about 90%, 95%, 96%, 97%, 98% or 99%. In some embodiments, the term “substantially free” means no more than about 10%, 5%, 4%, 3%, 2% or 1% by weight or molarity, or no more than about 1000 ppm, 500 ppm, 400 ppm, 300 ppm, 200 ppm or 100 ppm.

[0034] In some embodiments, the term “substantially pure” means at least about 90%, 95%, 96%, 97%, 98% or 99% pure. In some embodiments, the term “substantially stereochemically pure” means at least about 80% enantiomeric excess (90% of one enantiomer – 10% of the other enantiomer) or 90% enantiomeric excess (95% of one enantiomer – 5% of the other enantiomer), or at least about 80% diastereomeric excess (90% of one diastereomer – 10% of all the other diastereomers) or at least about 90% diastereomeric excess (95% of one diastereomer – 5% of all the other diastereomers).

[0035] Whenever the term “at least” or “greater than” precedes the first numerical value in a series of two or more numerical values, the term “at least” or “greater than” applies to each one of the numerical values in that series of numerical values.

[0036] Whenever the term “no more than” or “less than” precedes the first numerical value in a series of two or more numerical values, the term “no more than” or “less than” applies to each one of the numerical values in that series of numerical values.

[0037] The term “pharmaceutically acceptable” means that a substance (e.g., an active ingredient or an excipient) is generally safe, non-toxic and suitable for use in contact with the cells, tissues and organs of a subject without excessive irritation, allergic response, immunogenicity and other adverse reaction. A “pharmaceutically acceptable” excipient or carrier of a pharmaceutical composition is also compatible with the other ingredients of the composition.

[0038] The term “therapeutically effective amount” refers to an amount of a compound that, when administered to a subject or used *ex vivo*, is sufficient to prevent, reduce the risk of developing, delay the onset of, slow the progression of or cause regression of the medical condition being treated, or to alleviate or ameliorate to some extent the medical condition or one or more symptoms or complications of that condition, at least in some fraction of the subjects taking that compound or undergoing *ex vivo* treatment with that compound. The term “therapeutically effective amount” also refers to an amount of a compound that is sufficient to elicit the biological or medical response of a cell, tissue, organ, system, animal or human which is sought by a researcher, veterinarian, medical doctor or clinician.

[0039] The terms “treat”, “treating” and “treatment” include alleviating, ameliorating, reducing the incidence, frequency or severity of, slowing or stopping the progress of, reversing or abrogating a medical condition or one or more symptoms or complications associated with the condition, and alleviating, ameliorating or eradicating one or more causes of the condition.

Reference to “treatment” of a medical condition includes prevention of the condition. The terms “prevent”, “preventing” and “prevention” include precluding, reducing the risk or likelihood of developing, and delaying the onset of a medical condition or one or more symptoms or complications associated with the condition.

[0040] The term “medical conditions” (or “conditions” for brevity) includes diseases and disorders. The terms “diseases” and “disorders” are used interchangeably herein.

[0041] The term “subject” refers to an animal, including but not limited to a mammal, such as a primate (e.g., a human, a chimpanzee or a monkey), a rodent (e.g., a rat, a mouse, a guinea pig, a gerbil or a hamster), a lagomorph (e.g., a rabbit), a bovine (e.g., a cattle), a suid (e.g., a pig), a caprine (e.g., a sheep), an equine (e.g., a horse), a canine (e.g., a dog) or a feline (e.g., a cat). The terms “subject” and “patient” may be used interchangeably herein in reference to a subject/patient (e.g., a mammalian subject/patient such as a human subject/patient) having a medical condition.

[0042] A “modulator” of, e.g., a receptor or enzyme can be an activator or inhibitor of that receptor or enzyme, and can increase or reduce the activity or/and the level of that receptor or enzyme.

[0043] The term “compound” or the like (e.g., “molecule”) encompasses salts, solvates, hydrates, clathrates and polymorphs of that compound or a salt of that compound. A “solvate” of a compound comprises a stoichiometric or non-stoichiometric amount of a solvent molecule (e.g., water, acetone or an alcohol [e.g., ethanol]) bound non-covalently to the compound. A “hydrate” of a compound comprises a stoichiometric or non-stoichiometric amount of water molecule bound non-covalently to the compound. A “clathrate” of a compound contains molecules of a substance (e.g., a solvent) enclosed in a crystal structure of the compound. A “polymorph” of a compound is a crystalline form of the compound. The specific recitation of “salt”, “solvate”, “hydrate”, “clathrate” or “polymorph” with respect to a compound or a group of compounds in certain instances of the disclosure shall not be interpreted as an intended omission of any of these forms in other instances of the disclosure where the term “compound” or the like (e.g., “molecule”) is used, or where the compound or the group of compounds is mentioned or shown, without recitation of any of these forms, unless stated otherwise or the context clearly indicates otherwise.

[0044] The terms “halogen”, “halide” and “halo” refer to fluoride, chloride, bromide and iodide.

[0045] The term “alkyl” refers to a linear or branched, saturated monovalent hydrocarbon radical, wherein the alkyl group can optionally be substituted with one or more substituents as described herein. In certain embodiments, an alkyl group is a linear saturated monovalent hydrocarbon radical that has 1 to 10 (C_{1-10}) or 1 to 6 (C_{1-6}) carbon atoms, or is a branched saturated monovalent hydrocarbon radical that has 3 to 10 (C_{3-10}) or 3 to 6 (C_{3-6}) carbon atoms. As an example, the term “ C_{1-6} alkyl” refers to a linear saturated monovalent hydrocarbon radical of 1 to 6 carbon atoms or a branched saturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. Linear C_{1-6} and branched C_{3-6} alkyl groups may also be referred to as “lower alkyl”. Non-limiting examples of alkyl groups include methyl, ethyl, propyl (including n-propyl and isopropyl), butyl (including all isomeric forms, such as n-butyl, isobutyl, *sec*-butyl and *tert*-butyl), pentyl (including all isomeric forms, such as n-pentyl and isopentyl), and hexyl (including all isomeric forms, such as n-hexyl).

[0046] The terms “alkylene” and “-alkyl-” refer to a divalent alkyl group, which can optionally be substituted with one or more substituents as described herein.

[0047] The term “haloalkyl” refers to an alkyl group that is substituted with one or more halide atoms. A haloalkyl group can optionally be substituted with one or more additional substituents as described herein. Examples of haloalkyl groups include without limitation fluoroalkyl groups such as $-CH_2F$, $-CHF_2$, $-(CH_2)_nCHF_2$ and $-(CH_2)_nCF_3$, and perfluoroalkyl groups such as $-CF_3$ and $-(CF_2)_nCF_3$, wherein n is 1, 2, 3, 4 or 5.

[0048] The term “heteroalkyl” refers to a linear or branched, saturated monovalent hydrocarbon group containing one or more heteroatoms independently selected from O, N and S. In some embodiments, one or more heteroatoms are in the main chain of the linear or branched hydrocarbon group. The terms “heteroalkylene” and “-heteroalkyl-” refer to a divalent heteroalkyl group. A heteroalkyl group and a -heteroalkyl- group can optionally be substituted with one or more substituents as described herein. Examples of heteroalkyl and -heteroalkyl- groups include without limitation $-(CH_2)_m-(O \text{ or } S)-(CH_2)_nCH_3$ and $-(CH_2)_m-(O \text{ or } S)-(CH_2)_p-$, wherein m is 1, 2 or 3, n is 0, 1 or 2, and p is 1, 2 or 3.

[0049] The term “alkoxy” refers to an -O-alkyl group, which can optionally be substituted with one or more substituents as described herein.

[0050] The term “haloalkoxy” refers to an -O-haloalkyl group, which can optionally be substituted with one or more substituents as described herein.

[0051] Examples of -O-heteroalkyl and -O-heteroalkyl- groups include without limitation ethylene glycol groups and polyethylene glycol (PEG) groups, including but not limited to - $(\text{OCH}_2\text{CH}_2)_n\text{-OR}$ and $-(\text{OCH}_2\text{CH}_2)_n\text{-O-}$, wherein R is hydrogen or alkyl and n is 1, 2 or 3. An -O-heteroalkyl group and an -O-heteroalkyl- group can optionally be substituted with one or more substituents as described herein.

[0052] The term “cycloalkyl” refers to a cyclic saturated or partially unsaturated, bridged or non-bridged monovalent hydrocarbon radical, which can optionally be substituted with one or more substituents as described herein. In certain embodiments, a cycloalkyl group has from 3 to 10 (C_{3-10}), or from 3 to 8 (C_{3-8}), or from 3 to 6 (C_{3-6}) carbon atoms. Non-limiting examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, norbornyl, decalynyl and adamantyl. The term “-cycloalkyl-” refers to a divalent cycloalkyl group, which can optionally be substituted with one or more substituents as described herein.

[0053] The terms “heterocyclyl” and “heterocyclic” refer to a monocyclic non-aromatic group or a multicyclic group that contains at least one non-aromatic ring, wherein at least one non-aromatic ring contains one or more heteroatoms independently selected from O, N and S. The non-aromatic ring containing one or more heteroatoms may be attached or fused to one or more saturated, partially unsaturated or aromatic rings that may contain only ring carbon atoms or that may contain one or more ring heteroatoms. In certain embodiments, a heterocyclyl or heterocyclic group has from 3 to 15, or 3 to 12, or 3 to 10, or 3 to 8, or 3 to 6 ring atoms. In some embodiments, a heterocyclyl or heterocyclic group is a monocyclic, bicyclic or tricyclic ring system, which may include a fused or bridged ring system, and in which nitrogen or sulfur atoms can optionally be oxidized, nitrogen atoms can optionally be quaternized, and one or more rings may be fully or partially saturated, or aromatic. A heterocyclyl or heterocyclic group may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of heterocyclyl or heterocyclic groups include without limitation azepanyl, azepinyl, azetidiny, aziridinyl, azocanyl, benzodioxanyl (e.g., 1,4-benzodioxanyl), benzodioxolyl (e.g., 1,3-benzodioxolyl), benzofuranonyl, benzopyranonyl, benzopyranyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, benzothiopyranyl, β -carboline, chromanyl, decahydroisoquinolinyl, dihydrobenzothiazinyl, dihydrobenzoxazinyl, dihydrofuryl, dihydropyranyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrazolyl, dihydropyrimidinyl, dihydropyrrolyl, dioxolanyl, dithianyl, furanonyl, imidazolidinyl,

imidazoliny, indoliny, indoliziny, isobenzotetrahydrofurany, isobenzotetrahydrothieny, isochromany, isoindoliny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindoliny, octahydroisoindoliny, oxazolidinony, oxazolidiny, oxepany, oxetany, oxirany, oxocany, piperaziny, piperidiny, 4-piperidony, pyrrolidiny, pyrroliny, quinuclidiny, tetrahydrofury, tetrahydrofurany (oxolany), tetrahydroisoquinoliny, tetrahydropyrany, tetrahydrothieny (tetrahydrothiopheny or thiolany), thiamorpholiny (thiomorpholiny), thiazolidiny and 1,3,5-trithiany. The term “-heterocyclyl-” refers to a divalent heterocyclyl group. A heterocyclyl or heterocyclic group, and a -heterocyclyl- group, can optionally be substituted with one or more substituents as described herein.

[0054] The term “aryl” refers to a monocyclic aromatic hydrocarbon group or a multicyclic group that contains at least one aromatic hydrocarbon ring. In certain embodiments, an aryl group has from 6 to 15, or 6 to 12, or 6 to 10 ring atoms. Non-limiting examples of aryl groups include phenyl, naphthyl, fluorenyl, azuleny, anthryl, phenanthryl, biphenyl and terphenyl. The aromatic hydrocarbon ring of an aryl group may be attached or fused to one or more saturated, partially unsaturated or aromatic rings that may contain only ring carbon atoms (e.g., biphenyl, dihydronaphthyl, indenyl, indanyl and tetrahydronaphthyl [tetraliny]) or that may contain one or more ring heteroatoms (e.g., indoliny, isoindoliny, 2,3-dihydrobenzofurany, 1,3-benzodioxolyl, chromany and 1,4-benzodioxanyl). The term “-aryl-” refers to a divalent aryl group. An aryl group and an -aryl- group can optionally be substituted with one or more substituents as described herein.

[0055] The term “heteroaryl” refers to a monocyclic aromatic group or a multicyclic group that contains at least one aromatic ring, wherein at least one aromatic ring contains one or more heteroatoms independently selected from O, N and S. The heteroaromatic ring may be attached or fused to one or more saturated, partially unsaturated or aromatic rings that may contain only ring carbon atoms or that may contain one or more ring heteroatoms. A heteroaryl group may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. In certain embodiments, a heteroaryl group has from 5 to 15, or 5 to 12, or 5 to 10 ring atoms. Examples of monocyclic heteroaryl groups include without limitation pyrroly, pyrazolyl, pyrazoliny, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furany, thienyl (thiopheny), oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridony, pyraziny, pyrimidiny, pyridaziny, pyridazinony and triaziny. Non-limiting examples of bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzoisothiazolyl, benzothiadiazolyl,

benzoxazolyl, benzisoxazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzoxadiazolyl (benzofurazanyl), benzothienyl (benzothiophenyl), quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzotriazolyl, indolizinyl, benzofuranyl, isobenzofuranyl, chromonyl, coumarinyl, cinnolinyl, quinazolinyl, quinoxalinyl, indazolyl, naphthyridinyl, phthalazinyl, quinazolinyl, purinyl, pyrrolopyridinyl, furopyridinyl, thienopyridinyl, dihydroisoindolyl and tetrahydroquinolinyl. Examples of tricyclic heteroaryl groups include without limitation carbazolyl, benzindolyl, dibenzofuranyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and phenothiazinyl. The term “-heteroaryl-” refers to a divalent heteroaryl group. A heteroaryl group and a -heteroaryl- group can optionally be substituted with one or more substituents as described herein.

[0056] The terms “-alkylcycloalkyl”, “-alkylheterocyclyl”, “-alkylaryl” and “-alkylheteroaryl” refer to an alkyl group that is substituted with one or more cycloalkyl groups, one or more heterocyclyl groups, one or more aryl groups, or one or more heteroaryl groups, respectively. An -alkylcycloalkyl, -alkylheterocyclyl, -alkylaryl or -alkylheteroaryl group can optionally be substituted with one or more additional substituents as described herein.

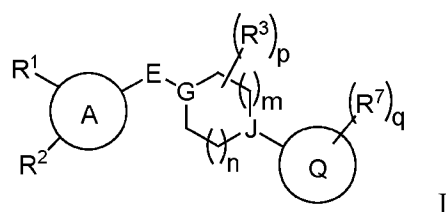
[0057] Each group described herein (including without limitation monovalent and divalent alkyl, haloalkyl, monovalent and divalent heteroalkyl, -O-alkyl, O-haloalkyl, -O-heteroalkyl, monovalent and divalent cycloalkyl, monovalent and divalent heterocyclyl, monovalent and divalent aryl, monovalent and divalent heteroaryl, -alkylcycloalkyl, -alkylheterocyclyl, -alkylaryl and -alkylheteroaryl), whether as a primary group or as a substituent group, can optionally be substituted with one or more substituents. In some embodiments, each group described herein can optionally be substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from halide, cyano (-CN), nitro (-NO₂), hydroxyl (-OH), sulfhydryl (-SH), amino (-NH₂), -OR¹¹, -SR¹¹, -NR¹²R¹³, -C(=O)R¹¹, -C(=O)OR¹¹, -OC(=O)R¹¹, -C(=O)NR¹²R¹³, -NR¹²C(=O)R¹¹, -OC(=O)OR¹¹, -OC(=O)NR¹²R¹³, -NR¹²C(=O)OR¹¹, -NR¹¹C(=O)NR¹²R¹³, alkyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein:

R¹¹ in each occurrence independently is hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, -alkylcycloalkyl, -alkylheterocyclyl, -alkylaryl or -alkylheteroaryl; and

R¹² and R¹³ in each occurrence independently are hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, -alkylcycloalkyl, -alkylheterocyclyl, -alkylaryl or -alkylheteroaryl, or R¹² and R¹³ and the nitrogen atom to which they are connected form a heterocyclic or heteroaryl ring.

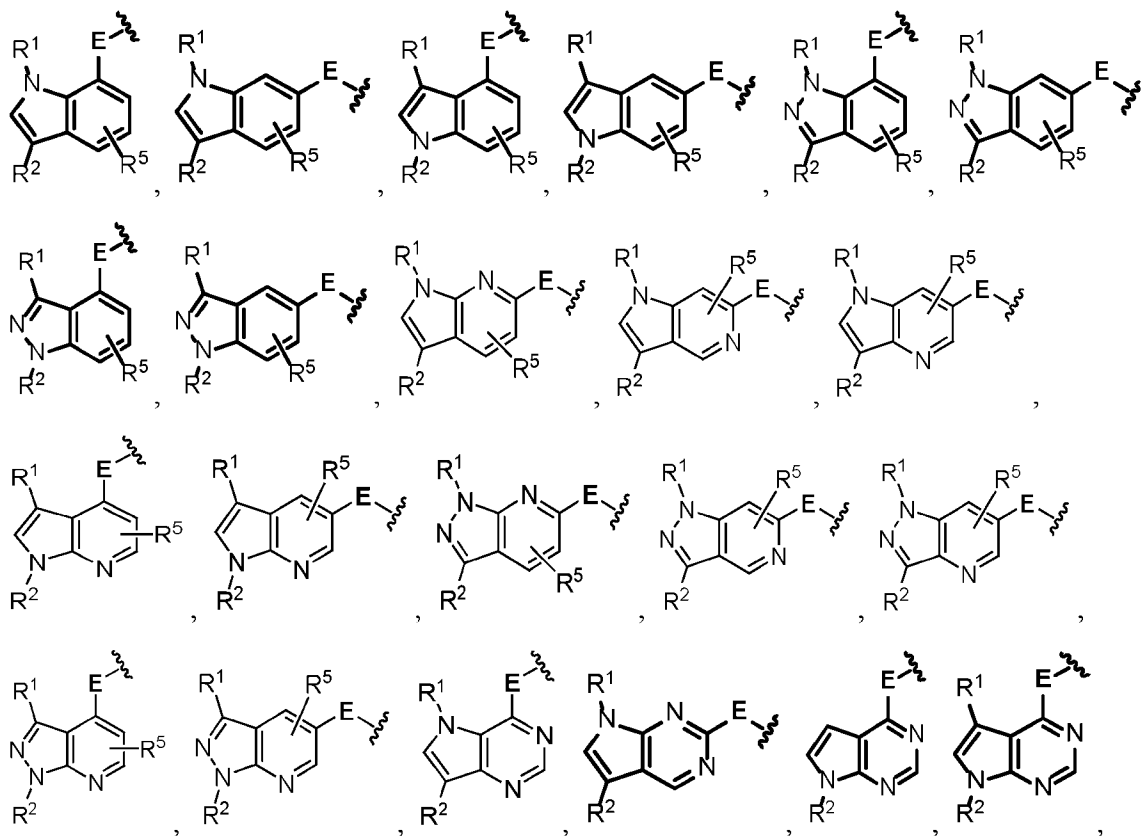
Indirect Inhibitors of Nav1.7

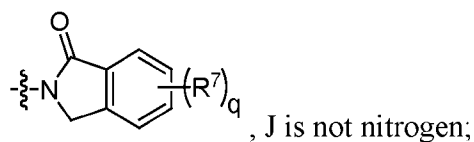
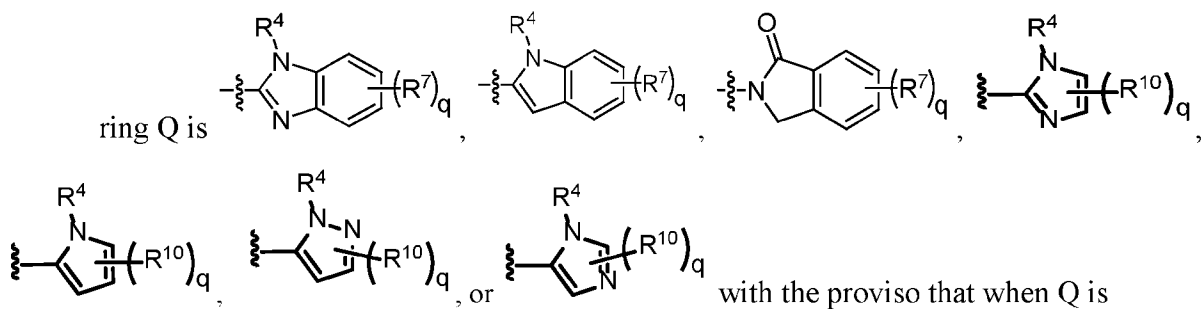
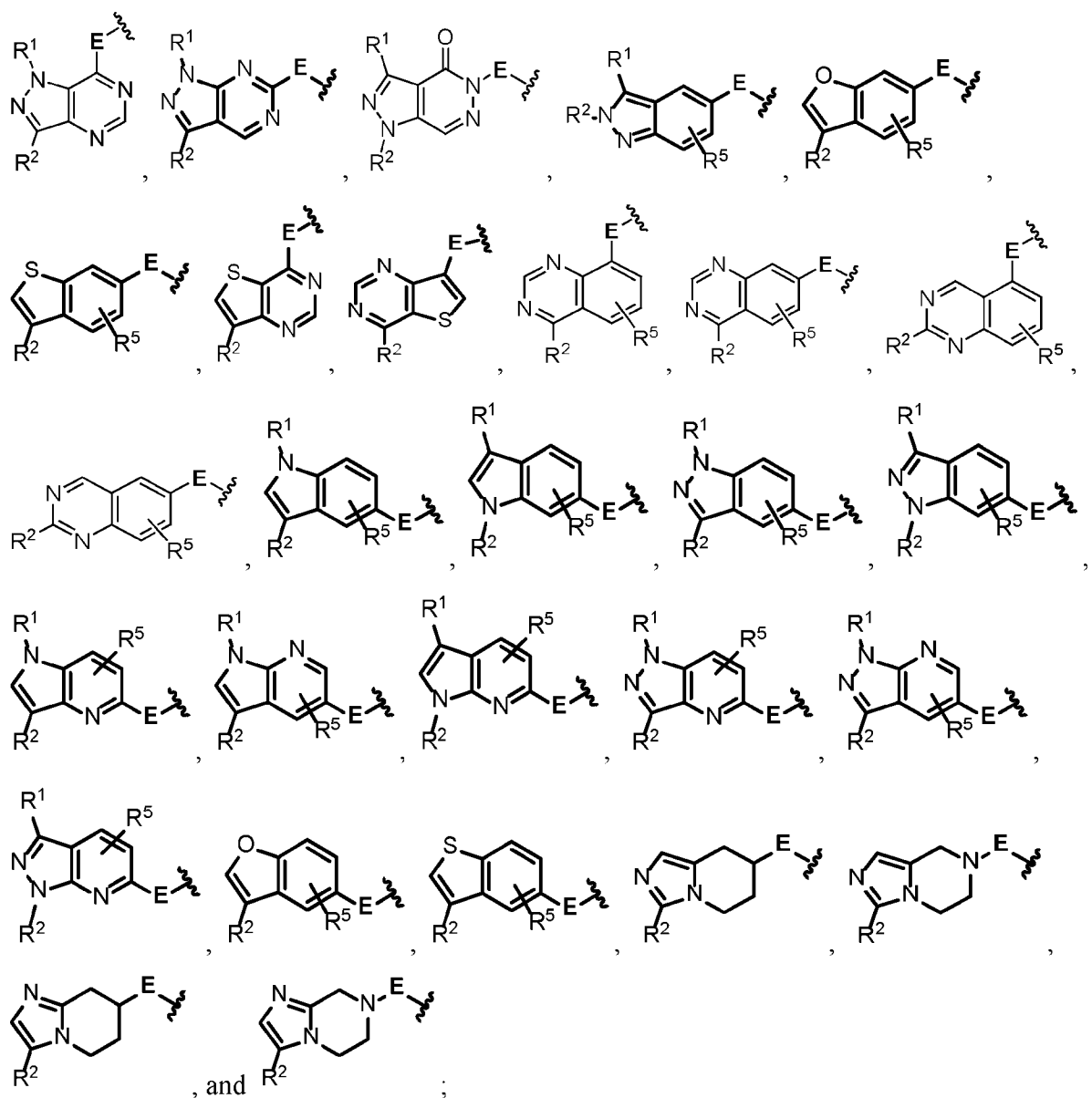
[0058] The compounds of the disclosure indirectly inhibit the function of the voltage-gated sodium ion channel 1.7 (Nav1.7) by selectively inhibiting SUMOylation of collapsin response mediator protein 2 (CRMP2) and hence trafficking of Nav1.7 to the plasma membrane of nociceptive neurons. The compounds have Formula I or are tautomers, pharmaceutically acceptable salts, solvates, hydrates, clathrates, isotopes, or isotopic forms including deuterated and tritiated forms, polymorphs or stereoisomers thereof:



wherein:

ring A attached to E is selected from:

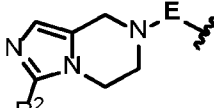
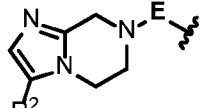




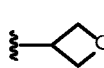
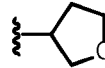
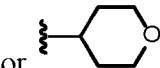
G and J independently are nitrogen or -CH-;

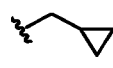
when G is nitrogen and J is -CH- or nitrogen, E is -C(=O)-, -CH₂-, NH, or -CHR⁶-;

when G is -CH- and J is nitrogen or -CH, E is -C(=O)-, -O-, -S-, -NH-, -N(C₁₋₄ alkyl)- [e.g., -N(methyl)- or -N(ethyl)-], or -N(C₁₋₄ haloalkyl)- (e.g., -NCHF₂- or -NCF₃-), wherein E and ring Q can be *cis* or *trans* to each other when both G and J are -CH;

when G is nitrogen, A is  or , wherein E is -C(=O)-;

R¹ is hydrogen, C₁₋₄ alkyl (e.g., methyl, ethyl or isopropyl), C₁₋₄ haloalkyl (e.g., -CHF₂-, -CF₃-, -CH₂CHF₂ or -CH₂CF₃), C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclobutyl or cyclopentyl), 3-6-

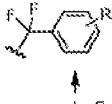
membered heterocyclyl (e.g., ,  or ) , -CH₂-(C₃₋₆ cycloalkyl) (e.g.,

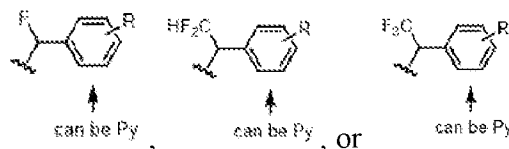
) , -CH₂-(3-6-membered heterocyclyl), phenyl, thiophenyl, C₅₋₆ aryl, C₅₋₆ heteroaryl, or halide, wherein the C₃₋₆ cycloalkyl, 3-6-membered heterocyclyl, -CH₂-(C₃₋₆ cycloalkyl), -CH₂-(3-6-membered heterocyclyl), phenyl, thiophenyl, C₅₋₆ aryl and C₅₋₆ heteroaryl can optionally have 1, 2 or 3 substituents independently selected from halide (e.g., F and Cl), -CN, -OH, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ alkoxy (e.g., methoxy), C₁₋₄ haloalkyl (e.g., -CHF₂ and -CF₃), C₁₋₄ haloalkoxy (e.g., -OCHF₂ and -OCF₃), and -(CH₂)_{1/2}OH (e.g., -CH₂OH);

R² is 6-10-membered aryl or 5-10-membered heteroaryl, wherein the aryl or heteroaryl can be connected to ring A directly or via -CH₂-, -NH-, -NCH₃-, -O- or -S-, and wherein the aryl or heteroaryl can optionally have 1, 2 or 3 substituents independently selected from halide (e.g., F and Cl), -CN, -OH, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ alkoxy (e.g., methoxy), C₁₋₄ haloalkyl (e.g., -CHF₂ and -CF₃), C₁₋₄ haloalkoxy (e.g., -OCHF₂ and -OCF₃), -(CH₂)_{1/2}OH (e.g., -CH₂OH), -(CH₂)_{1/2}-(C₁₋₄ alkoxy) (e.g., -CH₂OCH₃), -C(=O)NH₂, -C(=O)NR⁸R⁹ (e.g., -C(=O)NHCH₃), and -SO₂R⁸ (e.g., -SO₂CH₃); and wherein R² is not connected via -NH-, -NCH₃-, -O- or -S-, to the nitrogen of ring A;

R³ in each occurrence independently is halide (e.g., F), -OH, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ haloalkyl (e.g., -CHF₂ and -CF₃), or C₁₋₄ alkoxy (e.g., methoxy), wherein R³ is not -OH or C₁₋₄ alkoxy at a carbon atom that is directly connected to a ring nitrogen atom;

R⁴ is hydrogen, C₁₋₄ alkyl (e.g., methyl or ethyl), C₁₋₄ haloalkyl (e.g., -CHF₂ or -CH₂CHF₂), C₃₋₆ cycloalkyl (e.g., cyclopropyl), 3-6-membered heterocyclyl, -(CH₂)_{1/2}-(C₃₋₆ cycloalkyl) (e.g., -CH₂-cyclopropyl), -(CH₂)_{1/2}-(3-6-membered heterocyclyl) (e.g., -CH₂-

tetrahydropyranyl), $-(CH_2)_{1/2}$ -phenyl, $-(CH_2)_{1/2}$ -(5- or 6-membered heteroaryl),  ,



heterocyclyl, $-(CH_2)_{1/2}$ -cycloalkyl, $-(CH_2)_{1/2}$ -heterocyclyl, $-(CH_2)_{1/2}$ -phenyl and $-(CH_2)_{1/2}$ -heteroaryl can optionally have 1, 2 or 3 substituents independently selected from halide (e.g., F and Cl), -CN, -OH, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ alkoxy (e.g., methoxy), C₁₋₄ haloalkyl (e.g., -CHF₂ and -CF₃), C₁₋₄ haloalkoxy (e.g., -OCHF₂ and -OCF₃), and $-(CH_2)_{1/2}$ OH (e.g., -CH₂OH);

R⁵ is hydrogen, halide (e.g., F or Cl), -CN, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ haloalkyl (e.g., -CHF₂ or -CF₃), C₁₋₄ alkoxy (e.g., methoxy), C₁₋₄ haloalkoxy (e.g., -OCHF₂ or -OCF₃), or $-(CH_2)_{1/2}$ OH (e.g., -CH₂OH);

R⁶ is C₁₋₄ alkyl (e.g., methyl or ethyl), C₁₋₄ haloalkyl (e.g., -CHF₂ or -CF₃), cyclopropyl or -CH₂-cyclopropyl;

R⁷ in each occurrence independently is halide (e.g., F or Cl), -CN, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ haloalkyl (e.g., -CHF₂ or -CF₃), C₁₋₄ alkoxy (e.g., methoxy), C₁₋₄ haloalkoxy (e.g., -OCHF₂ or -OCF₃), or $-(CH_2)_{1/2}$ OH (e.g., -CH₂OH);

R⁸ and R⁹ independently are hydrogen or C₁₋₄ alkyl (e.g., methyl);

R¹⁰ is H, halide, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, thiophenyl, pyridine, C₅₋₆ aryl or C₅₋₆ heteroaryl, wherein the C₃₋₆ cycloalkyl, phenyl, thiophenyl, pyridine, C₅₋₆ aryl or C₅₋₆ heteroaryl can optionally have 1, 2 or 3 substituents independently selected from halide (e.g., F or Cl), -CN, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ haloalkyl (e.g., -CHF₂ or -CF₃), C₁₋₄ alkoxy (e.g., methoxy), C₁₋₄ haloalkoxy (e.g., -OCHF₂ or -OCF₃), or $-(CH_2)_{1/2}$ OH (e.g., -CH₂OH);

m is 0, 1 or 2;

n is 0, 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2; and

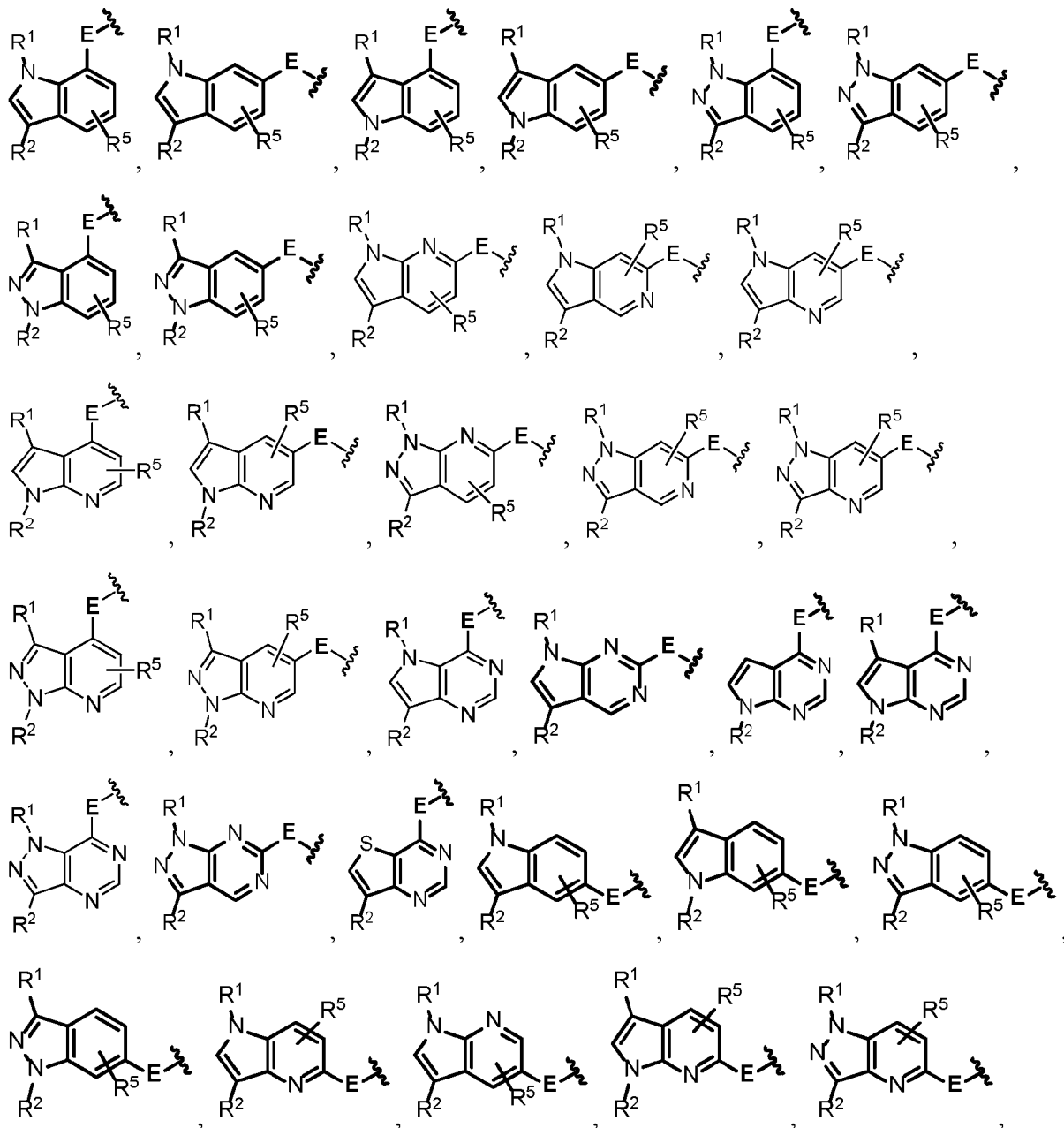
a group having a stereocenter can have the (*R*)-stereochemistry or the (*S*)-stereochemistry at the stereocenter or can be racemic at the stereocenter.

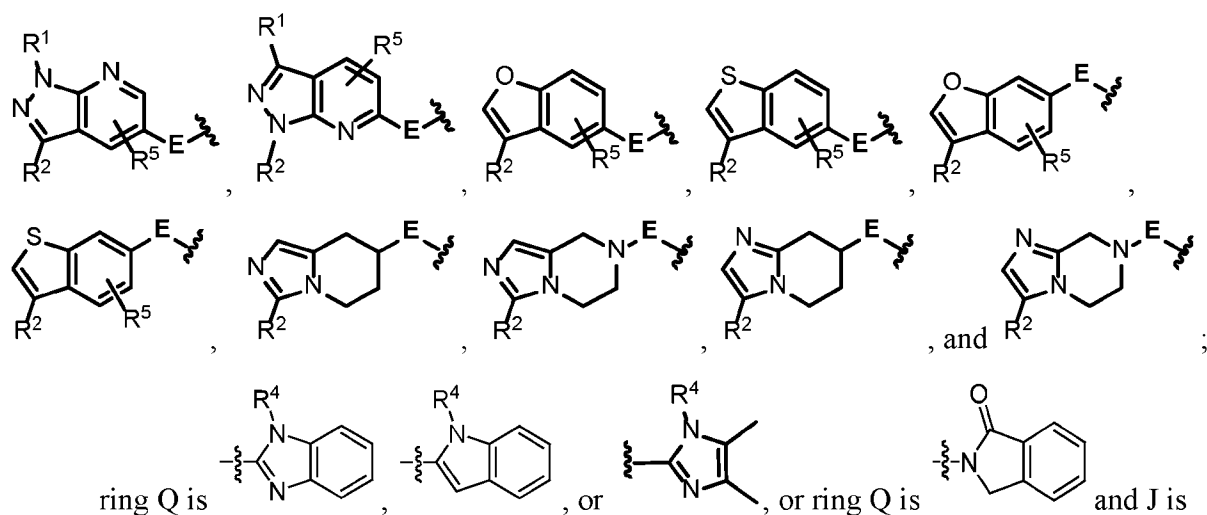
[0059] In some embodiments, the optionally substituted R² group is selected from phenyl, pyrrolyl, furanyl (furyl), thiophenyl (thienyl), pyrazolyl, imidazolyl, oxazolyl, isoxazolyl,

thiazolyl, isothiazolyl, pyridinyl (pyridyl), pyridazinyl, pyrimidinyl, pyrazinyl, 2-pyridinonyl, 3-pyridinonyl and 4-pyridinonyl, wherein the R^2 group can be connected to ring A directly or via $-CH_2-$, $-NH-$, $-NCH_3-$, $-O-$ or $-S-$, and wherein R^2 is not connected via $-NH-$, $-NCH_3-$, $-O-$ or $-S-$, to the nitrogen of ring A.

[0060] In some embodiments of the compounds of Formula I:

ring A attached to E is selected from:





not nitrogen;

the ring containing G and J is azetidine, pyrrolidine, piperidine, homopiperidine or piperazine;

when G is nitrogen and J is -CH- or nitrogen, E is -C(=O)-, -CH₂-, -CH(CH₃)-, -CH(CHF₂)-, -CH(CF₃)-, -CH(cyclopropyl)- or -CH(CH₂-cyclopropyl)-;

when G is -CH- and J is nitrogen, E is -O-, -NH-, -NCH₃- or -NCF₃-;

R¹ is hydrogen, methyl, ethyl, isopropyl, -CHF₂, -CF₃, -CH₂CHF₂, cyclopropyl,

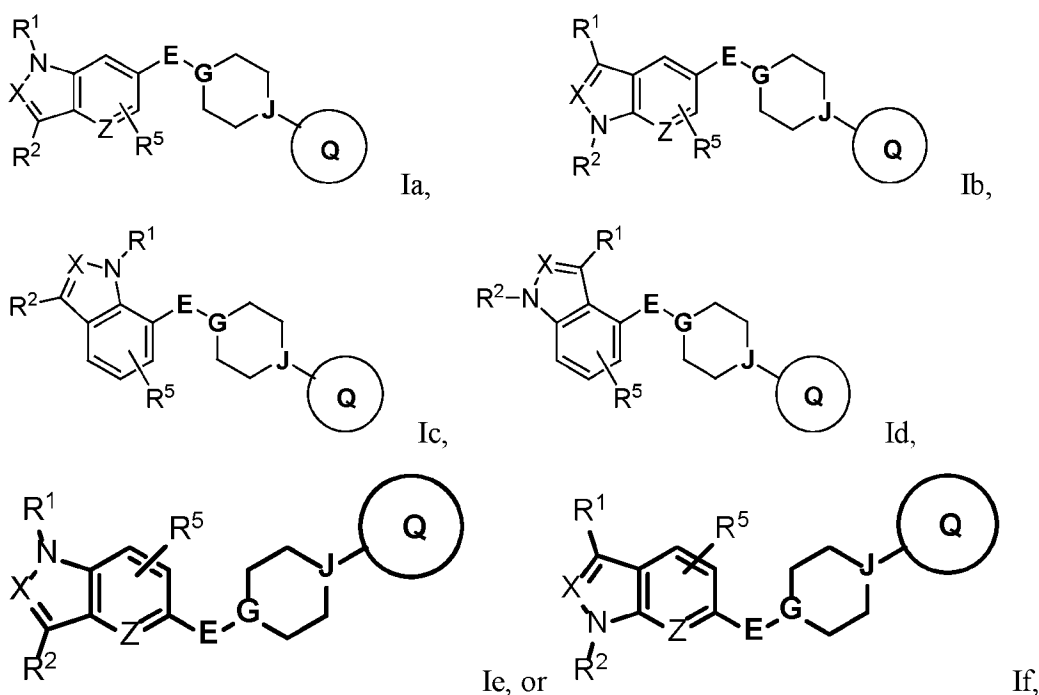
cyclobutyl, cyclopentyl,  or .

R² is thiophenyl, phenyl or pyridinyl, wherein the thiophenyl, phenyl or pyridinyl can be connected to ring A directly or via -CH₂- or -NH-, and wherein the thiophenyl, phenyl or pyridinyl can optionally have 1 or 2 substituents independently selected from halide (e.g., F and Cl), -CN, methyl, -CHF₂, -CF₃ and methoxy; and wherein R² is not connected via -NH- to the nitrogen of ring A;

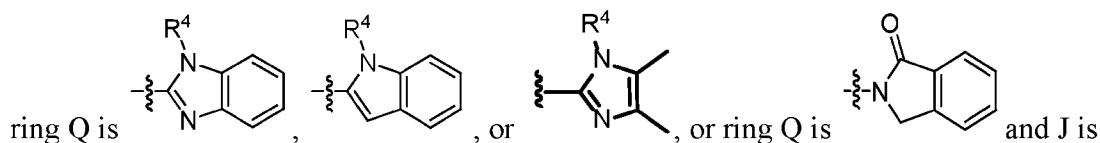
p is 0, or p is 1 and R³ is F or methyl; and

R⁵ is hydrogen, F, Cl or methyl.

[0061] In further embodiments, the compounds have Formula Ia, Ib, Ic, Id, Ie or If, or are tautomers, pharmaceutically acceptable salts, solvates, hydrates, clathrates, isotopes, or isotopic forms including deuterated and tritiated forms, polymorphs or stereoisomers thereof.



wherein:



not nitrogen;

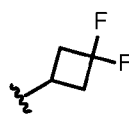
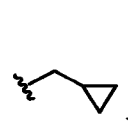
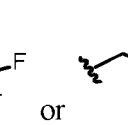
X and Z independently are carbon or nitrogen;

both G and J are not -CH-;

when G is nitrogen and J is -CH- or nitrogen, E is -C(=O)-, -CH₂-, -CH(CH₃)-, -CH(CHF₂)-, or -CH(CF₃)-;

when G is -CH- and J is nitrogen, E is -O-, -NH-, -NCH₃- or -NCF₃-;

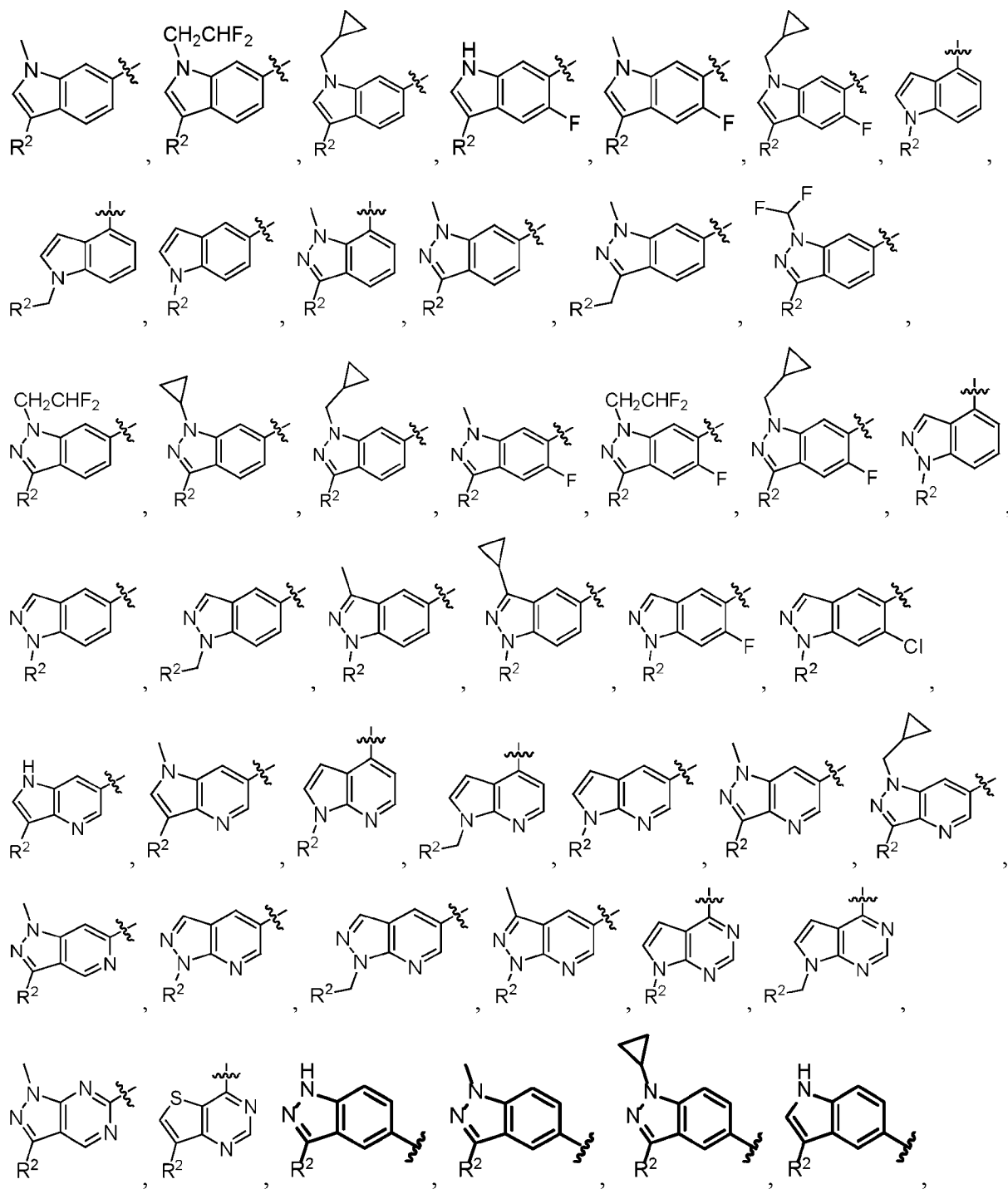
R¹ is hydrogen, methyl, ethyl, isopropyl, -CHF₂, -CF₃, -CH₂CHF₂, cyclopropyl,

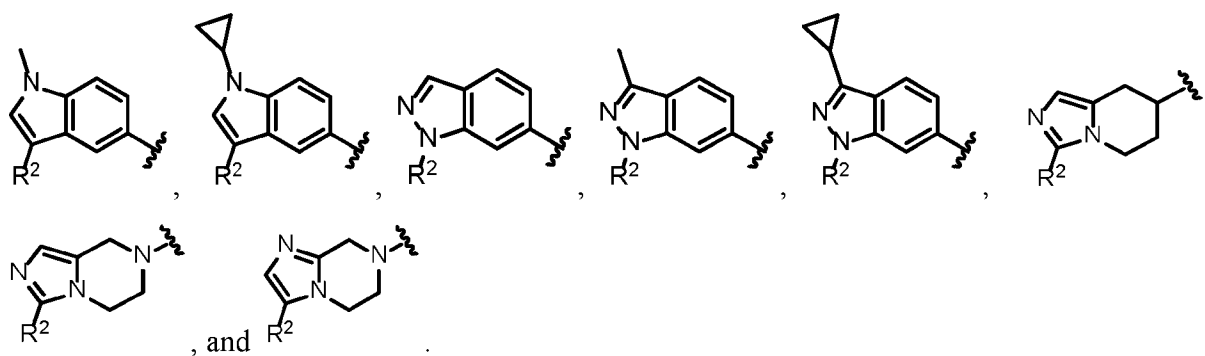
cyclobutyl, cyclopentyl, , , ,  or  F;

R² is thiophenyl, phenyl or pyridinyl, wherein the thiophenyl, phenyl or pyridinyl can be connected to ring A directly or via -CH₂-, and wherein the thiophenyl, phenyl or pyridinyl can optionally have 1 or 2 substituents independently selected from halide (e.g., F and Cl), -CN, methyl, -CHF₂, -CF₃ and methoxy; and

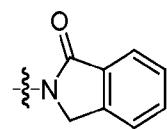
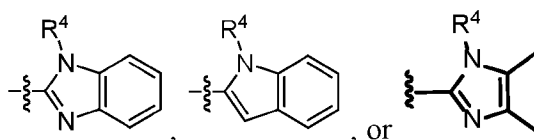
R⁵ is hydrogen, F, Cl or methyl.

[0062] In some embodiments of the compounds of Formula I, ring A is selected from:



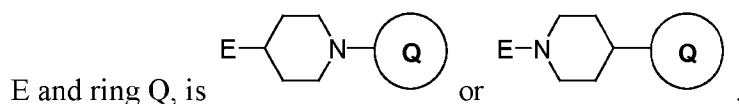


[0063] In some embodiments, ring Q is



and J is not nitrogen.

[0064] In some embodiments, the ring containing G and J, with indicated points of attachment to



[0065] In some embodiments, when G is nitrogen and J is -CH- or nitrogen, E is -C(=O)-, -CH₂-, -CH(CH₃)-, -, -CH(CHF₂)-, -CH(CF₃)-, -CH(cyclopropyl)- or -CH(CH₂-cyclopropyl)-, wherein a stereocenter can have the (*R*)-stereochemistry or the (*S*)-stereochemistry or can be racemic. In other embodiments, when G is -CH- and J is nitrogen or -CH, E is -O-, -NH-, -NCH₃- or -NCF₃-.

[0066] In some embodiments, R¹ is hydrogen, methyl, -CHF₂, -CH₂CHF₂, cyclopropyl or -CH₂-cyclopropyl.

[0067] In some embodiments, R² is 2-F-phenyl, 2-CH₃-phenyl, 3-F-phenyl, 3-Cl-phenyl, 3-CHF₂-phenyl, 3-CF₃-phenyl, 4-F-phenyl, 2,3-diF-phenyl, 3,5-diF-phenyl, 2-F-5-Cl-phenyl, 5-Cl-thiophen-3-yl, 5-CF₃-thiophen-3-yl, 5-F-pyridin-3-yl, or 5-Cl-pyridin-3-yl, wherein the R² group can be connected to ring A directly or via -CH₂- or -NH-; and wherein R² is not connected via -NH- to the nitrogen of ring A. In certain embodiments, R² is 3-F-phenyl, 3-Cl-phenyl or 3-CF₃-phenyl.

[0068] In certain embodiments, p is 0. In other embodiments, p is 1 or 2, and R³ in each occurrence independently is F or methyl.

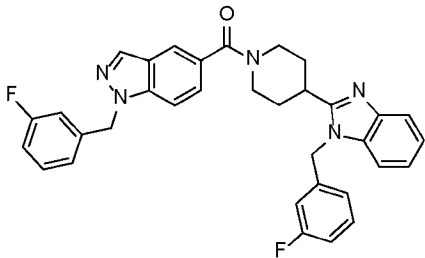
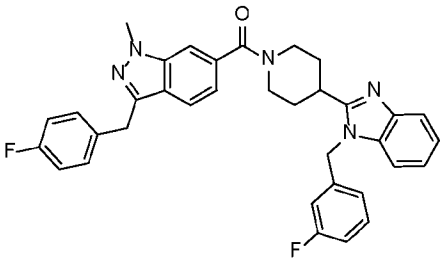
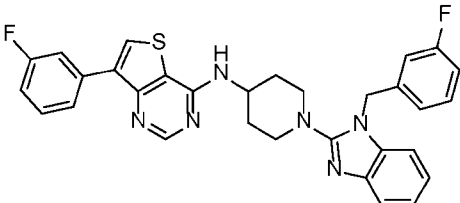
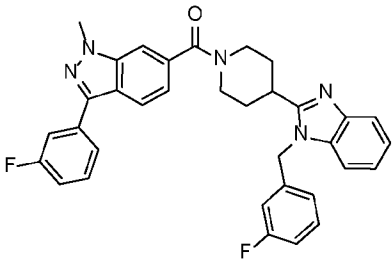
[0069] In some embodiments, R^4 is selected from $-\text{CHF}_2$, $-\text{CH}_2\text{CHF}_2$, cyclopropyl, $-\text{CH}_2$ -cyclopropyl, $-\text{CH}_2\text{CH}_2$ -cyclopropyl, *cis* or *trans* $-\text{CH}_2$ -3-OH-cyclobutane, $-\text{CH}_2$ -(3,3-diF-

cyclobutane), , , $-\text{CH}_2$ -tetrahydropyran-4-yl, $-\text{CH}_2\text{CH}_2$ -tetrahydropyran-4-yl, $-\text{CH}_2$ -phenyl, $-\text{CH}_2$ -(3-F-phenyl), $-\text{CH}(\text{CH}_3)$ -phenyl, $-\text{CH}(\text{CH}_3)$ -(3-F-phenyl), $-\text{CF}_2$ -phenyl, $-\text{CF}_2$ -(3-F-phenyl), $-\text{CH}_2$ -pyridin-2-yl and $-\text{CH}(\text{CH}_3)$ -pyridin-2-yl, wherein a stereocenter can have the (*R*)-stereochemistry or the (*S*)-stereochemistry or can be racemic. In certain embodiments, R^4 is $-\text{CHF}_2$, $-\text{CH}_2\text{CHF}_2$, cyclopropyl, $-\text{CH}_2$ -cyclopropyl, $-\text{CH}_2$ -(3-F-phenyl), $-\text{CF}_2$ -phenyl, $-\text{CF}_2$ -(3-F-phenyl), , $-\text{CH}(\text{CH}_3)$ -phenyl, or $-\text{CH}(\text{CH}_3)$ -pyridin-2-yl.

[0070] In some embodiments, R^5 is hydrogen, F or Cl.

[0071] In some embodiments, compounds of Formula I are selected from the compounds shown in Table 1, and tautomers, pharmaceutically acceptable salts, solvates, hydrates, clathrates, isotopes, or isotopic forms including deuterated and tritiated forms, polymorphs and stereoisomers thereof, wherein compounds having a stereocenter can have the (*R*)-stereochemistry or the (*S*)-stereochemistry at the stereocenter or can be racemic at the stereocenter.

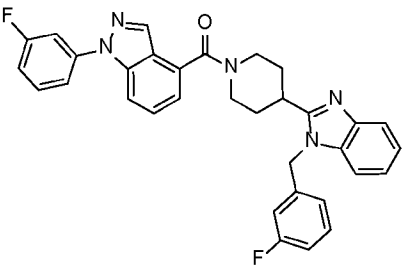
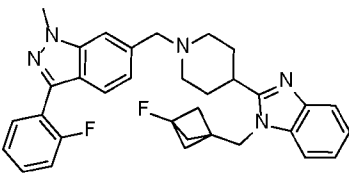
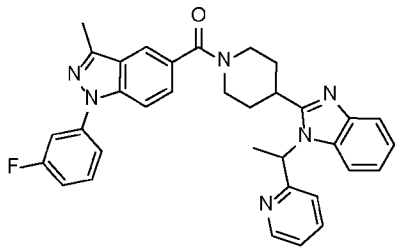
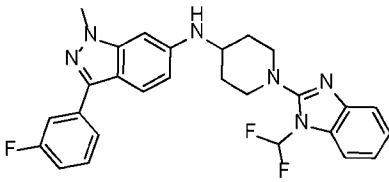
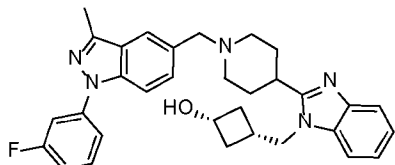
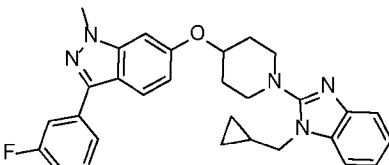
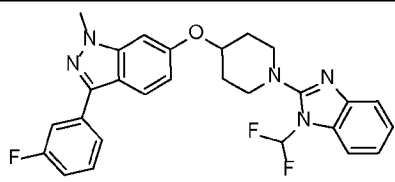
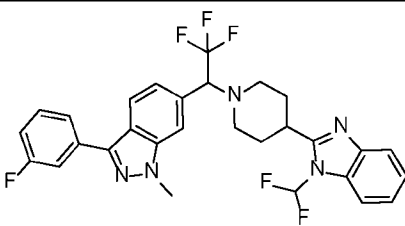
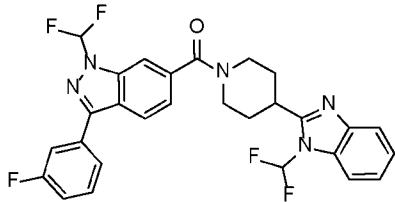
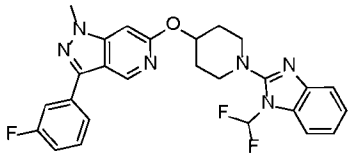
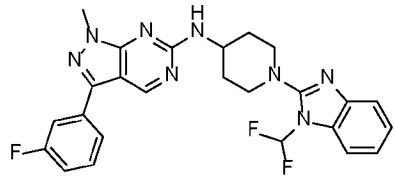
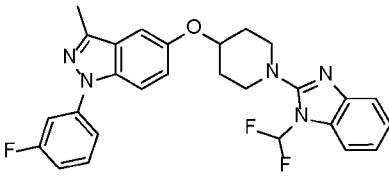
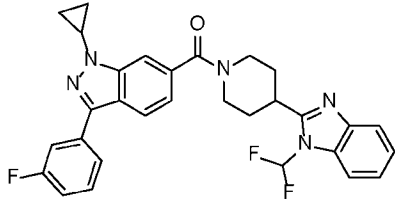
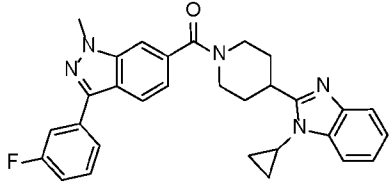
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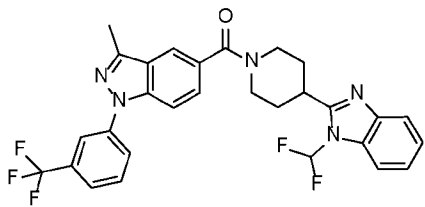
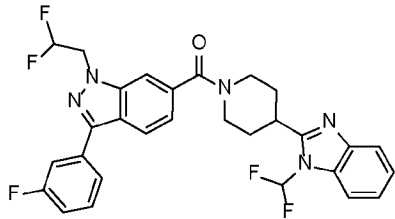
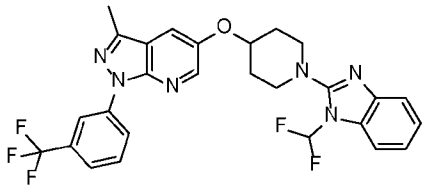
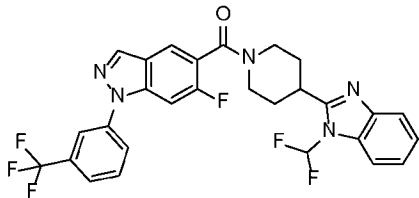
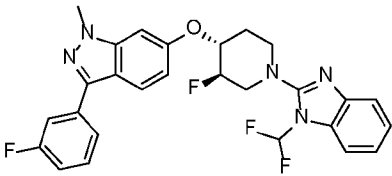
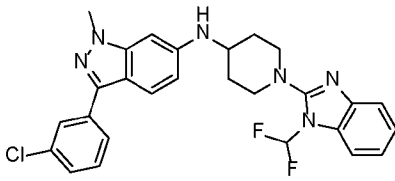
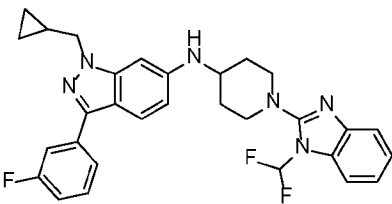
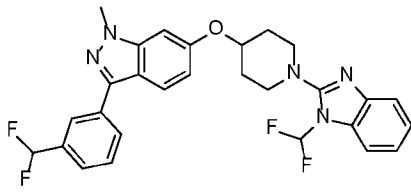
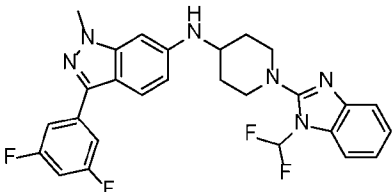
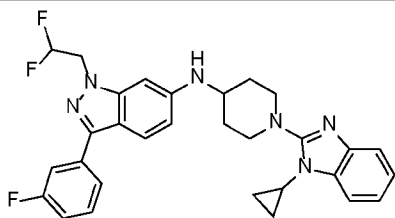
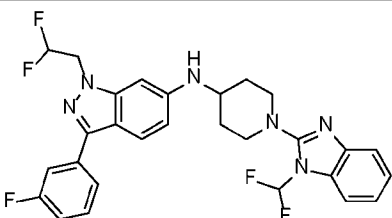
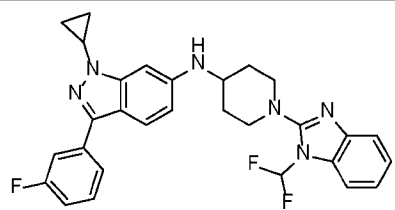
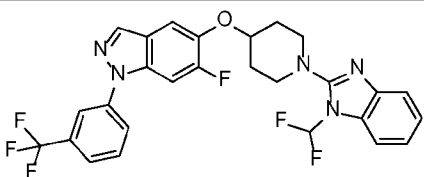
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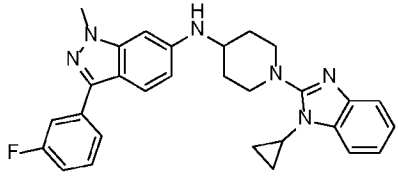
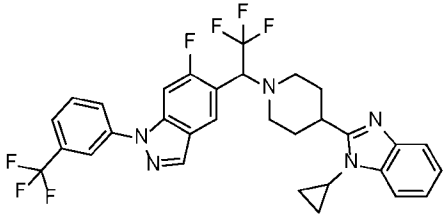
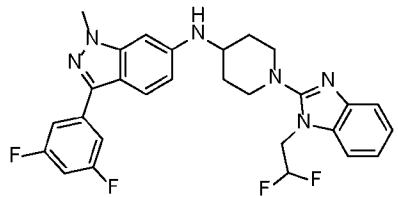
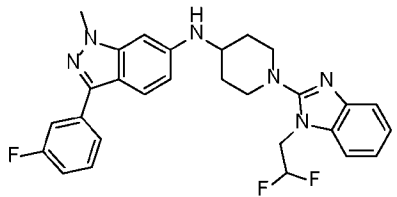
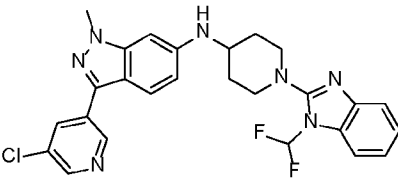
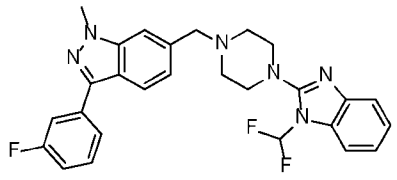
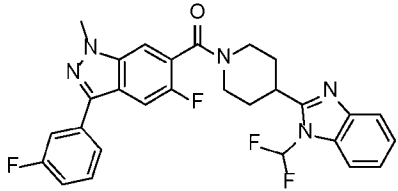
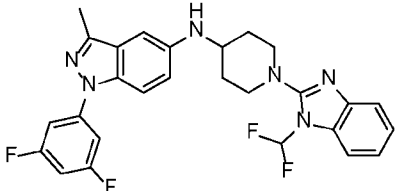
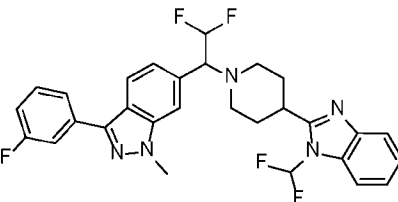
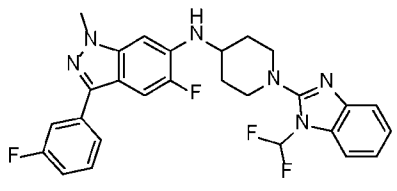
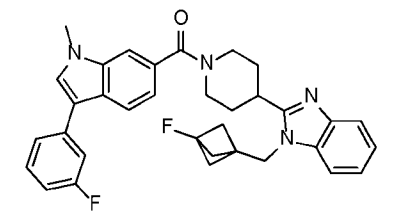
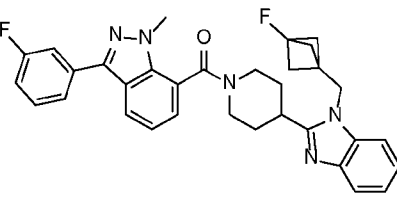
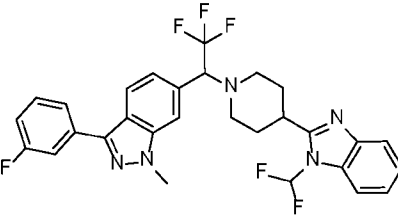
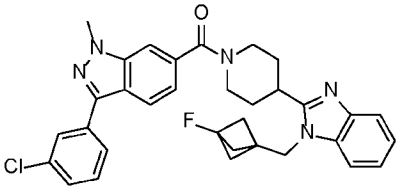
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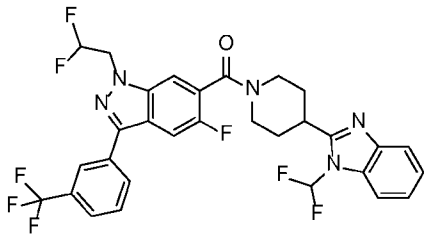
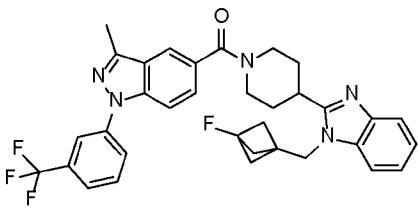
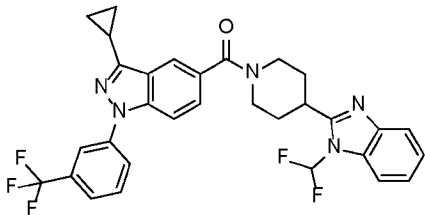
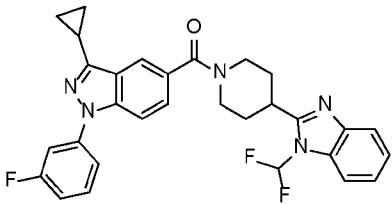
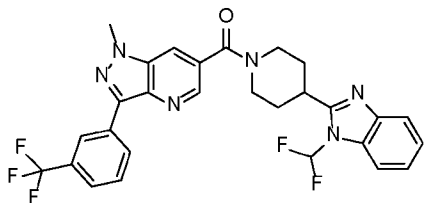
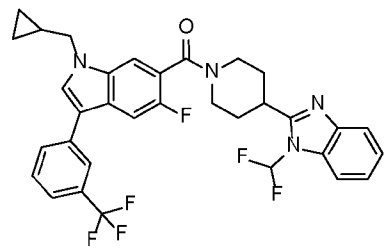
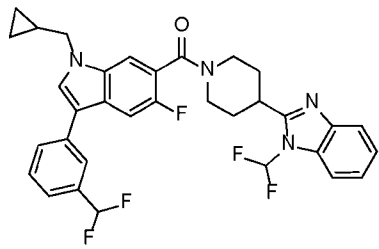
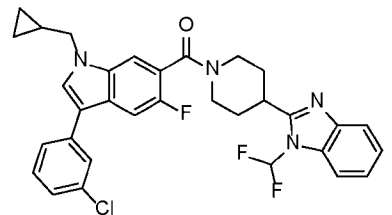
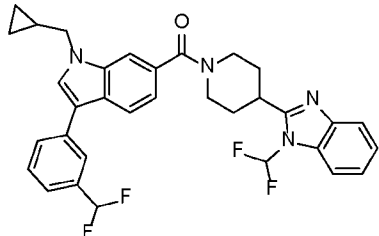
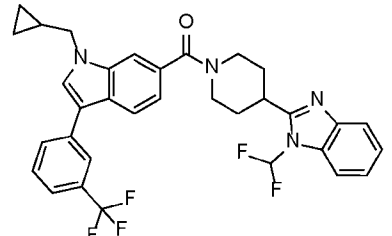
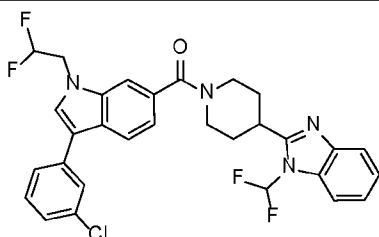
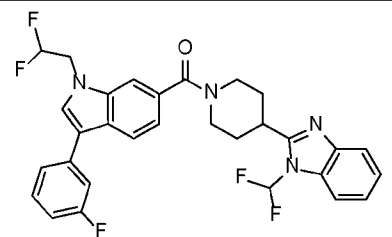
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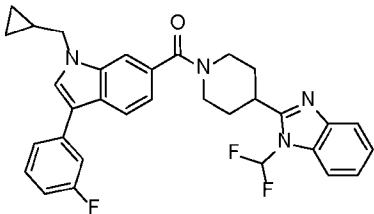
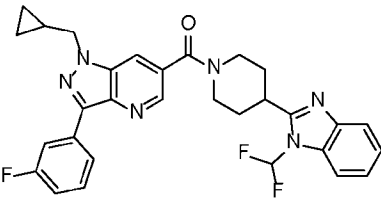
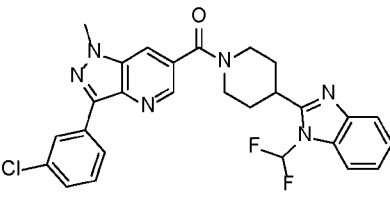
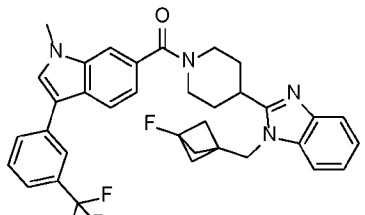
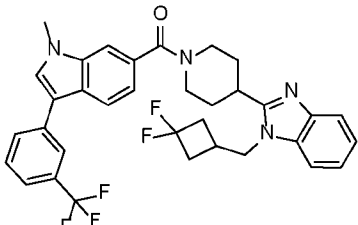
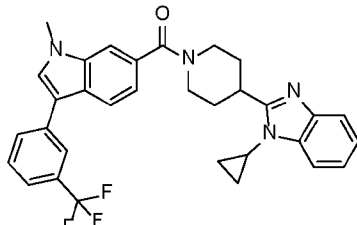
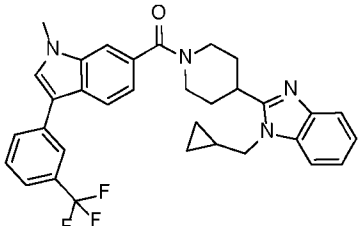
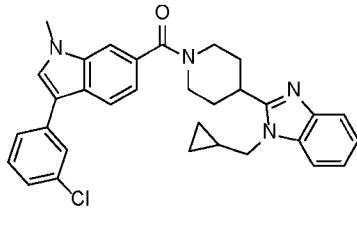
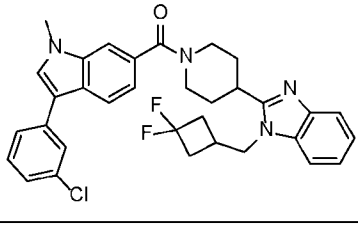
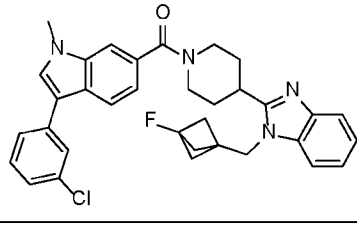
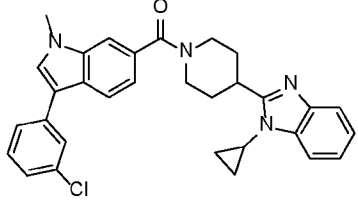
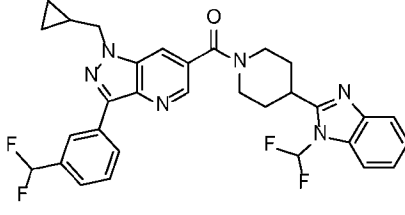
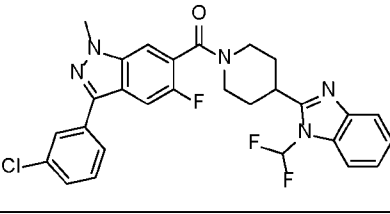
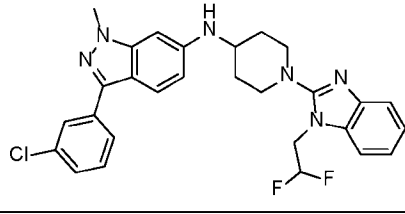
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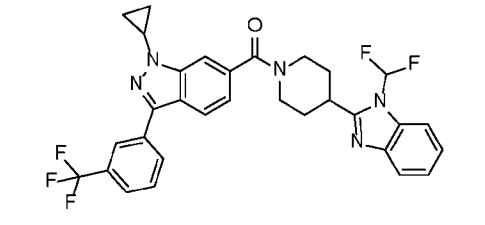
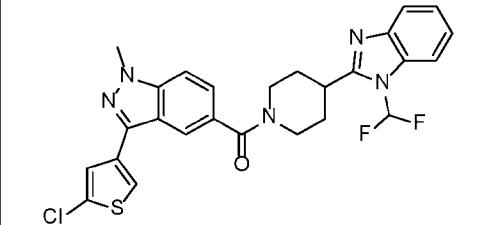
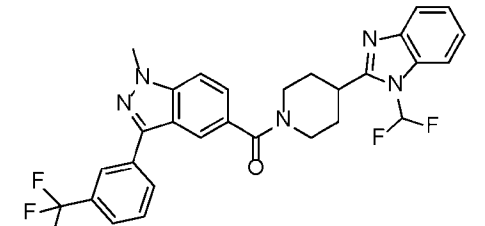
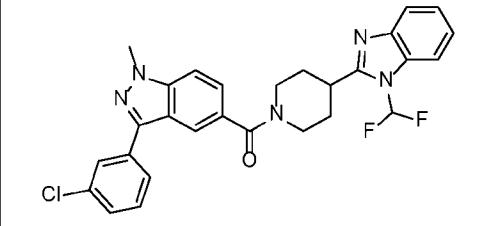
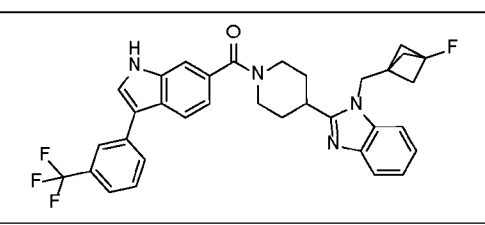
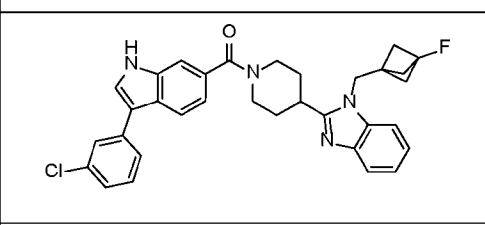
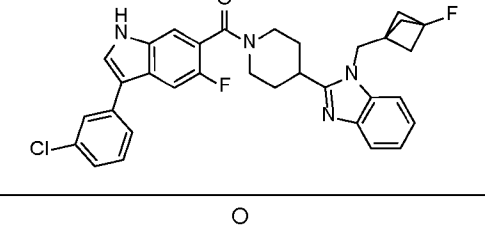
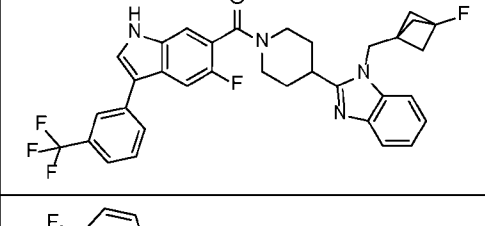
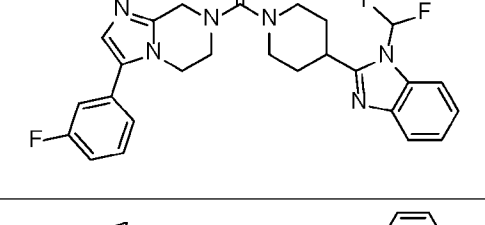
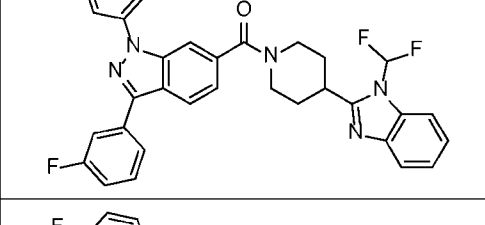
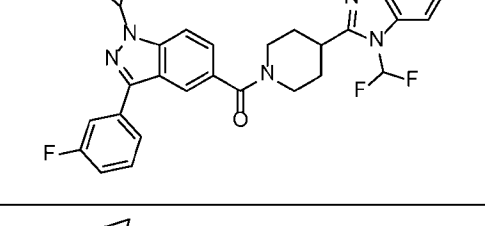
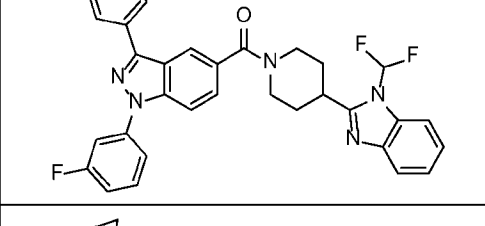
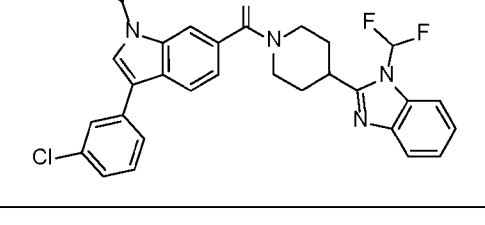
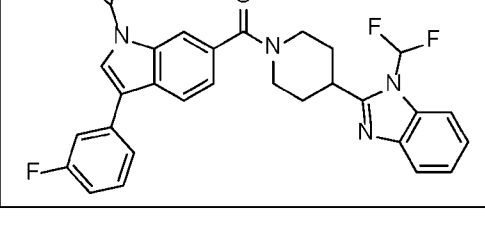
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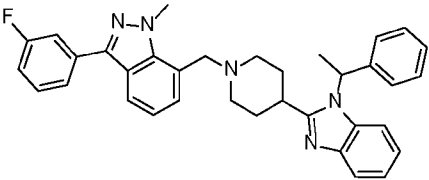
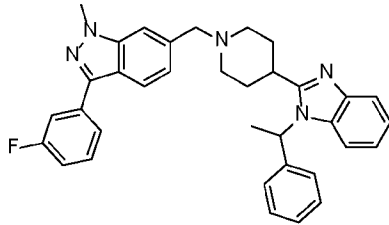
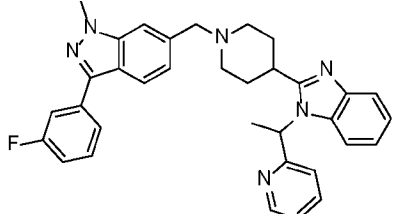
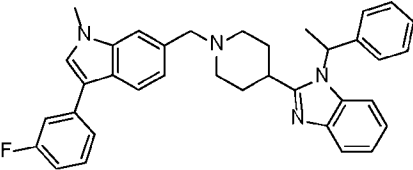
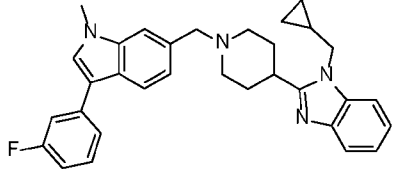
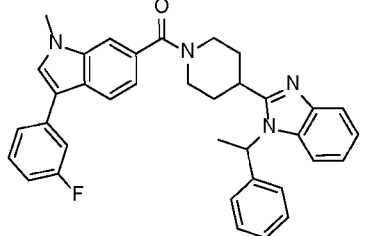
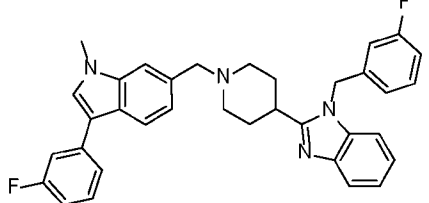
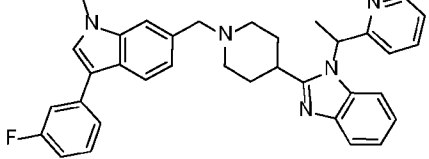
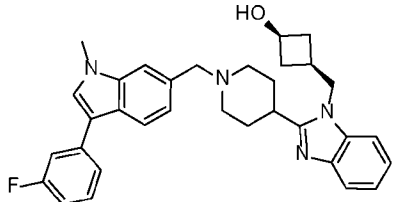
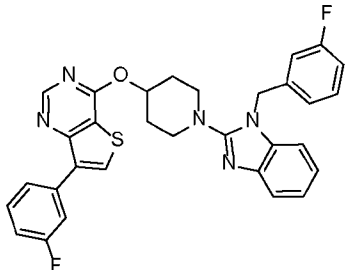
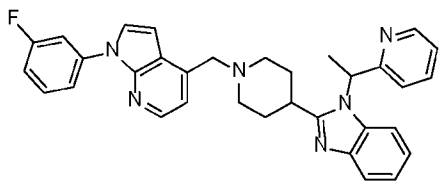
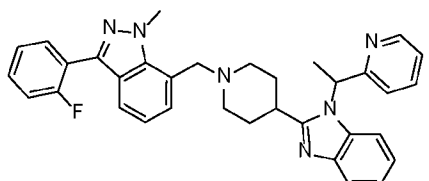
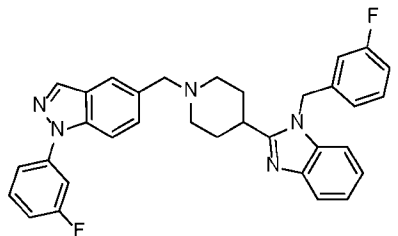
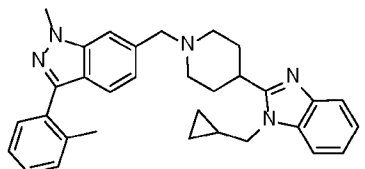
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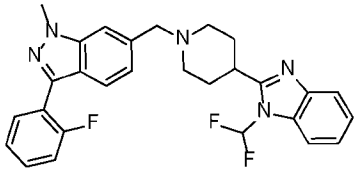
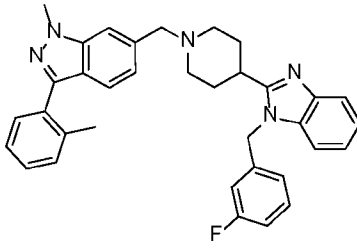
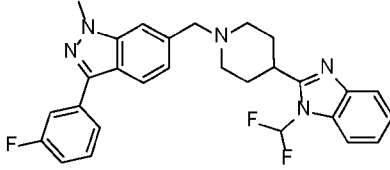
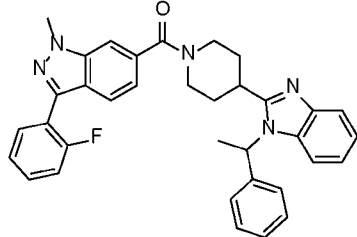
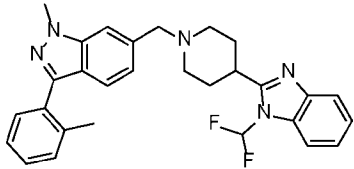
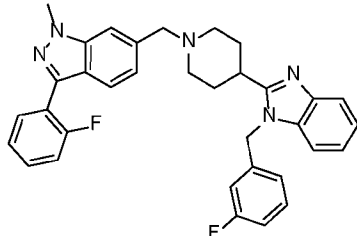
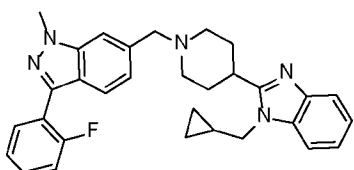
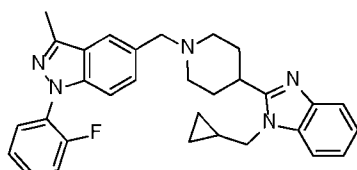
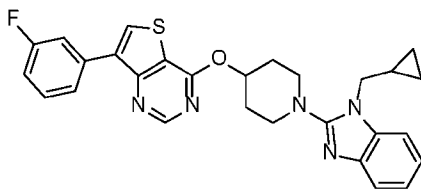
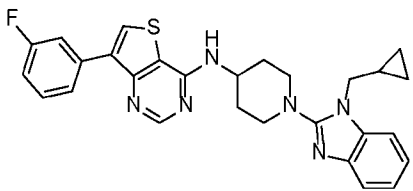
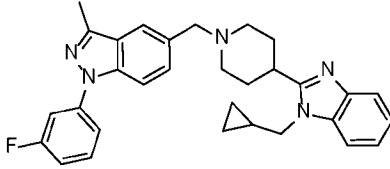
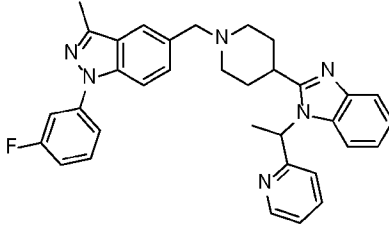
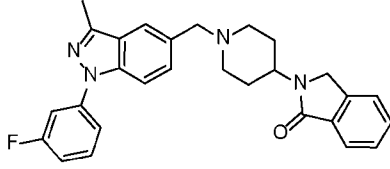
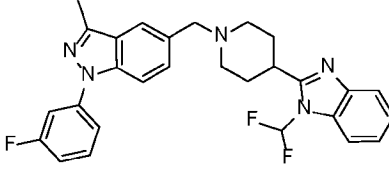
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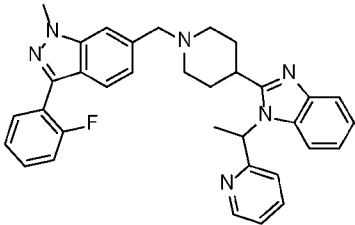
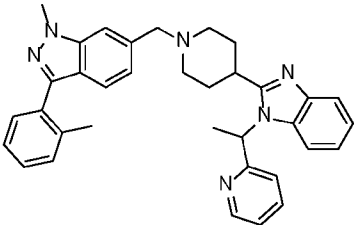
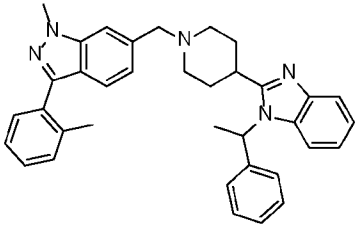
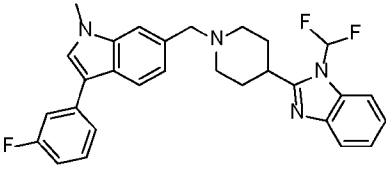
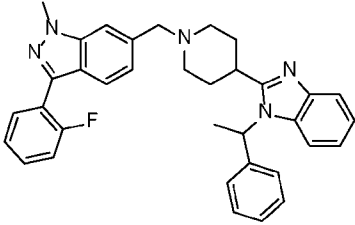
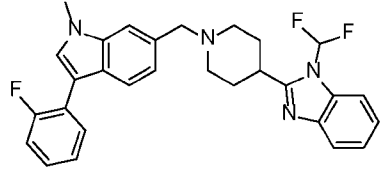
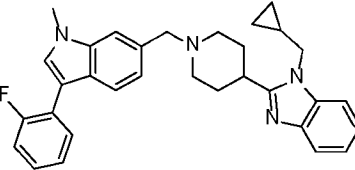
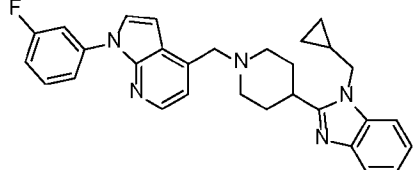
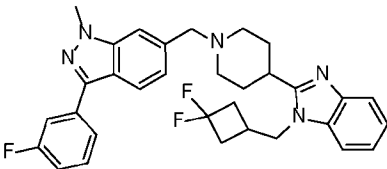
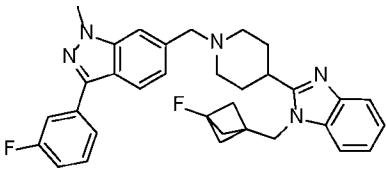
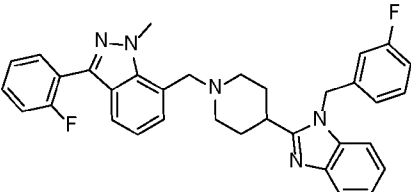
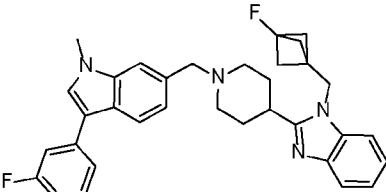
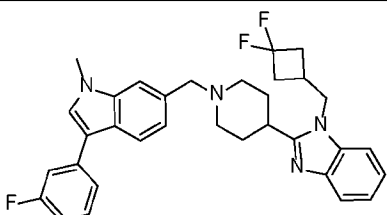
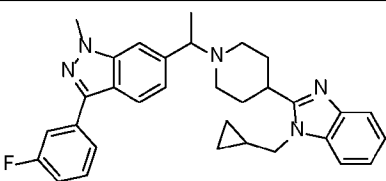
[0072] In other embodiments, compounds of Formula I are selected from the compounds shown in Table 2, and tautomers, pharmaceutically acceptable salts, solvates, hydrates, clathrates, isotopes, or isotopic forms including deuterated and tritiated forms, polymorphs and stereoisomers thereof, wherein compounds having a stereocenter can have the (*R*)-stereochemistry or the (*S*)-stereochemistry at the stereocenter or can be racemic at the stereocenter.

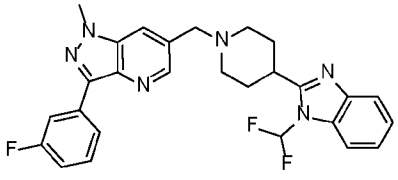
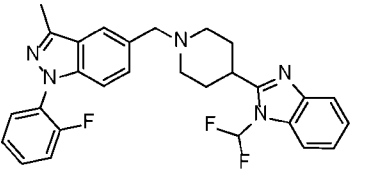
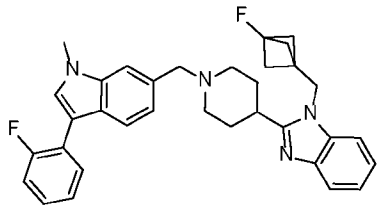
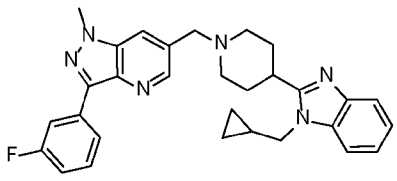
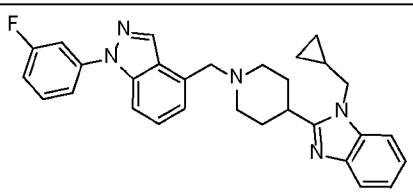
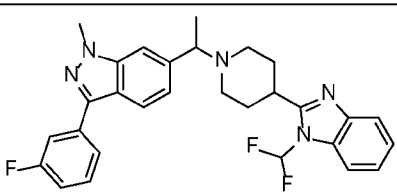
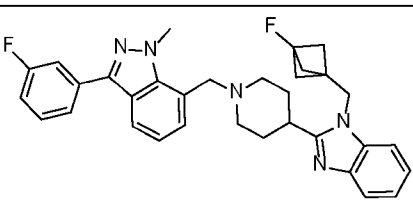
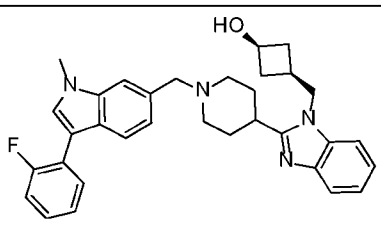
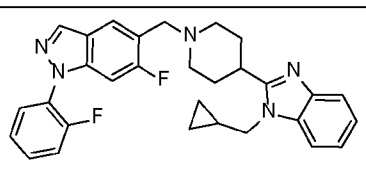
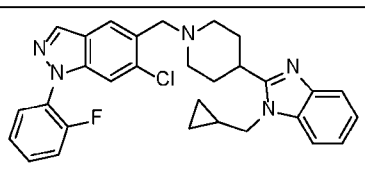
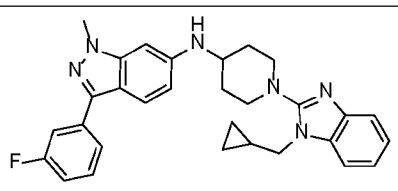
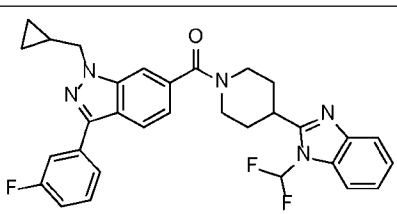
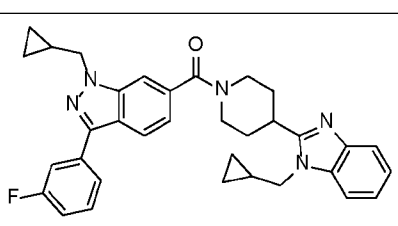
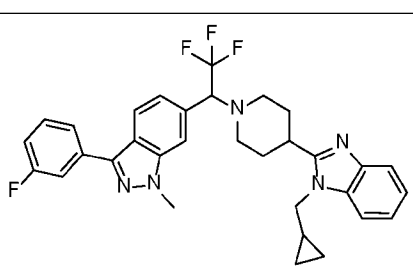
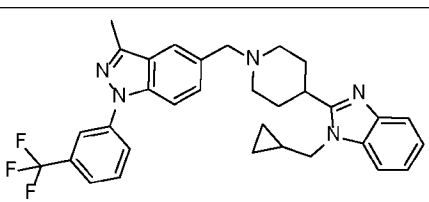
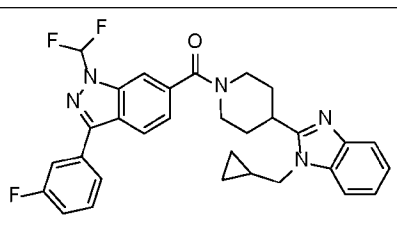
Table 2

Cpd	Structure	Cpd	Structure
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78		81	

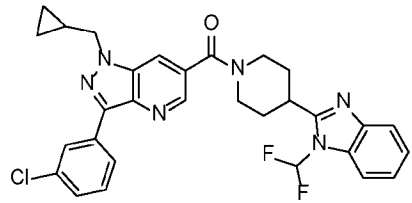
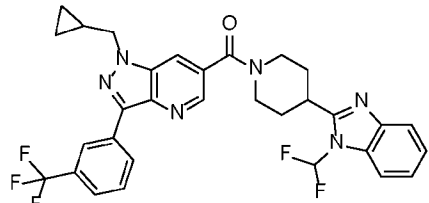
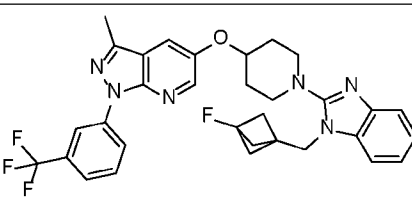
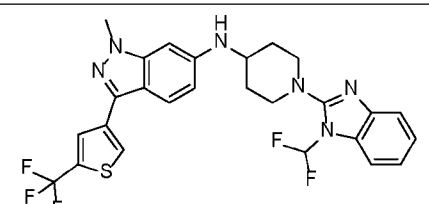
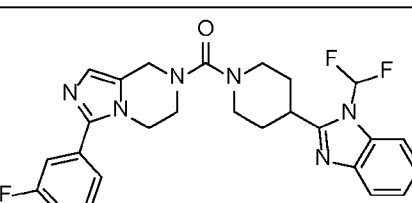
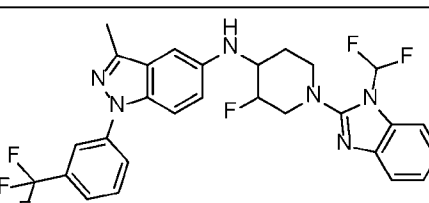
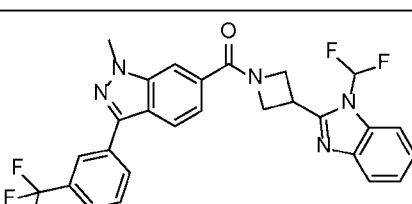
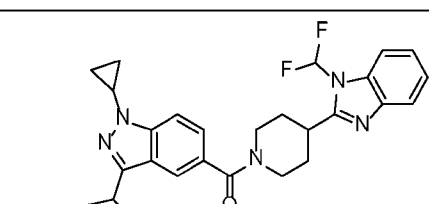
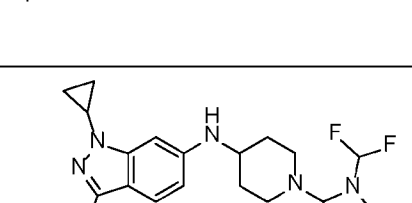
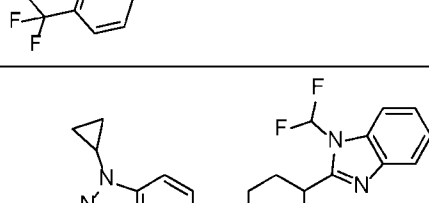
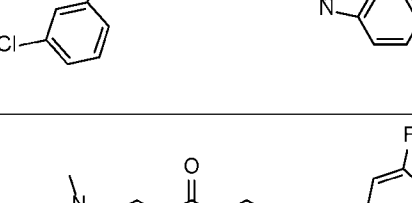
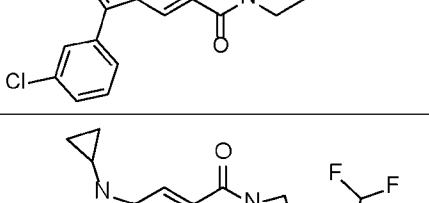
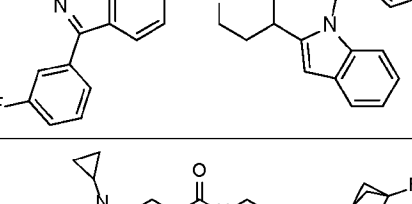
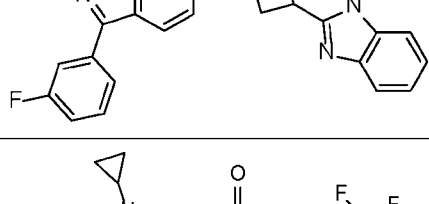
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115		122	

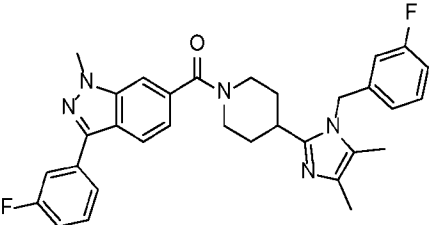
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155		157	
158		159	
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164		166	
168		170	

172		173	
174		175	
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181		183	
184		185	
192		194	
195		197	
198		204	

209		210	
220		255	
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261		273	
289		292	
293		328	
330		331	

335		336	
362		378	
406		408	
415		422	
423		424	
426		427	
428		429	

430			
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Salt Forms of Compounds

[0073] Compounds of Formula I may have a basic nitrogen atom, in which case they can exist as a free base or as salts. Such compounds can be used as a free base or as pharmaceutically acceptable salts. A basic nitrogen atom can form an addition salt with an acid, such as a mineral acid (e.g., HCl, HBr, HI, nitric acid, phosphoric acid or sulfuric acid) or an organic acid (e.g., a carboxylic acid or a sulfonic acid). Suitable acids for use in the preparation of pharmaceutically acceptable salts include without limitation acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, cyclohexanesulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, alpha-oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (±)-DL-lactic acid, (+)-L-lactic acid, lactobionic acid, lauric acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phosphoric acid, propionic acid, L-pyroglutamic acid, pyruvic acid, saccharic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (±)-DL-tartaric acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, undecylenic acid, and valeric acid.

[0074] If a compound has an acidic group (e.g., a carboxyl group), the acidic group can form an addition salt with a base. Pharmaceutically acceptable base addition salts can be formed with, e.g., metals (e.g., alkali metals or alkaline earth metals) or amines (e.g., organic amines). Examples of metals useful as cations include without limitation alkali metals (e.g., lithium, sodium, potassium and cesium), alkaline earth metals (e.g., magnesium, calcium and barium),

aluminum and zinc. Metal cations can be provided by way of, e.g., inorganic bases, such as hydroxides, carbonates and hydrogen carbonates. Non-limiting examples of organic amines useful for forming base addition salts include chlorprocaine, choline, cyclohexylamine, dibenzylamine, N,N'-dibenzylethylenediamine, dicyclohexylamine, diethanolamine, ethylenediamine, N-ethylpiperidine, histidine, isopropylamine, N-methylglucamine, procaine, pyrazine, triethylamine, trimethylamine and tromethamine. Pharmaceutically acceptable salts are discussed in detail in Handbook of Pharmaceutical Salts, Properties, Selection and Use, P. Stahl and C. Wermuth, Eds., Wiley-VCH (2011).

Pharmaceutical Compositions

[0075] The disclosure also provides pharmaceutical compositions comprising an indirect Nav1.7 inhibitor described herein ("Nav1.7 inhibitor" for brevity), or a tautomer, pharmaceutically acceptable salt, solvate, hydrate, clathrate, polymorph or stereoisomer thereof, and one or more pharmaceutically acceptable excipients or carriers. The compositions can optionally contain an additional therapeutic agent such as an additional analgesic. A pharmaceutical composition contains a therapeutically effective amount, or any appropriate fraction thereof, of a Nav1.7 inhibitor, one or more pharmaceutically acceptable excipients or carriers and optionally a therapeutically effective amount of an additional therapeutic agent, and is formulated for administration to a subject for therapeutic use. For purposes of the content of a pharmaceutical composition, the term "active ingredient", "active agent", "therapeutic agent", "drug" or the like encompasses a prodrug.

[0076] A pharmaceutical composition contains a Nav1.7 inhibitor and optionally an additional therapeutic agent in substantially pure form. In some embodiments, the purity of the Nav1.7 inhibitor and the optional additional therapeutic agent independently is at least about 95%, 96%, 97%, 98% or 99%. In addition, a pharmaceutical composition is substantially free of contaminants or impurities. In some embodiments, the level of contaminants or impurities other than residual solvent in a pharmaceutical composition is no more than about 5%, 4%, 3%, 2% or 1% relative to the combined weight of the intended active and inactive ingredients.

Pharmaceutical compositions generally are prepared according to current good manufacturing practice (GMP), as recommended or required by, e.g., the Federal Food, Drug, and Cosmetic Act §501(a)(2)(B) and the International Conference on Harmonisation Q7 Guideline.

[0077] Pharmaceutical compositions/formulations can be prepared in sterile form. For example, pharmaceutical compositions/formulations for parenteral administration by injection or infusion

generally are sterile. Sterile pharmaceutical compositions/formulations are compounded or manufactured according to pharmaceutical-grade sterilization standards known to those of skill in the art, such as those disclosed in or required by the United States Pharmacopeia Chapters 797, 1072 and 1211, and 21 Code of Federal Regulations 211.

[0078] Pharmaceutically acceptable excipients and carriers include pharmaceutically acceptable substances, materials and vehicles. Non-limiting examples of types of excipients include liquid and solid fillers, diluents, binders, lubricants, glidants, surfactants, dispersing agents, disintegration agents, emulsifying agents, wetting agents, suspending agents, thickeners, solvents, isotonic agents, buffers, pH adjusters, absorption-delaying agents, stabilizers, antioxidants, preservatives, antimicrobial agents, antibacterial agents, antifungal agents, chelating agents, adjuvants, sweetening agents, flavoring agents, coloring agents, encapsulating materials and coating materials. The use of such excipients in pharmaceutical formulations is known in the art. For example, conventional vehicles and carriers include without limitation oils (e.g., vegetable oils such as olive oil and sesame oil), aqueous solvents {e.g., saline, buffered saline (e.g., phosphate-buffered saline [PBS]) and isotonic solutions (e.g., Ringer's solution)}, and organic solvents (e.g., dimethyl sulfoxide [DMSO] and alcohols [e.g., ethanol, glycerol and propylene glycol]). Except insofar as any conventional excipient or carrier is incompatible with the active ingredient, the disclosure encompasses the use of conventional excipients and carriers in formulations containing Na_v1.7 inhibitors. See, e.g., Remington: The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins (Philadelphia, Pennsylvania) (2005); Handbook of Pharmaceutical Excipients, 5th Ed., Rowe et al., Eds., The Pharmaceutical Press and the American Pharmaceutical Association (2005); Handbook of Pharmaceutical Additives, 3rd Ed., Ash and Ash, Eds., Gower Publishing Co. (2007); and Pharmaceutical Pre-formulation and Formulation, Gibson, Ed., CRC Press (Boca Raton, Florida) (2004).

[0079] Appropriate formulation can depend on various factors, such as the route of administration chosen. Potential routes of administration of pharmaceutical compositions comprising Na_v1.7 inhibitors include without limitation oral, parenteral (including intradermal, subcutaneous, intramuscular, intravascular, intravenous, intra-arterial, intraperitoneal, intracavitary, intramedullary, intrathecal and topical), and topical (including dermal/epicutaneous, transdermal, mucosal, transmucosal, intranasal [e.g., by nasal spray or drop], ocular/intraocular [e.g., by eye drop], pulmonary [e.g., by oral or nasal inhalation], buccal,

sublingual, rectal [e.g., by suppository], and vaginal [e.g., by suppository]). Topical formulations can be designed to produce a local or systemic therapeutic effect.

[0080] As an example, formulations of Nav1.7 inhibitors suitable for oral administration can be presented in discrete units adapted for instant, controlled or sustained release as, e.g., boluses; capsules (including push-fit capsules and soft capsules), tablets, pills, cachets or lozenges; as powders or granules; as semisolids, electuaries, pastes or gels; as solutions or suspensions in an aqueous liquid or/and a non-aqueous liquid; or as oil-in-water liquid emulsions or water-in-oil liquid emulsions.

[0081] Push-fit capsules or two-piece hard gelatin capsules can contain a Nav1.7 inhibitor in admixture with, e.g., a filler or inert solid diluent (e.g., calcium carbonate, calcium phosphate, kaolin or lactose), a binder (e.g., a starch), a glidant or lubricant (e.g., talc or magnesium stearate), and a disintegrant (e.g., crospovidone), and optionally a stabilizer or/and a preservative. For soft capsules or single-piece gelatin capsules, a Nav1.7 inhibitor can be dissolved or suspended in a suitable liquid (e.g., liquid polyethylene glycol or an oil medium, such as a fatty oil, peanut oil, olive oil or liquid paraffin), and the liquid-filled capsules can contain one or more other liquid excipients or/and semi-solid excipients, such as a stabilizer or/and an amphiphilic agent (e.g., a fatty acid ester of glycerol, propylene glycol or sorbitol).

[0082] Tablets can contain a Nav1.7 inhibitor in admixture with, e.g., a filler or inert diluent (e.g., calcium carbonate, calcium phosphate, lactose, mannitol or microcrystalline cellulose), a binding agent (e.g., a starch, gelatin, acacia, alginic acid or a salt thereof, or microcrystalline cellulose), a lubricating agent (e.g., stearic acid, magnesium stearate, talc or silicon dioxide), and a disintegrating agent (e.g., crospovidone, croscarmellose sodium or colloidal silica), and optionally a surfactant (e.g., sodium lauryl sulfate). The tablets can be uncoated or can be coated with, e.g., an enteric coating that protects the active agent from the acidic environment of the stomach, or with a material that delays disintegration and absorption of the active agent in the gastrointestinal (GI) tract and thereby provides a sustained action over a longer time period.

[0083] Compositions for oral administration can also be formulated as solutions or suspensions in an aqueous liquid and/or a non-aqueous liquid, or as oil-in-water liquid emulsions or water-in-oil liquid emulsions. Dispersible powder or granules of a Nav1.7 inhibitor can be mixed with any suitable combination of an aqueous liquid, an organic solvent or/and an oil and any suitable

excipients (e.g., any combination of a dispersing agent, a wetting agent, a suspending agent, an emulsifying agent or/and a preservative) to form a solution, suspension or emulsion.

[0084] Nav1.7 inhibitors can also be formulated for parenteral administration by injection or infusion to circumvent gastrointestinal absorption and first-pass metabolism. An exemplary parenteral route is intravenous. Additional advantages of intravenous administration include direct administration of a therapeutic agent into systemic circulation to achieve a rapid systemic effect, and the ability to administer the agent continuously or/and in a large volume if desired. Formulations for injection or infusion can be in the form of, e.g., solutions, suspensions or emulsions in oily or aqueous vehicles, and can contain excipients such as suspending agents, dispersing agents or/and stabilizing agents. For example, aqueous or non-aqueous (e.g., oily) sterile injection solutions can contain a Nav1.7 inhibitor along with excipients such as an antioxidant, a buffer, a bacteriostat and solutes that render the formulation isotonic with the blood of the subject. Aqueous or non-aqueous sterile suspensions can contain a Nav1.7 inhibitor along with excipients such as a suspending agent and a thickening agent, and optionally a stabilizer and an agent that increases the solubility of the Nav1.7 inhibitor to allow for the preparation of a more concentrated solution or suspension. As another example, a sterile aqueous solution for injection or infusion (e.g., subcutaneously or intravenously) can contain a Nav1.7 inhibitor, an isotonic agent (e.g., sodium chloride), a buffering agent (e.g., sodium citrate), a preservative (e.g., meta-cresol), and optionally a base (e.g., NaOH) or/and an acid (e.g., HCl) to adjust pH.

[0085] Topical formulations for application to the skin or mucosa can be useful for transdermal or transmucosal administration of a therapeutic agent to the local target site of action, or into the blood for systemic distribution. Advantages of topical administration can include circumvention of the GI tract (including enzymes and acid in the GI tract and absorption through it) and first-pass metabolism; delivery of a therapeutic agent with a short half-life, a small therapeutic index or/and low oral bioavailability; controlled, continuous and sustained release of the therapeutic agent; a more uniform plasma level or delivery profile of the therapeutic agent; lower dose and less frequent dosing of the therapeutic agent; reduction of systemic side effects (e.g., side effects caused by a temporary overdose or an overly high peak plasma drug concentration); minimal or no invasiveness; ease of self-administration; and increased patient compliance.

[0086] Compositions suitable for topical administration include without limitation liquid or semi-liquid preparations such as sprays, gels, liniments, lotions, oil-in-water or water-in-oil

emulsions such as creams, foams, ointments and pastes, and solutions or suspensions such as drops (e.g., eye drops, nose drops and ear drops). See Remington: The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins (Philadelphia, Pennsylvania [2005]). Various excipients can be included in a topical formulation. For example, solvents, including a suitable amount of an alcohol, can be used to solubilize the active agent. Other optional excipients include without limitation gelling agents, thickening agents, emulsifiers, surfactants, stabilizers, buffers, antioxidants, preservatives, cooling agents (e.g. menthol), opacifiers, fragrances and colorants. For an active agent having a low rate of permeation through the skin or mucosal tissue, a topical formulation can contain a chemical permeation enhancer (e.g., a fatty acid ester [e.g., isopropyl myristate or isopropyl palmitate], a fatty acid [e.g., palmitic acid, oleic acid or palmitoleic acid], or/and an alcohol [e.g., propylene glycol or a fatty alcohol such as geraniol or farnesol]) to increase the permeation of the active agent through the skin or mucosal tissue. A topical formulation can also contain an irritation-mitigating excipient that reduces any irritation to the skin or mucosa caused by the active agent, the chemical permeation enhancer or any other component of the formulation. In some embodiments, a topical composition comprises a therapeutic agent dissolved, dispersed or suspended in a carrier. The carrier can be in the form of, e.g., a solution, a suspension, an emulsion, an ointment or a gel base, and can contain, e.g., petrolatum, lanolin, a wax (e.g., bee wax), mineral oil, a long-chain alcohol, polyethylene glycol or polypropylene glycol, a diluent (e.g., water or/and an alcohol [e.g., ethanol or propylene glycol]), a gel, an emulsifier, a thickening agent, a stabilizer or a preservative, or any combination thereof. A topical formulation can be administered by means of, e.g., a transdermal or transmucosal delivery device, such as a transdermal patch, a microneedle patch or an iontophoresis device. A topical composition can deliver a drug transdermally or transmucosally via a concentration gradient (with or without the use of a chemical permeation enhancer) or an active mechanism (e.g., iontophoresis or microneedles).

[0087] For topical administration, a Nav1.7 inhibitor can be formulated as, e.g., a buccal or sublingual tablet or pill. Advantages of a buccal or sublingual tablet or pill include avoidance of gastrointestinal absorption and first-pass metabolism, and rapid absorption into systemic circulation. A buccal or sublingual tablet or pill can be designed to provide faster release of the Nav1.7 inhibitor for more rapid uptake of it into systemic circulation. In addition to a therapeutically effective amount of a Nav1.7 inhibitor, the buccal or sublingual tablet or pill can contain suitable excipients, including without limitation any combination of fillers and diluents

(e.g., mannitol and sorbitol), binding agents (e.g., sodium carbonate), wetting agents (e.g., sodium carbonate), disintegrants (e.g., croscopovidone and croscarmellose sodium), lubricants (e.g., silicon dioxide [including colloidal silicon dioxide] and sodium stearyl fumarate), stabilizers (e.g., sodium bicarbonate), flavoring agents (e.g., spearmint flavor), sweetening agents (e.g., sucralose), and coloring agents (e.g., yellow iron oxide).

[0088] For topical administration, Nav1.7 inhibitors can also be formulated for intranasal administration. The nasal mucosa provides a big surface area, a porous endothelium, a highly vascular subepithelial layer and a high absorption rate, and hence allows for high bioavailability. Moreover, intranasal administration avoids first-pass metabolism. An intranasal formulation can comprise a Nav1.7 inhibitor along with excipients, such as a solubility enhancer (e.g., propylene glycol), a humectant (e.g., mannitol or sorbitol), a buffer and water, and optionally a preservative (e.g., benzalkonium chloride), a mucoadhesive agent (e.g., hydroxyethyl cellulose) or/and a penetration enhancer. An intranasal solution or suspension formulation can be administered to the nasal cavity by any suitable means, including but not limited to a dropper, a pipette, or a spray using, e.g., a metering atomizing spray pump. Table 3 shows exemplary excipients of nasal-spray formulations.

[0089] An additional mode of topical administration of Nav1.7 inhibitors is pulmonary, including by oral inhalation and nasal inhalation. A pulmonarily administered drug can treat a lung disease or/and a systemic disease, as the lungs serve as a portal to the systemic circulation. Advantages of pulmonary drug delivery include, for example: 1) avoidance of first-pass metabolism; 2) fast drug action; 3) large surface area of the alveolar region for absorption, high permeability of the lungs (thin air-blood barrier), and profuse vasculature of the airways; 4) reduced extracellular enzyme levels compared to the GI tract due to the large alveolar surface area; and 5) smaller doses to achieve equivalent therapeutic effect compared to other oral routes, and hence reduced systemic side effects. An advantage of oral inhalation over nasal inhalation includes deeper penetration/deposition of the drug into the lungs, although nasal inhalation can deliver the drug into systemic circulation transmucosally in the nasal cavity as well as in the lungs. Oral or nasal inhalation can be achieved by means of, e.g., a metered-dose inhaler (MDI), a dry powder inhaler (DPI) or a nebulizer, as is known in the art. In certain embodiments, a sterile aqueous solution for oral inhalation contains a Nav1.7 inhibitor, sodium chloride, a buffering agent (e.g., sodium citrate), optionally a preservative (e.g., meta-cresol), and optionally a base (e.g., NaOH) or/and an acid (e.g., HCl) to adjust pH. Table 3 shows other exemplary excipients of oral-inhalation formulations.

[0090] **Table 3.** Exemplary excipients and carriers of pulmonary and nasal formulations

Dosage Form	Ingredients in Addition to a Nav1.7 Inhibitor
inhalation (DPI)	lactose, starch, a starch derivative (e.g., hydroxypropylmethyl cellulose) or polyvinylpyrrolidone, and optionally magnesium stearate or/and leucine
inhalation (DPI)	mannitol, glycine, sodium citrate and NaOH
inhalation (MDI)	a propellant (e.g., 1,1,1,2-tetrafluoroethane), a surfactant (e.g., lecithin or oleic acid), and a co-solvent (e.g., ethanol)
inhalation (nebulizer)	polysorbate 80, edetate disodium, sodium chloride, pH buffering agents (e.g., citric acid/sodium citrate), and water
nasal spray	microcrystalline cellulose, sodium carboxymethylcellulose, dextrose, water, and optionally a pH adjuster (e.g., HCl)
nasal spray	microcrystalline cellulose, carboxymethyl cellulose sodium, dextrose, polysorbate 80, disodium edetate, potassium sorbate, a pH adjuster (e.g., HCl), water, and optionally an alcohol (e.g., ethanol)
nasal spray	microcrystalline cellulose, carboxymethyl cellulose sodium, dextrose, polysorbate 80, benzalkonium chloride, phenylethyl alcohol, water, and optionally an alcohol (e.g., ethanol)
nasal spray	hypromellose, benzalkonium chloride, NaCl, EDTA, citric acid, sodium phosphate dibasic, water, and optionally an alcohol (e.g., ethanol)

[0091] In some embodiments, a Nav1.7 inhibitor is administered transdermally. In certain embodiments, the topical composition or transdermal delivery system comprises a chemical permeation enhancer (e.g., a surfactant [e.g., sodium laureth sulfate], optionally in combination with an aromatic compound [e.g., phenylpiperazine]) that facilitates the transport of the Nav1.7 inhibitor across the skin. In further embodiments, the Nav1.7 inhibitor is administered via a transdermal patch. In certain embodiments, the transdermal patch is a reservoir-type patch comprising an impermeable backing layer/film, a liquid- or gel-based drug reservoir, a semi-permeable membrane that serves as a rate-limiting or rate-controlling diffusion barrier, and a skin-contacting adhesive layer. The semi-permeable membrane can be composed of, e.g., a suitable polymeric material such as cellulose nitrate or acetate, polyisobutene, polypropylene, polyvinyl acetate or a polycarbonate. In other embodiments, the transdermal patch is a drug-in-adhesive patch comprising an impermeable backing layer/film and a skin-contacting adhesive layer incorporating the drug in a polymeric or viscous adhesive. The adhesive of the drug-loaded, skin-contacting adhesive layer can be, e.g., a pressure-sensitive adhesive (PSA), such as a PSA composed of an acrylic polymer (e.g.,

polyacrylate), a polyalkylene (e.g., polyisobutylene) or a silicone-based polymer (e.g., silicone-2675 or silicone-2920). Transdermal drug-delivery systems, including patches, can be designed to provide controlled and prolonged release of a drug over a period of about 1 week, 2 weeks, 3 weeks, 1 month or longer.

[0092] Topical administration of a Nav1.7 inhibitor may be particularly advantageous for treatment of pain or a pain-associated disorder. Nav1.7 is expressed at high levels at peripheral endings in the skin and mucosa of nociceptive neurons whose cell bodies are located in the dorsal root ganglia or the trigeminal ganglia. A topical composition (e.g., a gel, ointment or cream) or a transdermal patch containing a Nav1.7 inhibitor can be applied to the skin from where the pain sensation emanates.

[0093] In some embodiments, a Nav1.7 inhibitor is delivered from a sustained-release composition. As used herein, the term “sustained-release composition” encompasses sustained-release, prolonged-release, extended-release, delayed-release, slow-release and controlled-release compositions, systems and devices. Advantages of a sustained-release composition include without limitation a more uniform blood level of the drug (e.g., avoidance of wide peak-to-trough fluctuations), delivery of a therapeutically effective amount of the drug over a prolonged time period, reduced frequency of administration, and reduced side effects (e.g., avoidance of a drug overdose). In some embodiments, the sustained-release composition delivers the Nav1.7 inhibitor over a period of at least about 3 days, 1 week, 2 weeks, 3 weeks, 1 month, 2 months or 3 months.

[0094] In some embodiments, the sustained-release composition is a drug-encapsulation system, such as nanoparticles, microparticles or a capsule made of, e.g., a biodegradable polymer or/and a hydrogel. In certain embodiments, the sustained-release composition comprises a hydrogel. Non-limiting examples of polymers of which a hydrogel can be composed include polyvinyl alcohol, acrylate polymers (e.g., sodium polyacrylate), and other homopolymers and copolymers having a relatively large number of hydrophilic groups (e.g., hydroxyl or/and carboxylate groups). In other embodiments, the sustained-release drug-encapsulation system comprises a membrane-enclosed reservoir, wherein the reservoir contains a drug and the membrane is permeable to the drug. Such a drug-delivery system can be in the form of, e.g., a transdermal patch.

[0095] In some embodiments, the sustained-release composition is formulated as polymeric nanoparticles or microparticles, wherein the polymeric particles can be delivered, e.g., by injection or from an implant. In some embodiments, the polymeric implant or polymeric nanoparticles or microparticles are composed of a biodegradable polymer. In certain embodiments, the

biodegradable polymer comprises lactic acid or/and glycolic acid [e.g., an L-lactic acid-based copolymer, such as poly(L-lactide-co-glycolide) or poly(L-lactic acid-co-D,L-2-hydroxyoctanoic acid)]. For example, biodegradable polymeric microspheres composed of polylactic acid or/and polyglycolic acid can serve as sustained-release pulmonary drug-delivery systems. The biodegradable polymer of the polymeric implant or polymeric nanoparticles or microparticles can be selected so that the polymer substantially completely degrades around the time the period of treatment is expected to end, and so that the byproducts of the polymer's degradation, like the polymer, are biocompatible.

[0096] In further embodiments, a sustained-release composition comprises a dendrimer. In certain embodiments, the dendrimer is a water-soluble dendrimer, such as a poly(amidoamine) (PAMAM) dendrimer. In some embodiments, a dendrimer encapsulates a drug through the formation of a dendrimer-drug supramolecular assembly. In other embodiments, a sustained-release composition comprises a water-soluble polymer [e.g., poly(DL-lactide)] or a liposome encapsulating a drug complexed with a dendrimer.

[0097] In other embodiments, the sustained-release composition is an oral dosage form, such as a tablet or capsule. For example, a drug can be embedded in an insoluble porous matrix such that the dissolving drug must make its way out of the matrix before it can be absorbed through the GI tract. Alternatively, a drug can be embedded in a matrix that swells to form a gel through which the drug exits. Sustained release can also be achieved by way of a single-layer or multi-layer osmotic controlled-release oral delivery system (OROS). An OROS is a tablet with a semi-permeable outer membrane and one or more small laser-drilled holes in it. As the tablet passes through the body, water is absorbed through the semi-permeable membrane via osmosis, and the resulting osmotic pressure pushes the drug out through the hole(s) in the tablet and into the GI tract where it can be absorbed.

[0098] For a delayed or sustained release of a $\text{Na}_v1.7$ inhibitor, a composition can also be formulated as, e.g., a depot that can be implanted in or injected into a subject, e.g., intramuscularly, intracutaneously or subcutaneously. A depot formulation can be designed to deliver the $\text{Na}_v1.7$ inhibitor over an extended period of time, e.g., over a period of at least about 1 week, 2 weeks, 3 weeks, 1 month, 6 weeks, 2 months, 3 months or longer. For example, a $\text{Na}_v1.7$ inhibitor can be formulated with a polymeric material (e.g., polyethylene glycol [PEG], polylactic acid [PLA] or polyglycolic acid [PGA], or a copolymer thereof [e.g., PLGA or PLA-PEG]), with a hydrophobic material (e.g., as an emulsion in an oil) and/or an ion-exchange resin,

as a more lipophilic derivative (e.g., as an ester of or a salt with a fatty acid such as a C₈-C₂₀ fatty acid [e.g., decanoic acid]), or as a sparingly soluble derivative (e.g., a sparingly soluble salt). As an illustrative example, a Nav1.7 inhibitor can be incorporated or embedded in sustained-release microparticles composed of PLGA and formulated as a monthly depot.

[0099] A Nav1.7 inhibitor can also be contained or dispersed in a matrix material. The matrix material can comprise a polymer (e.g., ethylene-vinyl acetate) and controls the release of the drug by controlling dissolution and/or diffusion of the drug from, e.g., a reservoir, and can enhance the stability of the drug while contained in the reservoir. Such a release system can be designed as a sustained-release system, can be configured as, e.g., a transdermal or transmucosal patch, and can contain an excipient that can accelerate the drug's release, such as a water-swallowable material (e.g., a hydrogel) that aids in expelling the drug out of the reservoir. US Pat. Nos. 4,144,317 and 5,797,898 describe examples of such a release system.

[00100] The release system can provide a temporally modulated release profile (e.g., pulsatile release) when time variation in plasma levels is desired, or a more continuous or consistent release profile when a constant plasma level is desired. Pulsatile release can be achieved from an individual reservoir or from a plurality of reservoirs. For example, where each reservoir provides a single pulse, multiple pulses ("pulsatile" release) are achieved by temporally staggering the single pulse release from each of multiple reservoirs. Alternatively, multiple pulses can be achieved from a single reservoir by incorporating several layers of a release system and other materials into a single reservoir. Continuous release can be achieved by incorporating a release system that degrades, dissolves, or allows diffusion of a drug through it over an extended time period. In addition, continuous release can be approximated by releasing several pulses of a drug in rapid succession ("digital" release). An active release system can be used alone or in conjunction with a passive release system, as described in US Pat. 5,797,898.

[00101] In addition, pharmaceutical compositions comprising a Nav1.7 inhibitor can be formulated as, e.g., liposomes, micelles (e.g., those composed of biodegradable natural or/and synthetic polymers, such as lactosomes), nanoparticles (e.g., lipid nanoparticles such as solid lipid nanoparticles), microparticles or microspheres, whether or not designed for sustained release. For example, liposomes can be used as sustained-release pulmonary drug-delivery systems that deliver drugs to the alveolar surface for treatment of lung diseases and systemic diseases. As another example, lipid nanoparticles containing a lipophilic drug can be delivered into the lungs by oral inhalation for treatment of a lung disorder or a systemic disorder.

[00102] In some embodiments, liposomes or micelles are composed of one or more phospholipids. Phospholipids include without limitation phosphatidic acids (e.g., DEPA, DLPA, DMPA, DOPA, DPPA and DSPA), phosphatidylcholines (e.g., DDPC, DEPC, DLPC, DLOPC, DMPC, DOPC, DPPC, DSPC, MPPC, MSPC, PLPC, PMPC, POPC, PSPC, SMPC, SOPC and SPPC), phosphatidylethanolamines (e.g., DEPE, DLPE, DMPE, DOPE, DPPE, DSPE and POPE), phosphatidylglycerols (e.g., DEPG, DLPG, DMPG, DOPG, DPPG, DSPG and POPG), phosphatidylserines (e.g., DLPS, DMPS, DOPS, DPPS and DSPS), and salts (e.g., sodium and ammonium salts) thereof. In certain embodiments, liposomes or micelles are composed of one or more phosphatidylcholines. Liposomes have a hydrophilic core, so liposomes are particularly suited for delivery of more hydrophilic drugs, whereas micelles have a hydrophobic core, so micelles are particularly suited for delivery of more hydrophobic drugs. Liposomes and micelles can permeate across biological membranes. Liposomes and micelles composed of a fusogenic lipid (e.g., DPPG) can fuse with the plasma membrane of cells and thereby deliver a drug into those cells. Liposomes and micelles can provide sustained release of a drug based in part on the rate of degradation of the liposomes and micelles.

[00103] The pharmaceutical compositions can be manufactured in any suitable manner known in the art, such as by means of conventional mixing, dissolving, suspending, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compressing processes, or any combination thereof.

[00104] The compositions can be presented in unit dosage form as a single dose wherein all active and inactive ingredients are combined in a suitable system, and components do not need to be mixed to form the composition to be administered. A unit dosage form generally contains a therapeutically effective dose of the drug, but can contain an appropriate fraction thereof so that taking multiple unit dosage forms achieves the therapeutically effective dose. Examples of a unit dosage form include a tablet, capsule, or pill for oral uptake; a solution in a pre-filled syringe of a single-use pen or a pen with a dose counter for parenteral (e.g., intravenous, subcutaneous or intramuscular) injection; a capsule, cartridge or blister pre-loaded in or manually loaded into an inhaler; and a reservoir-type transdermal patch or a drug-in-adhesive patch.

[00105] Alternatively, the compositions can be presented as a kit in which the active ingredient, excipient(s) and carrier(s) [e.g., solvent(s)] are provided in two or more separate containers (e.g., ampules, vials, tubes, bottles or syringes) and need to be combined to form the composition to be

administered. The kit can contain instructions for storing, preparing and administering the composition (e.g., a solution to be injected parenterally).

[0106] A kit can contain all active and inactive ingredients in unit dosage form or the active ingredient and inactive ingredients in two or more separate containers, and can contain instructions for administering or using the pharmaceutical composition to treat a medical condition. A kit can further contain a device for delivering the composition, such as a needle and a syringe, an injection pen, an inhaler or a transdermal patch.

[0107] In some embodiments, a kit contains a Nav1.7 inhibitor or a tautomer, pharmaceutically acceptable salt, solvate, hydrate, clathrate, isotopes, or isotopic forms including deuterated and tritiated forms, polymorph or stereoisomer thereof, or a pharmaceutical composition comprising the same, and instructions for administering or using the Nav1.7 inhibitor or the composition to treat pain or a pain-associated disorder. In certain embodiments, the kit further contains a device for delivering the Nav1.7 inhibitor or the composition, such as an injection pen, an inhaler or a transdermal patch.

Therapeutic Uses of Indirect Nav1.7 Inhibitors

[0108] The compounds disclosed herein indirectly inhibit the function of the voltage-gated sodium ion channel 1.7 (Nav1.7) by selectively inhibiting SUMOylation of collapsin response mediator protein 2 (CRMP2) and hence trafficking of Nav1.7 to the plasma membrane of nociceptive neurons. Nav1.7 plays a critical role in the transmission of acute pain and chronic pain. Therefore, the indirect Nav1.7 inhibitors ("Nav1.7 inhibitors" for brevity) disclosed herein are useful for treating pain and pain-associated disorders.

[0109] Types of pain that can be treated using the Nav1.7 inhibitors disclosed herein include without limitation acute pain, chronic pain, neuropathic pain, inflammatory pain, mechanical pain, pressure pain, tactile pain, thermal pain, cold pain, post-surgical pain, cancer pain, musculoskeletal pain (e.g., neck pain, spinal cord-related pain, lower back pain, hip pain, knee pain and joint pain), and spinal cord injury-related pain, wherein each of the preceding types of pain includes allodynia, algesia and hyperalgesia. In certain embodiments, a Nav1.7 inhibitor is used to treat acute pain. In further embodiments, a Nav1.7 inhibitor is used to treat post-surgical pain. In other embodiments, a Nav1.7 inhibitor is used to treat cancer pain. In additional embodiments, a Nav1.7 inhibitor is used to treat acute or chronic neuropathic pain. The Nav1.7 inhibitors disclosed herein can be used to treat all forms of neuropathic pain, including without

limitation chemotherapy-induced peripheral neuropathy, diabetic neuropathy, spinal cord injury-related pain, fibromyalgia and chronic regional pain syndrome.

[0110] Pain-associated disorders that can be treated using the Nav1.7 inhibitors disclosed herein include without limitation fibromyalgia, neuralgia, neuropathies (e.g., diabetic neuropathy), peripheral neuropathies (e.g., PNs induced by chemotherapy and nerve injury), chronic regional pain syndrome, musculoskeletal disorders (e.g., degenerative ones such as rheumatoid arthritis, osteoarthritis and spondylosis), headaches (e.g., migraine and tension headache), and disorders resulting from mutations in the gene encoding Nav1.7 (e.g., primary erythromelalgia and paroxysmal extreme pain disorder).

[0111] The therapeutically effective amount and frequency of administration of a Nav1.7 inhibitor may depend on various factors, including the type of pain or the pain-associated disorder being treated, the severity of the condition, the potency of the compound, the route of administration, the age, body weight, general health, gender and diet of the subject, and the response of the subject to the treatment, and can be determined by the treating physician. In some embodiments, the effective dose (e.g., maintenance dose) of a Nav1.7 inhibitor per day is about 1-500 mg, 1-100 mg, 100-200 mg, 200-300 mg, 300-400 mg or 400-500 mg, or as deemed appropriate by the treating physician, which can be administered in a single dose or in divided doses (e.g., 2, 3 or 4 times daily). In certain embodiments, the effective dose (e.g., maintenance dose) of a Nav1.7 inhibitor per day is about 1-200 mg, 1-50 mg, 50-100 mg, 100-150 mg or 150-200 mg. The dosing frequency may depend on, e.g., the route of administration chosen. For example, dosing by pulmonary administration (e.g., by oral inhalation) may occur more frequently (e.g., 2, 3 or 4 times daily). To more quickly establish a therapeutic level of the Nav1.7 inhibitor, a loading dose of the inhibitor that is greater (e.g., about 2- or 3-fold greater) than the maintenance dose can be administered at the beginning (e.g., in the first three days) of treatment followed by administration of the maintenance dose.

[0112] The length of treatment with a Nav1.7 inhibitor can be determined by the treating physician to achieve alleviation of or relief from pain. In some embodiments, an Nav1.7 inhibitor is administered for at least about 1 week, 2 weeks, 3 weeks or 4 weeks (1 month). In other embodiments, a Nav1.7 inhibitor is administered for at least about 6 weeks, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years or longer.

[0113] Furthermore, a Nav1.7 inhibitor can be taken *pro re nata* (as needed). For instance, a Nav1.7 inhibitor can be taken until relief from pain is achieved, when dosing of the Nav1.7 inhibitor can optionally be discontinued. If pain returns, use of the Nav1.7 inhibitor can be resumed. Under an alternative *pro re nata* treatment, the dose of a Nav1.7 inhibitor or/and its dosing frequency can be reduced upon alleviation of pain and then can be increased (e.g., to the previously effective dose or/and dosing frequency) if pain subsequently worsens. The appropriate dosage of, frequency of dosing of and length of treatment with a Nav1.7 inhibitor to treat pain or a pain-associated disorder can be determined by the treating physician.

[0114] A Nav1.7 inhibitor can be administered via any suitable route, which may depend on, e.g., the type of pain or the pain-associated disorder being treated and its location and the pharmacokinetics of the inhibitor. Potential routes of administration of a Nav1.7 inhibitor include without limitation oral, parenteral (including intradermal, subcutaneous, intramuscular, intravascular, intravenous, intra-arterial, intraperitoneal, intracavitary, intramedullary, intrathecal and topical), and topical (including dermal/epicutaneous, transdermal, mucosal, transmucosal, intranasal [e.g., by nasal spray or drop], ocular/intraocular [e.g., by eye drop], pulmonary [e.g., by oral or nasal inhalation], buccal, sublingual, rectal [e.g., by suppository], and vaginal [e.g., by suppository]). In certain embodiments, a Nav1.7 inhibitor is administered orally. In other embodiments, a Nav1.7 inhibitor is administered parenterally, such as intravenously, subcutaneously or intramuscularly. In further embodiments, a Nav1.7 inhibitor is administered topically, such as sublingually, transdermally (e.g., via a transdermal patch), by oral inhalation or by rectal suppository.

[0115] In some embodiments, a Nav1.7 inhibitor is used in combination with one or more additional therapeutic agents to treat pain or a pain-associated disorder. In certain embodiments, the one or more additional therapeutic agents comprise one or more additional analgesics. A Nav1.7 inhibitor may have a synergistic analgesic effect when used in combination with an additional analgesic such as an opioid (e.g., morphine, oxycodone or hydrocodone) or/and an NSAID (e.g., ibuprofen, naproxen or a COX-2 inhibitor).

[0116] Analgesics that can be used in combination with a Nav1.7 inhibitor to treat pain or a pain-associated disorder include without limitation:

acetaminophen (paracetamol);

non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, diclofenac, ibuprofen, naproxen, and cyclo-oxygenase 2 (COX-2) inhibitors (e.g., apicorib, celecoxib, etoricoxib,

firocoxib, fluorocoxibs [e.g., fluorocoxibs A-C], lumiracoxib, mavacoxib, parecoxib, rofecoxib, tilmacoxib and valdecoxib);

opioids, such as morphine, dihydromorphine, codeine, oxycodone, hydrocodone, pethidine and piritramide;

other agonists of the μ -opioid receptor, such as buprenorphine;

serotonin-norepinephrine reuptake inhibitors (SNRIs), such as duloxetine, milnacipran, tapentadol, tramadol and venlafaxine;

N-methyl-D-aspartate (NMDA) receptor antagonists, such as dextromethorphan, ketamine, ketobemidone and methadone;

anticholinergics, such as hyoscine (scopolamine) and orphenadrine;

antihistamines, such as hydroxyzine, promethazine and tripeleminamine;

cannabinoids, such as cannabidiol;

muscle relaxants, such as cyclobenzaprine; and

other types of analgesics, including carisoprodol, flupirtine, mexiletine, nefopam and ziconotide.

[0117] Other types of analgesics that are used to treat primarily neuropathic pain include anticonvulsants (e.g., carbamazepine, gabapentin, pregabalin and phenibut) and tricyclic antidepressants (e.g., amitriptyline).

Examples

[0118] The following examples are intended only to illustrate the disclosure. Other synthetic processes, assays, studies, protocols, procedures, methodologies, techniques, reagents and conditions may alternatively be used as appropriate.

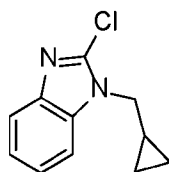
Synthesis of Compounds

[0119] All air- or moisture-sensitive reactions were performed under a positive pressure of nitrogen with oven-dried glassware. Chemical reagents and anhydrous solvents were obtained from commercial sources and used as is. Preparative purification was performed on a Waters semi-preparative HPLC. The column used was a Phenomenex LunaTM C18 (5 microns, 30 x 75 mm) at a flow rate of 45 mL/min. The mobile phase consisted of acetonitrile and water (each containing 0.1% trifluoroacetic acid [TFA]). A gradient of 10% to 50% acetonitrile over 8 minutes was used during the purification. Fraction collection was triggered by UV detection (220 nm). Purity was determined by two different methods denoted as Final QC Methods 1 and

2. **Method 1:** Analysis was performed on an Agilent 1290 Infinity Series HPLC. UHPLC Long Gradient Equivalent 4% to 100% acetonitrile (0.05% TFA) in water over 3 minutes run time of 4.5 minutes (i.e., the solvent gradient changed from 4% MeCN/H₂O to 100% MeCN in the first 0-3 min, and then remained at 100% MeCN for another 1.5 min) with a flow rate of 0.8 mL/min. A Phenomenex LunaTM C18 column (3 microns, 3 x 75 mm) was used at a temperature of 50 °C. **Method 2:** Analysis was performed on an Agilent 1260 with a 7 minute gradient of 4% to 100% acetonitrile (containing 0.025% TFA) in water (containing 0.05% TFA) over 8 minute run time at a flow rate of 1 mL/min. A Phenomenex LunaTM C18 column (3 microns, 3 x 75 mm) was used at a temperature of 50 °C. Purity determination was performed using an Agilent Diode Array Detector for both Method 1 and Method 2. Mass determination was performed using an Agilent 6130 mass spectrometer with electrospray ionization in the positive mode. All the compounds tested in the rat dorsal root ganglion (DRG) assay have a purity greater than 95% based on both analytical methods. ¹H spectra were recorded on Varian 400 (100) and 600 MHz spectrometers. High-resolution mass spectrometry was recorded on an Agilent 6210 Time-of-Flight LC/MS system.

Synthesis of Intermediates

Synthesis of 2-chloro-1-(cyclopropylmethyl)-1H-benzo[d]imidazole (**Int-1**):

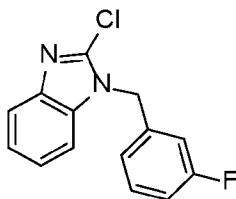


Int-1

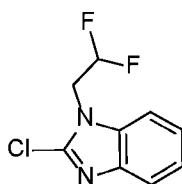
[0120] To a mixture of 2-chloro-1H-benzo[d]imidazole (3.05 g, 20 mmol) and K₂CO₃ (5.53 g, 40.0 mmol) was added a solution of (bromomethyl)cyclopropane (4.05 g, 30.0 mmol) in acetone (25 ml). The mixture was stirred at 65 °C for 5 hr. The solvent was removed and to the residue was added H₂O (60 mL)/EtOAc (60 mL) and stirred for another 15 min. The aqueous layer was extracted with EtOAc (30 mL). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 5-35% EtOAc/hexane as the eluent to give 2-chloro-1-(cyclopropylmethyl)-1H-benzo[d]imidazole (4.02 g, 19.45 mmol, 97 % yield) as an oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.65 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.59 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.31 – 7.21 (m, 2H), 4.15 (d, *J* = 7.1 Hz, 2H), 1.31 – 1.17 (m, 1H), 0.54 – 0.39 (m, 4H);); LC-MS (Method 1): *t*_R = 3.23 min, *m/z* (M+H)⁺ = 207.

Synthesis of 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole (**Int-2**):**Int-2**

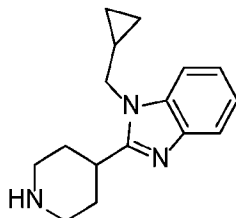
[0121] To a mixture of 2-chloro-1H-benzo[d]imidazole (6.10 g, 40 mmol) and potassium fluoride (5.23 g, 90 mmol) in MeCN (80 ml) under N₂ was added diethyl (bromodifluoromethyl)phosphonate (12.4 ml, 70.0 mmol). The mixture was stirred at rt for overnight. To the mixture was added hexane (40 mL) and the mixture was filtered through celite and eluted with CH₂Cl₂. The filtrate was concentrated and purified by silica gel chromatography using 5-25% EtOAc/hexane as the eluent to give 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole (7.75 g, 38.3 mmol, 96 % yield) as a solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.13 (t, *J* = 57.0 Hz, 1H), 7.72 (ddd, *J* = 6.9, 4.6, 1.5 Hz, 2H), 7.47 – 7.34 (m, 2H); LC-MS (Method 1): *t*_R = 3.11 min, *m/z* (M+H)⁺ = 203.

Synthesis of 2-chloro-1-(3-fluorobenzyl)-1H-benzo[d]imidazole (**Int-3**):**Int-3**

[0122] The title compound was prepared from 2-chloro-1H-benzo[d]imidazole and 1-(bromomethyl)-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-1**. LC-MS (Method 1): *t*_R = 3.24 min, *m/z* (M+H)⁺ = 261.

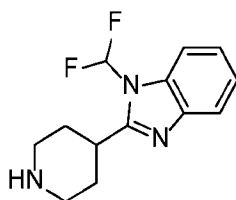
Synthesis of 2-chloro-1-(2,2-difluoroethyl)-1H-benzo[d]imidazole (**Int-4**):**Int-4**

[0123] The title compound was prepared from 2-chloro-1H-benzo[d]imidazole and 1,1-difluoro-2-iodoethane following a similar procedure as described in the synthesis of **Int-1**. LC-MS (Method 1): *t*_R = 2.86 min, *m/z* (M+H)⁺ = 217.

Synthesis of 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (**Int-5**):**Int-5**

[0124] STEP 1: In a microwave tube was placed tert-butyl 4-(1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate (3.01 g, 10 mmol) and Cs₂CO₃ (3.26 g, 10.0 mmol), and then DMF (12 ml) was added. After few minutes, (bromomethyl)cyclopropane (2.03 g, 15.0 mmol) was added. The mixture was sealed and then stirred at 60 °C for 2 hr. After cooling to rt, the mixture was poured into EtOAc (60 mL). The organic layer was washed with H₂O (60 mL x 3), dried (Na₂SO₄), and filtered. After removal of solvent, the product was purified by silica gel chromatography using 10-80% EtOAc/hexane as the eluent to give tert-butyl 4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate (2.8 g, 7.88 mmol, 79 % yield).

[0125] STEP 2: To a solution of tert-butyl 4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate (2.8 g, 7.88 mmol) in CH₂Cl₂ (20 ml) was added HCl (4M in dioxane, 47.3 mmol, 11.8 mL, 6 equiv). The mixture was stirred at rt for 2 hr. Then, hexane (30 mL) was added slowly and stirred for 30 min. After standing for 30 min, the solvent was carefully decanted by transfer pipette. The product was then dried *in vacuo* to give 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (2.50 g, 7.62 mmol, 97 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.51 – 9.38 (m, 1H), 9.14 – 9.11 (m, 1H), 8.01 – 7.94 (m, 1H), 7.83 – 7.75 (m, 1H), 7.58 – 7.48 (m, 2H), 4.39 (d, *J* = 7.1 Hz, 2H), 3.80 – 3.72 (m, 1H), 3.41 (d, *J* = 12.7 Hz, 2H), 3.22 – 3.02 (m, 2H), 2.17 (td, *J* = 10.0, 3.5 Hz, 4H), 1.31 (hept, *J* = 6.9 Hz, 1H), 0.60 – 0.50 (m, 4H) (including one salt NH); LC-MS (Method 1): *t*_R = 2.42 min, *m/z* (M+H)⁺ = 256.

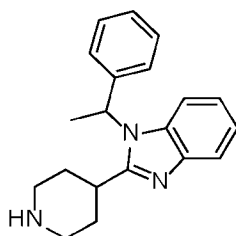
Synthesis of 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (**Int-6**):

Int-6

[0126] STEP 1: To a mixture of tert-butyl 4-(1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate (4.52 g, 15 mmol) and potassium fluoride (2.179 g, 37.5 mmol) in MeCN (30 ml) under N₂ was added diethyl (bromodifluoromethyl)phosphonate (5.33 ml, 30.0 mmol). The mixture was stirred at rt for 2 hr. To the mixture was added hexane (30 mL) and the mixture was filtered through celite and eluted with 50% EtOAc/hexane. The filtrate was concentrated and purified by silica gel chromatography using 10-50% EtOAc/hexane as the eluent to give tert-butyl 4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate (5.11 g, 14.54 mmol, 97 % yield).

[0127] STEP 2: To a solution of tert-butyl 4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate (5.11 g, 14.54 mmol) in CH₂Cl₂ (50 ml) was added HCl (4M in dioxane, 116 mmol, 29 mL, 8 equiv). The mixture was stirred at rt for 2 hr. Then, hexane (80 mL) was added and stirred for 10 min. The solid was filtered and washed with hexane (20 mL x 2). The product was transferred to a vial and dried *in vacuo* to give 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (4.097 g, 12.64 mmol, 87 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 9.23 (s, 1H), 9.04 (d, *J* = 10.4 Hz, 1H), 8.24 (t, *J* = 57.3 Hz, 1H), 7.74 – 7.62 (m, 2H), 7.39 – 7.28 (m, 2H), 3.57 – 3.45 (m, 1H), 3.37 (dt, *J* = 12.7, 3.3 Hz, 2H), 3.07 – 2.94 (m, 2H), 2.07 (h, *J* = 3.5 Hz, 4H) (including one salt NH); LC-MS (Method 1): *t*_R = 2.36 min, *m/z* (M+H)⁺ = 252.

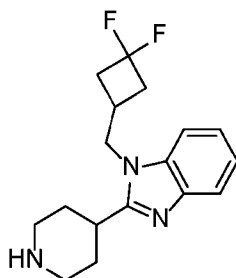
Synthesis of 1-(1-phenylethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (**Int-7**):

**Int-7**

[0128] The title compound was prepared from tert-butyl 4-(1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate and (1-bromoethyl)benzene following a similar procedure as described in the synthesis of **Int-5**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.40 (d, *J* = 11.1 Hz, 1H), 9.21 (d, *J* = 11.4 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.50 – 7.25 (m, 7H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.34 (q, *J* = 6.9 Hz, 1H), 3.88 (t, *J* = 11.5 Hz, 1H), 3.41 (d, *J* = 12.6 Hz, 2H), 3.13 – 3.02 (m,

2H), 2.39 – 2.06 (m, 4H), 2.01 (d, $J = 6.9$ Hz, 3H) (including one salt NH); LC-MS (Method 1): $t_R = 2.71$ min, m/z ($M+H$)⁺ = 306.

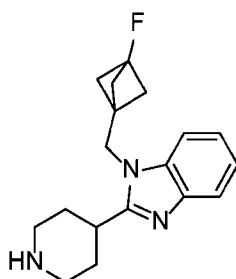
Synthesis of 1-((3,3-difluorocyclobutyl)methyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (Int-8):



Int-8

[0129] The title compound was prepared from tert-butyl 4-(1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate and 3-(bromomethyl)-1,1-difluorocyclobutane following a similar procedure as described in the synthesis of **Int-5**. ¹H NMR (400 MHz, DMSO- d_6) δ 9.52 (d, $J = 11.2$ Hz, 1H), 9.11 (d, $J = 11.2$ Hz, 1H), 8.02 (d, $J = 7.6$ Hz, 1H), 7.79 (dd, $J = 6.8, 2.2$ Hz, 1H), 7.56-7.50 (m, 2H), 4.65 (d, $J = 6.4$ Hz, 2H), 3.80 – 3.71 (m, 1H), 3.41 (d, $J = 12.7$ Hz, 2H), 3.18 – 3.04 (m, 2H), 2.75 – 2.53 (m, 5H), 2.22 – 2.13 (m, 4H) (including one salt NH).

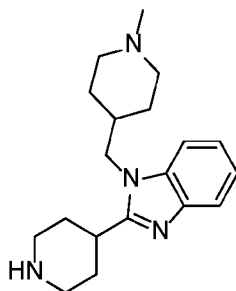
Synthesis of 1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (Int-9):



Int-9

[0130] The title compound was prepared from tert-butyl 4-(1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate and 1-(bromomethyl)-3-fluorobicyclo[1.1.1]pentane following a similar procedure as described in the synthesis of **Int-5**. ¹H NMR (400 MHz, DMSO- d_6) δ 9.52 (d, $J = 11.1$ Hz, 1H), 9.13 (d, $J = 11.1$ Hz, 1H), 7.94 – 7.87 (m, 1H), 7.81 (dt, $J = 8.3, 2.9$ Hz, 1H), 7.59 – 7.49 (m, 2H), 4.90 (s, 2H), 3.64 – 3.56 (m, 1H), 3.41 (d, $J = 12.8$ Hz, 2H), 3.12 (q, $J = 11.8$ Hz, 2H), 2.25 – 2.08 (m, 4H), 2.04 (d, $J = 2.5$ Hz, 6H) (including one salt NH).

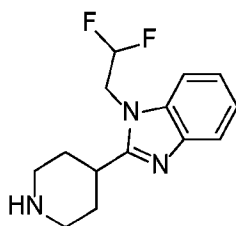
Synthesis of 1-((1-methylpiperidin-4-yl)methyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 3HCl (**Int-10**):



Int-10

[0131] The title compound was prepared from tert-butyl 4-(1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate and 4-(chloromethyl)-1-methylpiperidine, HCl following a similar procedure as described in the synthesis of **Int-5**. LC-MS (Method 1): t_R = 0.75 min, m/z ($M+H$)⁺ = 313.

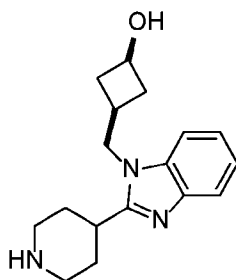
Synthesis of 1-(2,2-difluoroethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (**Int-11**):



Int-11

[0132] The title compound was prepared from tert-butyl 4-(1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate and 1,1-difluoro-2-iodoethane following a similar procedure as described in the synthesis of **Int-5**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.52 – 9.34 (m, 1H), 9.13 (d, J = 11.4 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.77 (dd, J = 6.9, 2.1 Hz, 1H), 7.53 – 7.42 (m, 2H), 6.54 (tt, J = 53.9, 3.2 Hz, 1H), 5.07 (td, J = 15.6, 3.2 Hz, 2H), 3.69 (tt, J = 10.6, 4.1 Hz, 1H), 3.41 (d, J = 12.7 Hz, 2H), 3.04 (q, J = 11.5 Hz, 2H), 2.22 – 2.09 (m, 4H) (including one salt NH); LC-MS (Method 1): t_R = 2.26 min, m/z ($M+H$)⁺ = 266.

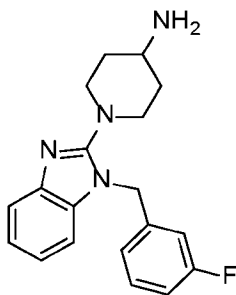
Synthesis of (1s,3s)-3-((2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol, 2HCl (**Int-12**):



Int-12

[0133] The title compound was prepared from tert-butyl 4-(1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate and (1s,3s)-3-(bromomethyl)cyclobutan-1-ol following a similar procedure as described in the synthesis of **Int-5**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.44 (d, *J* = 11.1 Hz, 1H), 9.10 (d, *J* = 11.2 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.82 – 7.74 (m, 1H), 7.61 – 7.47 (m, 2H), 4.51 (d, *J* = 5.8 Hz, 2H), 3.98 – 3.85 (m, 1H), 3.79 – 3.70 (m, 1H), 3.41 (d, *J* = 12.6 Hz, 2H), 3.14 (q, *J* = 11.4 Hz, 2H), 2.27 – 2.08 (m, 7H), 1.71 (q, *J* = 7.8 Hz, 2H); LC-MS (Method 1): *t*_R = 2.28 min, *m/z* (M+H)⁺ = 286.

Synthesis of 1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-amine, 2HCl (**Int-13**):

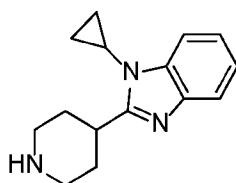


Int-13

[0134] STEP 1: To a mixture of 2-chloro-1-(3-fluorobenzyl)-1H-benzo[d]imidazole (2.61 g, 10 mmol) and tert-butyl piperidin-4-ylcarbamate (2.60 g, 13.0 mmol) was added DMSO (10 ml) and hunig's base (2.62 ml, 15.0 mmol). The tube was sealed and heated at 150 °C for overnight. After cooled to rt, the mixture was diluted with EtOAc (30 mL) and washed with H₂O (30 mL x 3). The organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 20-90% EtOAc/hexane as the eluent to give tert-butyl (1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)carbamate (3.82 g, 8.99 mmol, 90 % yield).

[0135] STEP 2: To a solution of tert-butyl (1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)carbamate (3816 mg, 8.99 mmol) in CH₂Cl₂ (12 ml) was added HCl (4M in dioxane, 54 mmol, 13.5 mL, 6 equiv). The mixture was stirred at rt for 2 hr. Some product precipitated out and hexane (60 mL) was added. The solid was filtered and washed with hexane (5 mL x2). The solid was dried in vacuo to give 1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-amine, 2HCl (3.42 g, 8.60 mmol, 96 % yield). The material was used without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 8.42 – 8.26 (m, 3H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.46 – 7.38 (m, 1H), 7.35 – 7.24 (m, 3H), 7.19 – 7.13 (m, 2H), 7.10 (d, *J* = 7.7 Hz, 1H), 5.45 (s, 2H), 3.80 (d, *J* = 13.2 Hz, 2H), 3.35 – 3.28 (m, 3H), 2.00 (dd, *J* = 13.1, 3.8 Hz, 2H), 1.74 (qd, *J* = 12.1, 4.0 Hz, 2H) (including one salt NH); LC-MS (Method 1): *t*_R = 2.36 min, *m/z* (M+H)⁺ = 325.

Synthesis of 1-cyclopropyl-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (Int-14):



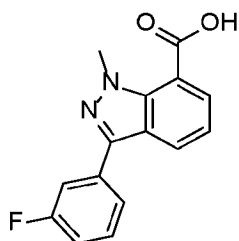
Int-14

[0136] STEP 1: To a mixture of tert-butyl 4-(1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate (3.01 g, 10 mmol), cyclopropylboronic acid (1.72 g, 20.0 mmol), copper (II) acetate (1.82 g, 10.0 mmol), 2,2'-bipyridine (1.56 g, 10.0 mmol), and Na₂CO₃ (2.12 g, 20.0 mmol) was added 1,2-dichloroethane (50 ml). The mixture equipped with a condenser was opened to air and stirred at 65 °C for overnight. After cooling to rt, the mixture was filtered through celite and eluted with CH₂Cl₂. The filtrate was concentrated and then purified by silica gel chromatography using 40-50-70% EtOAc/hexane (120g column) as the eluent to give tert-butyl 4-(1-cyclopropyl-1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate (1.896 g, 5.55 mmol, 55.5 % yield). LC-MS (Method 1): *t*_R = 2.76 min, *m/z* (M+H)⁺ = 342.

[0137] STEP 2: To a solution of tert-butyl 4-(1-cyclopropyl-1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate (1.9 g, 5.55 mmol) in CH₂Cl₂ (25 ml) was added HCl (4M in dioxane, 51.8 mmol, 12.9 mL, 8 equiv). The mixture was stirred at rt for 1.5 hr. Then, hexane (75 mL) was added and stirred for 5 min. The solvent was carefully decanted by transfer pipette. Repeat adding/removing hexane for 3 times. The left solid was dried in vacuo to give 1-cyclopropyl-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (1.692 g, 5.38 mmol, 97 % yield).

^1H NMR (400 MHz, DMSO- d_6) δ 9.47 (d, J = 11.0 Hz, 1H), 9.18 (d, J = 11.1 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.52 (t, J = 6.6 Hz, 2H), 3.79 (tt, J = 11.7, 3.4 Hz, 1H), 3.58 (tt, J = 7.4, 4.1 Hz, 1H), 3.42 (d, J = 12.7 Hz, 2H), 3.14 (q, J = 12.0 Hz, 2H), 2.27 (d, J = 13.5 Hz, 2H), 2.16 (tt, J = 12.7, 6.5 Hz, 2H), 1.33 (dt, J = 7.2, 3.5 Hz, 2H), 1.20 (p, J = 4.9 Hz, 2H) (including one salt NH); LC-MS (Method 1): t_R = 2.00 min, m/z ($M+H$) $^+$ = 242.

Synthesis of 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carboxylic acid (**Int-15**):



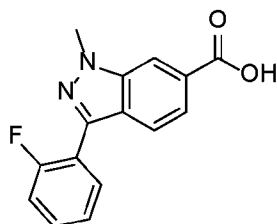
Int-15

[0138] STEP 1: In a flask was placed methyl 3-bromo-1-methyl-1H-indazole-7-carboxylate (0.54 g, 2 mmol), (3-fluorophenyl)boronic acid (0.34 g, 2.40 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (0.16 g, 0.20 mmol), and K₂CO₃ (0.99 g, 7.20 mmol). The air was removed and re-filled with N₂ (repeat for 3 times). Then, 1,4-dioxane (8 ml)/water (4 ml) was added and the mixture was stirred at 95 °C for 1.5 hr. After cooling to rt, the layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 2). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 5-40% EtOAc/hexane as the eluent to give methyl 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carboxylate (563 mg, 1.980 mmol, 99 % yield). ^1H NMR (400 MHz, CDCl₃) δ 8.14 (dd, J = 8.2, 1.2 Hz, 1H), 7.96 (dd, J = 7.5, 1.2 Hz, 1H), 7.68 (dd, J = 7.6, 1.5 Hz, 1H), 7.61 (ddd, J = 9.9, 2.8, 1.5 Hz, 1H), 7.47 (td, J = 7.9, 5.8 Hz, 1H), 7.28 – 7.19 (m, 1H), 7.11 (td, J = 8.4, 2.6 Hz, 1H), 4.30 (d, J = 0.9 Hz, 3H), 4.01 (d, J = 0.9 Hz, 3H); LC-MS (Method 1): t_R = 3.76 min, m/z ($M+H$) $^+$ = 285.

[0139] STEP 2: To a suspension of methyl 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carboxylate (555 mg, 1.95 mmol) in THF (7 ml)/MeOH (1 ml) was added 1N NaOH_(aq) (7.81 mL, 7.81 mmol, 4 equiv). The mixture was heated at 55 °C for 1.5 hr. After cooling to rt, 1N HCl_(aq) was added until the pH of aqueous layer is ca. 3.5-4. Then, hexane (35 mL) was added and the solid was filtered, washed with H₂O (5 mL x 2), hexane (5 mL x 2), and then dried to give 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carboxylic acid (450 mg, 1.665 mmol, 85 % yield). The material was pure and was used for next step without further purification. ^1H NMR

(400 MHz, DMSO- d_6) δ 13.35 (s, 1H), 8.28 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 7.2 Hz, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.69 (dt, J = 10.5, 2.0 Hz, 1H), 7.57 (q, J = 7.8 Hz, 1H), 7.35 – 7.22 (m, 2H), 4.21 (s, 3H); LC-MS (Method 1): t_R = 3.31 min, m/z (M+H) $^+$ = 271.

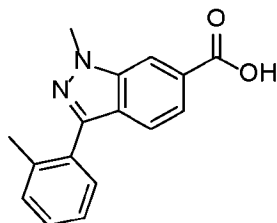
Synthesis of 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid (Int-16):



Int-16

[0140] The title compound was prepared from methyl 3-bromo-1-methyl-1H-indazole-6-carboxylate and (2-fluorophenyl)boronic acid following a similar procedure as described in the synthesis of **Int-15**. ^1H NMR (400 MHz, DMSO- d_6) δ 13.11 (s, 1H), 8.32 (s, 1H), 7.85 – 7.71 (m, 3H), 7.56 – 7.46 (m, 1H), 7.45 – 7.31 (m, 2H), 4.20 (s, 3H); LC-MS (Method 1): t_R = 3.17 min, m/z (M+H) $^+$ = 271.

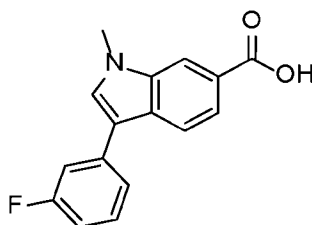
Synthesis of 1-methyl-3-(o-tolyl)-1H-indazole-6-carboxylic acid (Int-17):



Int-17

[0141] The title compound was prepared from methyl 3-bromo-1-methyl-1H-indazole-6-carboxylate and (2-methylphenyl)boronic acid following a similar procedure as described in the synthesis of **Int-15**. ^1H NMR (400 MHz, DMSO- d_6) δ 13.08 (s, 1H), 8.30 (s, 1H), 7.75 – 7.63 (m, 2H), 7.47 (d, J = 7.3 Hz, 1H), 7.42 – 7.28 (m, 3H), 4.17 (d, J = 1.1 Hz, 3H), 2.33 (s, 3H); LC-MS (Method 1): t_R = 3.31 min, m/z (M+H) $^+$ = 267.

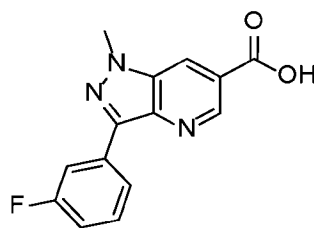
Synthesis of 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carboxylic acid (Int-18):



Int-18

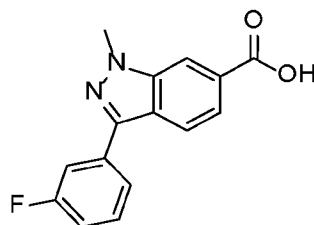
[0142] The title compound was prepared from methyl 3-bromo-1-methyl-1H-indole-6-carboxylate and (3-fluorophenyl)boronic acid following a similar procedure as described in the synthesis of **Int-15**. ¹H NMR (400 MHz, DMSO-d₆) δ 12.68 (s, 1H), 8.12 (s, 1H), 8.00 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.78 – 7.70 (m, 1H), 7.56 – 7.41 (m, 3H), 7.06 (td, *J* = 8.0, 2.2 Hz, 1H), 3.90 (s, 3H); LC-MS (Method 1): *t*_R = 3.34 min, *m/z* (M+H)⁺ = 270.

Synthesis of 3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-b]pyridine-6-carboxylic acid (**Int-19**):

**Int-19**

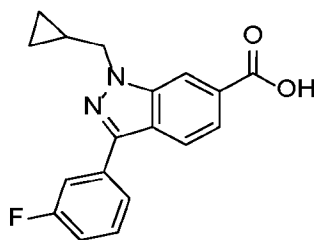
[0143] The title compound was prepared from methyl 3-bromo-1-methyl-1H-pyrazolo[4,3-b]pyridine-6-carboxylate and (3-fluorophenyl)boronic acid following a similar procedure as described in the synthesis of **Int-15**. LC-MS (Method 1): *t*_R = 3.27 min, *m/z* (M+H)⁺ = 272.

Synthesis of 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid (**Int-20**):

**Int-20**

[0144] The title compound was prepared from methyl 3-bromo-1-methyl-1H-indazole-6-carboxylate and (3-fluorophenyl)boronic acid following a similar procedure as described in the synthesis of **Int-15**. ¹H NMR (400 MHz, DMSO-d₆) δ 13.11 (s, 1H), 8.32 (s, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 7.87 – 7.68 (m, 3H), 7.57 (q, *J* = 7.7 Hz, 1H), 7.25 (td, *J* = 8.6, 2.6 Hz, 1H), 4.19 (s, 3H); LC-MS (Method 1): *t*_R = 3.32 min, *m/z* (M+H)⁺ = 271.

Synthesis of 1-(cyclopropylmethyl)-3-(3-fluorophenyl)-1H-indazole-6-carboxylic acid (**Int-21**):

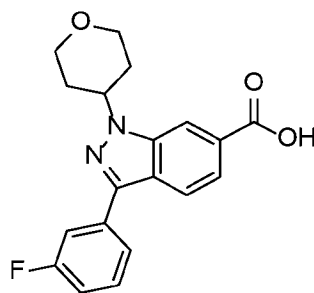
**Int-21**

[0145] STEP 1: To a mixture of methyl 3-bromo-1H-indazole-6-carboxylate (5.10 g, 20 mmol) and Cs_2CO_3 (7.82 g, 24.0 mmol) was added DMF (20 ml). The mixture was stirred at rt for 5 min and (bromomethyl)cyclopropane (2.91 ml, 30.0 mmol) was added. The mixture was sealed and heated to 60 °C for 2 hr. After cooling to rt, the mixture was diluted with EtOAc (80 mL) and the mixture was washed with H_2O (100 mL x 3). The organic layer was dried (Na_2SO_4) and filtrated. After removal of solvent, the product purified by silica gel chromatography using 5-25% EtOAc/hexane as the eluent to give methyl 3-bromo-1-(cyclopropylmethyl)-1H-indazole-6-carboxylate (4.56 g, 14.75 mmol, 73.7 % yield) [^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.40 (d, J = 1.7 Hz, 1H), 7.76 (dd, J = 8.5, 1.4 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 4.40 (d, J = 7.0 Hz, 2H), 3.90 (s, 3H), 1.27 (pd, J = 7.4, 3.5 Hz, 1H), 0.48 (dt, J = 7.7, 2.8 Hz, 2H), 0.45 – 0.35 (m, 2H); LC-MS (Method 1): t_R = 3.73 min, m/z ($\text{M}+\text{H}$) $^+$ = 310] and methyl 3-bromo-2-(cyclopropylmethyl)-2H-indazole-6-carboxylate (0.894 g, 2.89 mmol, 14.46 % yield) [^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.30 (t, J = 1.2 Hz, 1H), 7.62 (d, J = 1.4 Hz, 2H), 4.39 (d, J = 7.2 Hz, 2H), 3.87 (s, 3H), 1.38 (qq, J = 7.4, 3.7 Hz, 1H), 0.59 – 0.43 (m, 4H); LC-MS (Method 1): t_R = 3.58 min, m/z ($\text{M}+\text{H}$) $^+$ = 310].

[0146] STEP 2: In a flask was placed methyl 3-bromo-1-(cyclopropylmethyl)-1H-indazole-6-carboxylate (0.618 g, 2 mmol), (3-fluorophenyl)boronic acid (0.42 g, 3.0 mmol), $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ adduct (0.163 g, 0.20 mmol), and K_2CO_3 (1.24 g, 9.0 mmol). The air was removed and re-filled with N_2 (repeat for 3 times). Then, 1,4-Dioxane (10 ml)/Water (4.5 ml) was added and the mixture was stirred at 95 °C for 1.5 hr. After cooling to rt, the layers were separated. The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic layer was dried (Na_2SO_4) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 5-40% EtOAc/hexane as the eluent to give methyl 1-(cyclopropylmethyl)-3-(3-fluorophenyl)-1H-indazole-6-carboxylate (640 mg, 1.973 mmol, 99 % yield). LC-MS (Method 1): t_R = 3.83 min, m/z ($\text{M}+\text{H}$) $^+$ = 325.

[0147] STEP 3: To a suspension of methyl 1-(cyclopropylmethyl)-3-(3-fluorophenyl)-1H-indazole-6-carboxylate (0.64 g, 1.97 mmol) in THF (10 mL)/MeOH (1 mL) was added 1N NaOH_(aq) (10 mL, 10 mmol, ca. 5 equiv). The mixture was heated at 55 °C for 2 hr. After cooling to rt, 1N HCl_(aq) was added until the pH of aqueous layer is ca. 3. Then, hexane (40 mL) was added. The solid was filtered, washed with H₂O (3 mL x 3), hexane (3 mL x 2), and dried *in vacuo* to give 1-(cyclopropylmethyl)-3-(3-fluorophenyl)-1H-indazole-6-carboxylic acid (562 mg, 1.811 mmol, 92 % yield). The material was quite pure and used for next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 13.13 (s, 1H), 8.38 (s, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.81 – 7.69 (m, 2H), 7.57 (td, *J* = 8.1, 6.2 Hz, 1H), 7.25 (td, *J* = 8.6, 2.6 Hz, 1H), 4.47 (d, *J* = 7.0 Hz, 2H), 1.34 (ddt, *J* = 12.1, 7.8, 4.9 Hz, 1H), 0.50 (dtd, *J* = 8.4, 5.7, 2.9 Hz, 2H), 0.49 – 0.39 (m, 2H) LC-MS (Method 1): *t*_R = 3.46 min, *m/z* (M+H)⁺ = 311.

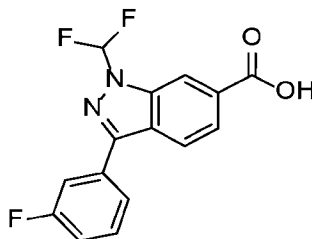
Synthesis of 3-(3-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)-1H-indazole-6-carboxylic acid (Int-22):



Int-22

The title compound was prepared from methyl 3-bromo-1H-indazole-6-carboxylate and tetrahydro-2H-pyran-4-yl methanesulfonate following a similar procedure as described in the synthesis of **Int-21**. The regio-isomers were separated in step 2. ¹H NMR (400 MHz, DMSO-d₆) δ 13.16 (s, 1H), 8.46 (s, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.78 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.73 (dt, *J* = 10.0, 2.2 Hz, 1H), 7.57 (td, *J* = 8.0, 6.2 Hz, 1H), 7.25 (td, *J* = 8.7, 2.6 Hz, 1H), 5.15 (dq, *J* = 11.1, 5.5 Hz, 1H), 4.01 (dd, *J* = 11.3, 4.4 Hz, 2H), 3.67 – 3.54 (m, 2H), 2.20 (qd, *J* = 12.1, 4.4 Hz, 2H), 1.95 (dd, *J* = 13.0, 3.9 Hz, 2H); LC-MS (Method 1): *t*_R = 3.34 min, *m/z* (M+H)⁺ = 341.

Synthesis of 1-(difluoromethyl)-3-(3-fluorophenyl)-1H-indazole-6-carboxylic acid (**Int-23**):



Int-23

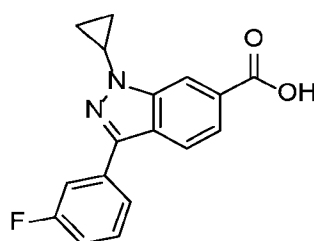
[0148] STEP 1: To a mixture of methyl 3-bromo-1H-indazole-6-carboxylate (2.55 g, 10 mmol) and potassium fluoride (1.16 g, 20.0 mmol) in MeCN (20 ml) under N₂ was added diethyl (bromodifluoromethyl)phosphonate (2.66 ml, 15.0 mmol). The mixture was stirred at rt for 24h. Another diethyl (bromodifluoromethyl)phosphonate (1.77 ml, 10.0 mmol, 1 equiv) and KF (581 mg, 10 mmol, 1 equiv) were added and stirred for another 24 h at rt. To the mixture was added hexane (10 mL) and the mixture was filtered through celite and eluted with CH₂Cl₂. The filtrate was concentrated and purified by silica gel chromatography using 5-25% EtOAc/hexane as the eluent to give methyl 3-bromo-1-(difluoromethyl)-1H-indazole-6-carboxylate (850 mg, 2.79 mmol, 27.9 % yield) (LC-MS (Method 1): *t*_R = 3.57 min, *m/z* (M+H)⁺ = 306) and methyl 3-bromo-2-(difluoromethyl)-2H-indazole-6-carboxylate (1140 mg, 3.74 mmol, 37.4 % yield) (LC-MS (Method 1): *t*_R = 3.37 min, *m/z* (M+H)⁺ = 306).

[0149] STEP 2: In a flask was placed methyl 3-bromo-1-(difluoromethyl)-1H-indazole-6-carboxylate (0.610 g, 2 mmol), (3-fluorophenyl)boronic acid (0.364 g, 2.60 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (0.163 g, 0.20 mmol), and K₂CO₃ (1.078 g, 7.80 mmol). The air was removed and re-filled with N₂ (repeat for 3 times). Then, 1,4-Dioxane (8 ml)/Water (4 ml) was added and the mixture was stirred at 90 °C for 1.5 hr. After cooling to rt, the layers were separated and the aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-20% EtOAc/hexane as the eluent to give methyl 1-(difluoromethyl)-3-(3-fluorophenyl)-1H-indazole-6-carboxylate (534 mg, 1.667 mmol, 83 % yield). LC-MS (Method 1): *t*_R = 3.75 min, *m/z* (M+H)⁺ = 321.

[0150] STEP 3: To a suspension of methyl 1-(difluoromethyl)-3-(3-fluorophenyl)-1H-indazole-6-carboxylate (0.641 g, 2 mmol) in THF (8 ml)/MeOH (1 ml) was added 1N NaOH_(aq) (8 mL, 8 mmol, 4 equiv). The mixture was heated at 55 °C for 1.5 hr. After cooling to rt, 1N HCl_(aq) was added until the pH of aqueous layer is ca. 3. Then hexane (20 mL) was added, but no solid

formed. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (15 mL x 2). The organic layers were combined, dried (Na_2SO_4) and filtered. After removal of solvent, the product became solid and was triturated with 1% CH_2Cl_2 /hexane and then dried to give 1-(difluoromethyl)-3-(3-fluorophenyl)-1H-indazole-6-carboxylic acid (605 mg, 1.976 mmol, 99 % yield). The material was pure and was used for next step without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 13.45 (s, 1H), 8.49 (s, 1H), 8.40 (t, $J = 57.6$ Hz, 1H), 8.29 (d, $J = 8.6$ Hz, 1H), 7.96 (dd, $J = 8.5, 1.3$ Hz, 1H), 7.87 (d, $J = 7.7$ Hz, 1H), 7.77 (dt, $J = 10.1, 2.1$ Hz, 1H), 7.64 (td, $J = 8.0, 6.0$ Hz, 1H), 7.38 (td, $J = 8.6, 2.5$ Hz, 1H); LC-MS (Method 1): $t_R = 3.42$ min, m/z ($\text{M}+\text{H}$) $^+ = 307$.

Synthesis of 1-cyclopropyl-3-(3-fluorophenyl)-1H-indazole-6-carboxylic acid (Int-24):



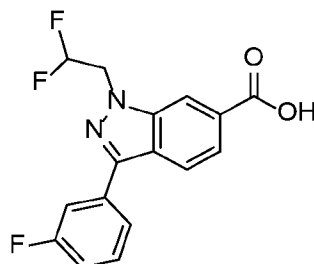
Int-24

[0151] STEP 1: To a mixture of methyl 3-(3-fluorophenyl)-1H-indazole-6-carboxylate (0.27 g, 1 mmol), cyclopropylboronic acid (0.172 g, 2.0 mmol), copper (II) acetate (0.182 g, 1.0 mmol), 2,2'-bipyridine (0.156 g, 1.0 mmol), and Na_2CO_3 (0.212 g, 2.0 mmol) was added 1,2-dichloroethane (5 ml). The mixture was opened to air and stirred at 65 °C for 8 hr. After cooling to rt, the mixture was filter through celite and eluted with CH_2Cl_2 . The filtrate was concentrated and then purified by silica gel chromatography using 0-20% EtOAc/hexane as the eluent to give methyl 1-cyclopropyl-3-(3-fluorophenyl)-1H-indazole-6-carboxylate (269 mg, 0.867 mmol, 87 % yield). LC-MS (Method 1): $t_R = 3.85$ min, m/z ($\text{M}+\text{H}$) $^+ = 311$.

[0152] STEP 2: To a suspension of methyl 1-cyclopropyl-3-(3-fluorophenyl)-1H-indazole-6-carboxylate (269 mg, 0.87 mmol) in THF (4 ml)/MeOH (1 ml) was added 1N $\text{NaOH}_{(\text{aq})}$ (4.33 mL, 4.33 mmol, 5 equiv). The mixture was heated at 55 °C for 1.5 hr. After cooling to rt, 1N $\text{HCl}_{(\text{aq})}$ was added until the pH of aqueous layer is ca. 3. Then hexane (30 mL) was added and the solid was filtered, washed with H_2O (5 mL x 2), hexane (5 mL x 2), and then dried to give 1-cyclopropyl-3-(3-fluorophenyl)-1H-indazole-6-carboxylic acid (200 mg, 0.675 mmol, 78 % yield). The material was pure enough and used for next step without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 13.21 (s, 1H), 8.34 (t, $J = 1.0$ Hz, 1H), 8.17 (d, $J = 8.6$ Hz, 1H),

7.85 – 7.75 (m, 2H), 7.71 (ddd, $J = 10.3, 2.6, 1.5$ Hz, 1H), 7.56 (td, $J = 8.0, 6.2$ Hz, 1H), 7.25 (td, $J = 8.5, 2.3$ Hz, 1H), 3.94 (p, $J = 5.4$ Hz, 1H), 1.21 (d, $J = 4.7$ Hz, 4H); LC-MS (Method 1): $t_R = 3.42$ min, m/z (M+H)⁺ = 297.

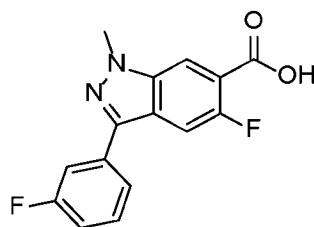
Synthesis of 1-(2,2-difluoroethyl)-3-(3-fluorophenyl)-1H-indazole-6-carboxylic acid (**Int-25**):



Int-25

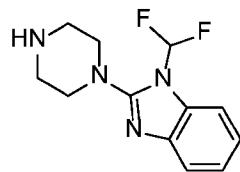
[0153] The title compound was prepared from methyl 3-bromo-1H-indazole-6-carboxylate and 1,1-difluoro-2-iodoethane following a similar procedure as described in the synthesis of **Int-21**. The regio-isomers were separated in step 1. ¹H NMR (400 MHz, DMSO-d₆) δ 13.21 (s, 1H), 8.44 (s, 1H), 8.20 (d, $J = 8.6$ Hz, 1H), 7.88 – 7.78 (m, 2H), 7.73 (dt, $J = 10.2, 2.2$ Hz, 1H), 7.59 (td, $J = 8.0, 6.2$ Hz, 1H), 7.29 (td, $J = 8.6, 2.6$ Hz, 1H), 6.50 (tt, $J = 54.6, 3.4$ Hz, 1H), 5.13 (td, $J = 15.5, 3.3$ Hz, 2H); LC-MS (Method 1): $t_R = 3.29$ min, m/z (M+H)⁺ = 321.

Synthesis of 5-fluoro-3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid (**Int-26**):



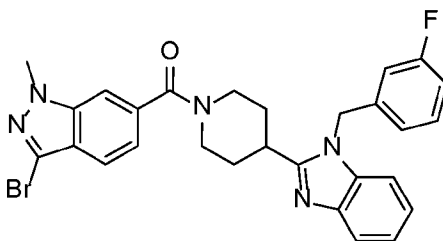
Int-26

[0154] The title compound was prepared from methyl 3-bromo-5-fluoro-1H-indazole-6-carboxylate and iodomethane following a similar procedure as described in the synthesis of **Int-21**. The regio-isomers were separated in step 2. ¹H NMR (400 MHz, DMSO-d₆) δ 13.42 (s, 1H), 8.25 (d, $J = 5.9$ Hz, 1H), 8.00 (d, $J = 11.4$ Hz, 1H), 7.83 (dt, $J = 7.8, 1.2$ Hz, 1H), 7.72 (ddd, $J = 10.4, 2.6, 1.6$ Hz, 1H), 7.55 (td, $J = 8.0, 6.2$ Hz, 1H), 7.28 – 7.19 (m, 1H), 4.18 (s, 3H); LC-MS (Method 1): $t_R = 3.27$ min, m/z (M+H)⁺ = 289.

Synthesis of 1-(difluoromethyl)-2-(piperazin-1-yl)-1H-benzo[d]imidazole, 2HCl (**Int-27**):**Int-27**

[0155] STEP 1: To a mixture of 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole (506 mg, 2.5 mmol) and tert-butyl piperazine-1-carboxylate (559 mg, 3.0 mmol) was added DMSO (2.5 ml) and hunig's base (1.092 ml, 6.25 mmol). The mixture was sealed and heated at 150 °C for 1 hr. After cooling to rt, the mixture was diluted with EtOAc (10 mL) and washed with H₂O (10 mL x3). The organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 10-40% EtOAc/hexane as the eluent to give tert-butyl 4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperazine-1-carboxylate (863 mg, 2.449 mmol, 98 % yield). LC-MS (Method 1): *t_R* = 3.34 min, *m/z* (M+H)⁺ = 353.

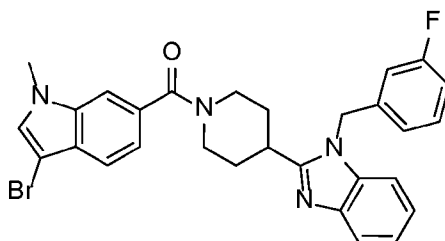
[0156] STEP 2: To a solution of tert-butyl 4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperazine-1-carboxylate (863 mg, 2.45 mmol) in CH₂Cl₂ (6 ml) was added HCl (4M in dioxane, 19.6 mmol, 4.9 mL, 8 equiv). The mixture was stirred at rt for 2 hr. Then, hexane (20 mL) was added slowly and was stirred for 10 min. Carefully removed the solvent and repeated adding/removal of hexane for 3 times. The residue was dried *in vacuo* to give 1-(difluoromethyl)-2-(piperazin-1-yl)-1H-benzo[d]imidazole, 2HCl (785 mg, 2.414 mmol, 99 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.41 (s, 2H), 7.82 (t, *J* = 57.5 Hz, 1H), 7.54 (ddd, *J* = 6.0, 3.4, 1.8 Hz, 2H), 7.26 (tt, *J* = 7.6, 5.9 Hz, 2H), 3.49 (dd, *J* = 6.7, 3.6 Hz, 4H), 3.29 (p, *J* = 4.7 Hz, 4H). (including one salt NH); LC-MS (Method 1): *t_R* = 2.35 min, *m/z* (M+H)⁺ = 253.

Synthesis of (3-bromo-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (**Int-28**):**Int-28**

[0157] To a mixture of 3-bromo-1-methyl-1H-indazole-6-carboxylic acid (0.77 g, 3 mmol), 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (1.147 g, 3.0 mmol), and HATU

(1.71 g, 4.5 mmol) was added DMF (6 ml) and then Hunig's base (2.62 ml, 15.00 mmol). The mixture was stirred at rt for 1.5 hr. The mixture was dropped into EtOAc/H₂O (50 mL/50 mL). The organic layer was washed with H₂O (50 mL). Some insoluble side product was filtered out. The filtrate was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-5% MeOH/EtOAc as the eluent to give (3-bromo-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (1.396 g, 2.55 mmol, 85 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 7.81 (s, 1H), 7.63 – 7.59 (m, 2H), 7.40 – 7.31 (m, 2H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.19 – 7.12 (m, 2H), 7.08 (td, *J* = 8.6, 2.6 Hz, 1H), 6.93 (dd, *J* = 10.0, 2.7 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 5.58 (s, 2H), 4.56 (br s, 1H), 4.06 (s, 3H), 3.64 – 3.58 (m, 1H), 3.36 – 3.18 (m, 1H), 3.18 (br s, 1H), 2.99 (br s, 1H), 1.93 – 1.61 (m, 4H); LC-MS (Method 1): *t*_R = 3.01 min, *m/z* (M+H)⁺ = 546, 548.

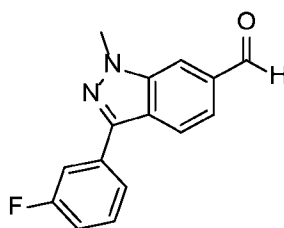
Synthesis of (3-bromo-1-methyl-1H-indol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Int-29):



Int-29

[0158] The title compound was prepared from 3-bromo-1-methyl-1H-indole-6-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in the synthesis of **Int-28**. LC-MS (Method 1): *t*_R = 3.18 min, *m/z* (M+H)⁺ = 545, 547.

Synthesis of 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde (Int-30):



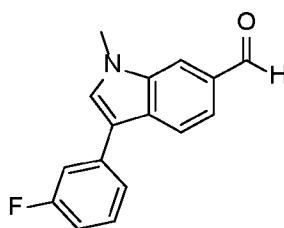
Int-30

[0159] STEP 1: To a solution of methyl 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylate (0.711 g, 2.5 mmol) in THF (5 ml) at rt was added DIBAL-H (1M in CH₂Cl₂, 7.5 mL, 7.5 mmol, 3 equiv) dropwise. The mixture was stirred for another 2 hr. The mixture was slowly poured into

a vigorously stirred mixture of sat. Rochelle salt aqueous/H₂O/EtOAc (20 mL/10 mL/40 mL). The mixture was stirred for 4-5 hr and the layers were separated. The organic layer was washed with H₂O (40 mL), dried (Na₂SO₄) and filtered. After removal of solvent, the product was dried to give (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanol (630 mg, 2.458 mmol, 98 % yield). The product was pure and used for next step without further purification. LC-MS (Method 1): t_R = 3.11 min, m/z (M+H)⁺ = 257.

[0160] STEP 2: To a solution of (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanol (0.4 g, 1.56 mmol) in CH₂Cl₂ (8 ml) was added activated MnO₂ (2 g, 23 mmol, 15 equiv). The mixture was stirred at rt for 2 hr. The mixture was filtered through a pad of celite and eluted with CH₂Cl₂. The filtrate was concentrated and the product was dried *in vacuo* to give 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde (323 mg, 1.27 mmol, 81 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 10.15 (s, 1H), 8.39 (s, 1H), 8.26 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 7.7 Hz, 1H), 7.77 – 7.68 (m, 2H), 7.58 (td, J = 8.0, 6.3 Hz, 1H), 7.26 (td, J = 8.9, 2.6 Hz, 1H), 4.22 (s, 3H); LC-MS (Method 1): t_R = 3.54 min, m/z (M+H)⁺ = 255.

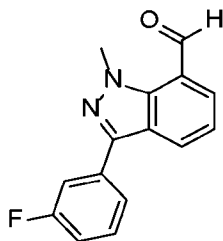
Synthesis of 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde (Int-31):



Int-31

[0161] The title compound was prepared from methyl 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carboxylate following a similar procedure as described in the synthesis of **Int-30**. ¹H NMR (400 MHz, DMSO-d₆) δ 10.05 (s, 1H), 8.15 (s, 1H), 8.10 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 8.4, 1.4 Hz, 1H), 7.57 – 7.42 (m, 3H), 7.13 – 7.03 (m, 1H), 3.95 (d, J = 1.3 Hz, 3H); LC-MS (Method 1): t_R = 3.58 min, m/z (M+H)⁺ = 254.

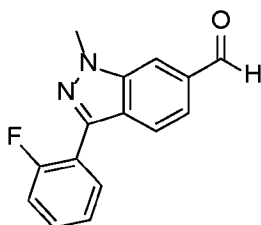
Synthesis of 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde (Int-32):



Int-32

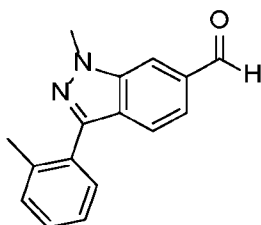
[0162] The title compound was prepared from methyl 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carboxylate following a similar procedure as described in the synthesis of **Int-30**. ¹H NMR (400 MHz, DMSO-d₆) δ 10.35 (d, *J* = 1.1 Hz, 1H), 8.41 (dd, *J* = 8.2, 1.3 Hz, 1H), 8.09 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.83 – 7.76 (m, 1H), 7.69 (ddd, *J* = 10.3, 2.8, 1.5 Hz, 1H), 7.58 (q, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.28 (td, *J* = 8.7, 2.8 Hz, 1H), 4.41 (d, *J* = 1.2 Hz, 3H); LC-MS (Method 1): *t*_R = 3.65 min, *m/z* (M+H)⁺ = 255.

Synthesis of 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde (**Int-33**):

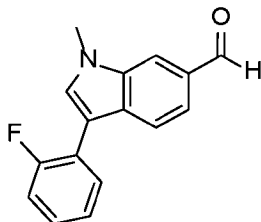
**Int-33**

[0163] The title compound was prepared from methyl 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carboxylate following a similar procedure as described in the synthesis of **Int-30**. ¹H NMR (400 MHz, DMSO-d₆) δ 10.15 (s, 1H), 8.39 (s, 1H), 7.89 (dd, *J* = 8.5, 3.1 Hz, 1H), 7.78 (td, *J* = 7.6, 2.0 Hz, 1H), 7.72 – 7.65 (m, 1H), 7.53 (dt, *J* = 9.2, 6.6 Hz, 1H), 7.46 – 7.32 (m, 2H), 4.24 (d, *J* = 1.2 Hz, 3H); LC-MS (Method 1): *t*_R = 3.46 min, *m/z* (M+H)⁺ = 255.

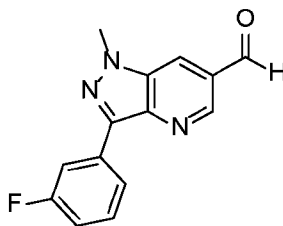
Synthesis of 1-methyl-3-(o-tolyl)-1H-indazole-6-carbaldehyde (**Int-34**):

**Int-34**

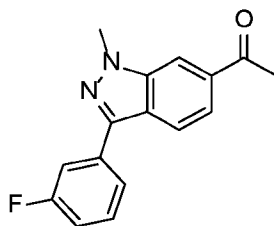
[0164] The title compound was prepared from methyl 1-methyl-3-(o-tolyl)-1H-indazole-6-carboxylate following a similar procedure as described in the synthesis of **Int-30**. ¹H NMR (400 MHz, DMSO-d₆) δ 10.15 (s, 1H), 8.37 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.64 (dt, *J* = 8.3, 1.3 Hz, 1H), 7.48 (d, *J* = 7.1 Hz, 1H), 7.43 – 7.29 (m, 3H), 4.21 (d, *J* = 1.2 Hz, 3H), 2.33 (s, 3H); LC-MS (Method 1): *t*_R = 3.54 min, *m/z* (M+H)⁺ = 251.

Synthesis of 3-(2-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde (**Int-35**):**Int-35**

[0165] The title compound was prepared from methyl 3-(2-fluorophenyl)-1-methyl-1H-indole-6-carboxylate following a similar procedure as described in the synthesis of **Int-30**. ¹H NMR (400 MHz, DMSO-d₆) δ 10.06 (s, 1H), 8.16 (s, 1H), 7.95 (d, J = 1.8 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.72 – 7.61 (m, 2H), 7.40 – 7.25 (m, 3H), 3.97 (s, 3H); LC-MS (Method 1): t_R = 3.57 min, m/z (M+H)⁺ = 254.

Synthesis of 3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-b]pyridine-6-carbaldehyde (**Int-36**):**Int-36**

[0166] The title compound was prepared from methyl 3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-b]pyridine-6-carboxylate following a similar procedure as described in the synthesis of **Int-30**. LC-MS (Method 1): t_R = 3.48 min, m/z (M+H)⁺ = 256.

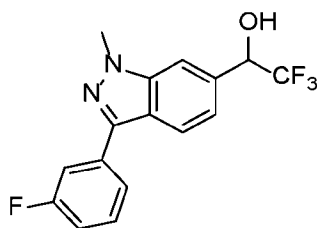
Synthesis of 1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethan-1-one (**Int-37**):**Int-37**

[0167] STEP 1: To a solution of 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde (0.763 g, 3 mmol) in 0 °C was added methylmagnesium bromide (4.29 ml, 6.0 mmol) (1.4 M in THF/toluene=1/3) dropwise. The mixture was allowed to warm to rt and stirred for another 1 hr. The mixture was cooled to 0 °C and quenched with NH₄Cl (aq) (3 mL). The mixture was poured

into EtOAc/H₂O (30 mL/30 mL). The organic layer was separated, dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 20-70% EtOAc/hexane as the eluent to give 1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethan-1-ol (684 mg, 2.53 mmol, 84 % yield). LC-MS (Method 1): t_R = 3.31 min, m/z (M+H)⁺ = 271.

[0168] STEP 2: To a solution of 1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethan-1-ol (0.684 g, 2.53 mmol) in CH₂Cl₂ (20 ml) was added activated MnO₂ (4.4 g, 50.6 mmol, 20 eq). The mixture was stirred at rt for overnight. The mixture was filtered through a pad of celite and eluted with CH₂Cl₂. The filtrate was concentrated and the product was dried *in vacuo* to give 1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethan-1-one (630 mg, 2.348 mmol, 93 % yield). The product was pure and was used for next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 8.40 (s, 1H), 8.18 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.77-7.70 (m, 2H), 7.57 (td, J = 8.1, 6.3 Hz, 1H), 7.25 (td, J = 8.7, 2.6 Hz, 1H), 4.21 (d, J = 1.2 Hz, 3H), 2.71 (d, J = 1.2 Hz, 3H); LC-MS (Method 1): t_R = 3.55 min, m/z (M+H)⁺ = 269.

Synthesis of 2,2,2-trifluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethan-1-ol (Int-38):

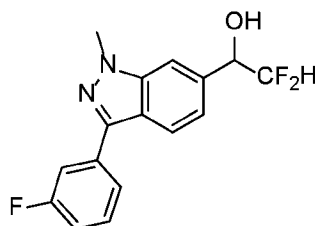


Int-38

[0169] To a solution of 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde (1.02 g, 4 mmol) in DMF (6 ml) at rt was added trimethyl(trifluoromethyl)silane (0.89 ml, 6.0 mmol) and then catalytic amount of tetrabutylammonium fluoride (0.08 ml, 0.08 mmol) (1M in THF, 0.08 mL). The mixture was stirred at rt for 1 hr. Then, the reaction was quenched with H₂O (2 mL) and TBAF (1M in THF, 0.5 mL). The mixture was stirred at rt for another 1 hr to make sure cleavage of TMS group. The mixture was diluted with EtOAc (30 mL) and washed with H₂O (30 mL x 2), dried (Na₂SO₄), and filtered. After removal of solvent, the product was dried *in vacuo* to give 2,2,2-trifluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethan-1-ol (1.29 g, 3.98 mmol, 99 % yield). The material was pure and used for next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 8.12 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 6.4 Hz, 2H), 7.71 (dt, J = 10.6, 2.1 Hz, 1H), 7.55 (td, J = 8.0, 6.1 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.22 (td, J = 8.6, 2.5

Hz, 1H), 7.01 (d, $J = 5.6$ Hz, 1H), 5.33 (p, $J = 7.0$ Hz, 1H), 4.12 (s, 3H); LC-MS (Method 1): $t_R = 3.48$ min, m/z (M+H)⁺ = 325.

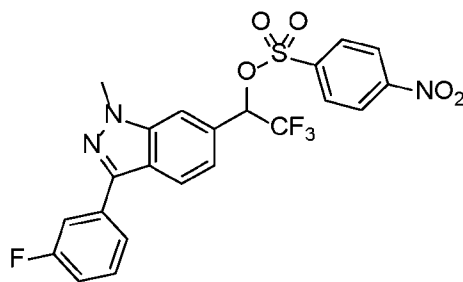
Synthesis of 2,2-difluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethan-1-ol (Int-39):



Int-39

[0170] To a solution of 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde (1.27 g, 5 mmol) in DMF (6 ml) at rt was added (difluoromethyl)trimethylsilane (1.24 g, 10.0 mmol) and then catalytic amount of CsF (0.152 g, 1.0 mmol). The mixture was stirred at rt for 1 hr. Then the reaction was quenched with TBAF (1M in THF, 5 mL). The mixture was stirred at rt for another 1 hr to make sure cleavage of TMS group. The mixture was diluted with EtOAc (30 mL) and washed with H₂O (30 mL x 2), dried (Na₂SO₄), and filtered. After removal of solvent, the product was dried *in vacuo* to give 2,2-difluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethan-1-ol (1.341 g, 4.38 mmol, 88 % yield). The material was pure and used for next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 8.08 (d, $J = 8.5$ Hz, 1H), 7.83 (d, $J = 7.7$ Hz, 1H), 7.75 (s, 1H), 7.70 (dt, $J = 10.4, 2.2$ Hz, 1H), 7.55 (td, $J = 8.0, 6.2$ Hz, 1H), 7.31 (d, $J = 8.5$ Hz, 1H), 7.22 (td, $J = 8.6, 2.6$ Hz, 1H), 6.37 (d, $J = 5.1$ Hz, 1H), 6.10 (td, $J = 55.6, 4.0$ Hz, 1H), 4.93 (td, $J = 11.6, 5.6$ Hz, 1H), 4.11 (s, 3H); LC-MS (Method 1): $t_R = 3.33$ min, m/z (M+H)⁺ = 307.

Synthesis of 2,2,2-trifluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethyl 4-nitrobenzenesulfonate (Int-40):

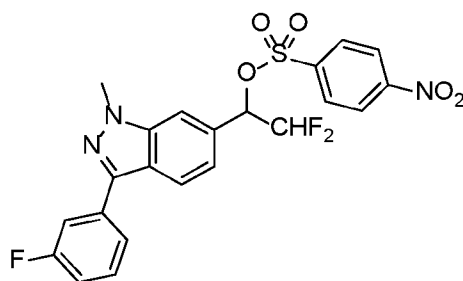


Int-40

[0171] To a solution of 2,2,2-trifluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethan-1-ol (324 mg, 1 mmol) in CH₂Cl₂ (3 ml) was added DMAP (6.11 mg, 0.05 mmol), Et₃N (0.348 ml,

2.50 mmol), and then 4-nitrobenzenesulfonyl chloride (332 mg, 1.50 mmol). The mixture was stirred at rt for 1.5 hr. The mixture was poured into EtOAc/H₂O (15 mL/15 mL). The organic layer was then washed with H₂O (15 mL), 1N HCl (aq)/H₂O (5 mL/10 mL), H₂O (15 mL). The organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography (24g gold column) using 5-35% EtOAc/hexane as the eluent to give 2,2,2-trifluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethyl 4-nitrobenzenesulfonate (460 mg, 0.903 mmol, 90 % yield). LC-MS (Method 1): *t*_R = 3.77 min, *m/z* (M+H)⁺ = 510.

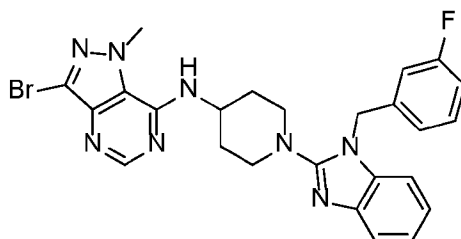
Synthesis of 2,2-difluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethyl 4-nitrobenzenesulfonate (Int-41):



Int-41

[0172] The title compound was prepared from 2,2-difluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethan-1-ol following a similar procedure as described in the synthesis of **Int-40**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.21 – 8.13 (m, 2H), 8.05 – 7.96 (m, 3H), 7.75 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.69 (s, 1H), 7.64 (ddd, *J* = 10.4, 2.7, 1.5 Hz, 1H), 7.55 (td, *J* = 8.1, 6.2 Hz, 1H), 7.29 – 7.18 (m, 2H), 6.56 (td, *J* = 53.7, 3.8 Hz, 1H), 6.12 (ddd, *J* = 12.6, 7.9, 3.7 Hz, 1H), 4.05 (s, 3H); LC-MS (Method 1): *t*_R = 3.65 min, *m/z* (M+H)⁺ = 492.

Synthesis of 3-bromo-N-(1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine (Int-42):

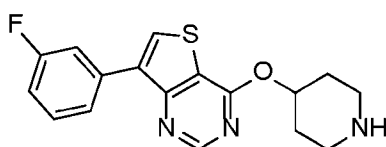


Int-42

[0173] To a mixture of 3-bromo-7-chloro-1-methyl-1H-pyrazolo[4,3-d]pyrimidine (0.247 g, 1 mmol) and 1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-amine, 2HCl (0.437 g,

1.10 mmol) was added EtOH (3 ml) and then hunig's base (0.611 ml, 3.50 mmol). The mixture was stirred at 80 °C for 1.5 hr. After cooling to rt, the mixture was concentrated to removed most of EtOH. Then, H₂O (20 mL) was added and stirred vigorously for 1 hr. The resulting solid was filtered, triturated with H₂O (5 mL x 2), hexane (5 mL x 2), and then dried to give 3-bromo-N-(1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine (525 mg, 0.981 mmol, 98 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.27 (s, 1H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.36 (q, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.13 – 6.92 (m, 6H), 5.32 (s, 2H), 4.42 (q, *J* = 7.5 Hz, 1H), 4.23 (s, 3H), 3.58 (d, *J* = 12.7 Hz, 2H), 3.14 – 2.99 (m, 2H), 1.99 – 1.93 (m, 4H); LC-MS (Method 1): *t*_R = 2.82 min, *m/z* (M+H)⁺ = 535, 537.

Synthesis of 7-(3-fluorophenyl)-4-(piperidin-4-yloxy)thieno[3,2-d]pyrimidine, 2HCl (Int-43):



Int-43

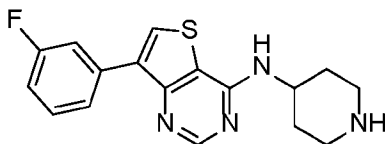
[0174] STEP 1: To a mixture of 7-bromo-4-chlorothieno[3,2-d]pyrimidine (3.74 g, 15 mmol) and tert-butyl 4-hydroxypiperidine-1-carboxylate (3.62 g, 18.0 mmol) in DMF (30 ml) (partial suspension) at rt was added NaH (60% in mineral oil, 22.5 mmol, 900 mg, 1.5 equiv). The mixture was stirred at rt for 1 hr. After cooling to rt, the mixture was slowly poured into vigorously stirred water (400 mL) and stirred for overnight. The solid was filtered and triturated with H₂O (10 mL x 2) and then hexane (5 ml x 2). After dried, the product was dissolved in CH₂Cl₂ and filtered out some insoluble impurity. The filtrate was concentrated and purified by silica gel chromatography using 10-50% EtOAc/hexane as the eluent to give tert-butyl 4-((7-bromothieno[3,2-d]pyrimidin-4-yl)oxy)piperidine-1-carboxylate (3.97 g, 9.58 mmol, 63.9 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.84 (s, 1H), 8.54 (s, 1H), 5.53 (dq, *J* = 8.2, 4.1 Hz, 1H), 3.67 (dt, *J* = 13.4, 4.9 Hz, 2H), 3.24 (t, *J* = 11.0 Hz, 2H), 2.02 (dt, *J* = 14.0, 4.8 Hz, 2H), 1.67 (dtd, *J* = 12.7, 8.5, 3.8 Hz, 2H), 1.40 (s, 9H); LC-MS (Method 1): *t*_R = 3.75 min, *m/z* (M+H)⁺ = 414, 416.

[0175] STEP 2: In a microwave vial was placed tert-butyl 4-((7-bromothieno[3,2-d]pyrimidin-4-yl)oxy)piperidine-1-carboxylate (1.657 g, 4 mmol), (3-fluorophenyl)boronic acid (0.840 g, 6.0 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (0.327 g, 0.40 mmol), and K₂CO₃ (2.488 g, 18.0 mmol). The tube was sealed. The air was removed and re-filled with N₂ (repeat for 3 times). Then, 1,4-dioxane (18 ml)/water (9 ml) was added and the mixture was stirred at 95 °C for 2 hr. After

cooling to rt, the layers were separated. The aqueous layer was extracted with EtOAc (3 mL x 2). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 5-35% EtOAc/hexane as the eluent to give tert-butyl 4-((7-(3-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl)oxy)piperidine-1-carboxylate (1.671 g, 3.89 mmol, 97 % yield). LC-MS (Method 1): *t*_R = 4.08 min, *m/z* (M+H)⁺ = 430.

[0176] STEP 3: To a solution of tert-butyl 4-((7-(3-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl)oxy)piperidine-1-carboxylate (1.671 g, 3.89 mmol) in CH₂Cl₂ (10 mL) was added HCl (4M in dioxane, 27.2 mmol, 6.8 mL, 7 equiv). The mixture was stirred at rt for 2 hr. The hexane (40 mL) was added and stirred for 5 minutes. The solid was filtered and triturated with hexane (5 mL x 2). The solid was dried *in vacuo* to give 7-(3-fluorophenyl)-4-(piperidin-4-yloxy)thieno[3,2-d]pyrimidine, 2HCl (1.494 g, 3.71 mmol, 95 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.15 (br s, 1H), 8.88 (s, 1H), 8.75 (s, 1H), 8.02 (dd, *J* = 10.8, 2.6 Hz, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.53 (q, *J* = 7.6 Hz, 1H), 7.23 (td, *J* = 8.6, 2.6 Hz, 1H), 7.05 (br s, 2H), 5.61 (tt, *J* = 7.8, 3.7 Hz, 1H), 3.33 – 3.09 (m, 4H), 2.26 (ddt, *J* = 14.7, 7.4, 3.8 Hz, 2H), 2.04 (dtd, *J* = 12.8, 8.2, 3.9 Hz, 2H) (including two salt NH); LC-MS (Method 1): *t*_R = 2.75 min, *m/z* (M+H)⁺ = 330.

Synthesis of 7-(3-fluorophenyl)-N-(piperidin-4-yl)thieno[3,2-d]pyrimidin-4-amine, 2HCl (Int-44):



Int-44

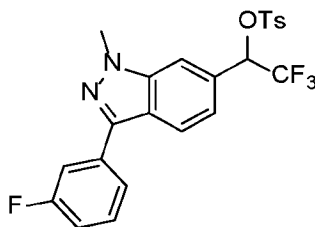
[0177] STEP 1: To a mixture of 7-bromo-4-chlorothieno[3,2-d]pyrimidine (2.495 g, 10 mmol) and tert-butyl 4-aminopiperidine-1-carboxylate (2.103 g, 10.50 mmol) was added EtOH (20 mL) and then Hunig's base (2.62 mL, 15.0 mmol). The mixture was stirred at 80 °C for 2.5 hr. After cooling to rt, the mixture was concentrated to removed most of EtOH. Then, H₂O (50 mL) was added and stirred vigorously for 1 hr. The resulting solid was filtered, triturated with H₂O (5 mL x 2), hexane (5 mL x 2), and then dried to give tert-butyl 4-((7-bromothieno[3,2-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (4.03 g, 8.29 mmol, 83 % yield). LC-MS (Method 1): *t*_R = 2.94 min, *m/z* (M+H)⁺ = 413, 415.

[0178] STEP 2: In a microwave vial was placed tert-butyl 4-((7-bromothieno[3,2-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (1.46 g, 3 mmol), (3-fluorophenyl)boronic acid (0.63 g, 4.50 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (0.245 g, 0.30 mmol), and K₂CO₃ (1.866 g, 13.50 mmol). The tube was sealed. The air was removed and re-filled with N₂ (repeat for 3 times). Then, 1,4-dioxane

(14 ml)/water (7 ml) was added and the mixture was stirred at 95 °C for 2 hr. After cooling to rt, the layers were separated. The aqueous layer was extracted with EtOAc (3 mL x 2). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-60% EtOAc/hexane as the eluent to give tert-butyl 4-((7-(3-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (1.27 g, 2.96 mmol, 99 % yield). LC-MS (Method 1): *t*_R = 3.17 min, *m/z* (M+H)⁺ = 429.

[0179] STEP 3: To a solution of tert-butyl 4-((7-(3-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (1.27 g, 2.96 mmol) in CH₂Cl₂ (7 ml) was added HCl (4M in dioxane, 20.9 mmol, 5.2 mL, 7 equiv). The mixture was stirred at rt for 2 hr. The hexane (30 mL) was added and stirred for 3 minutes. Carefully decanted the solvent by transfer pipette. Repeat adding/removal of hexane for 3 times. The solid was dried in vacuo to give 7-(3-fluorophenyl)-N-(piperidin-4-yl)thieno[3,2-d]pyrimidin-4-amine, 2HCl (1.181 g, 2.94 mmol, 99 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.88 (br s, 2H), 8.61 (s, 1H), 8.51 (s, 1H), 7.91 (d, *J* = 10.7 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.52 (q, *J* = 7.6 Hz, 1H), 7.22 (td, *J* = 8.6, 2.6 Hz, 1H), 4.44 (td, *J* = 10.2, 6.1 Hz, 1H), 3.34 (d, *J* = 12.6 Hz, 2H), 3.10 – 2.95 (m, 2H), 2.08 (dd, *J* = 14.0, 3.7 Hz, 2H), 1.93 – 1.78 (m, 2H) (salt NH not shown); LC-MS (Method 1): *t*_R = 2.38 min, *m/z* (M+H)⁺ = 329.

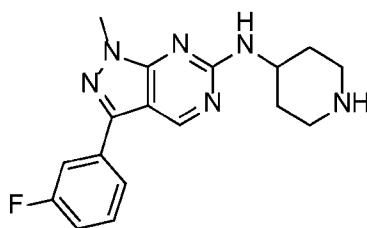
Synthesis of 2,2,2-trifluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethyl 4-methylbenzenesulfonate (Int-45):



Int-45

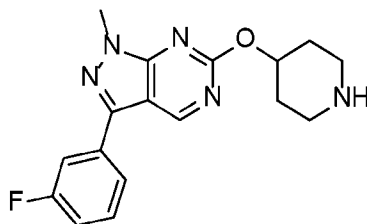
[0180] The title compound was prepared from 2,2,2-trifluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethan-1-ol following a similar procedure as described in the synthesis of **Int-40**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.06 (d, *J* = 8.6 Hz, 1H), 7.79 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.74 – 7.64 (m, 4H), 7.56 (td, *J* = 8.0, 6.2 Hz, 1H), 7.28 – 7.21 (m, 4H), 6.52 (q, *J* = 6.5 Hz, 1H), 4.07 (s, 3H), 2.19 (s, 3H); LC-MS (Method 1): *t*_R = 3.87 min, *m/z* (M+H)⁺ = 479.

Synthesis of 3-(3-fluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine, 2HCl (Int-46):

**Int-46**

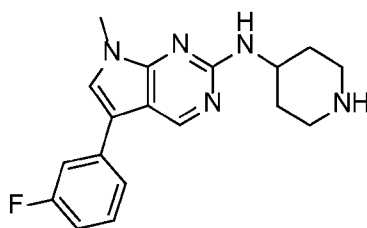
[0181] The title compound was prepared from 3-bromo-6-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine and tert-butyl 4-aminopiperidine-1-carboxylate following a similar procedure as described in the synthesis of **Int-44**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.24 (s, 1H), 8.94 (br s, 1H), 8.72 (br s, 1H), 7.97 (br s, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.72 (dt, *J* = 10.4, 2.2 Hz, 1H), 7.53 (td, *J* = 8.0, 6.1 Hz, 1H), 7.26 (td, *J* = 8.6, 2.6 Hz, 1H), 4.10 (br s, 1H), 3.87 (s, 3H), 3.29 (d, *J* = 12.6 Hz, 2H), 3.02 (q, *J* = 11.1 Hz, 2H), 2.09 (d, *J* = 13.5 Hz, 2H), 1.83 – 1.69 (m, 2H). (including 1 salt NH); LC-MS (Method 1): *t*_R = 2.66 min, *m/z* (M+H)⁺ = 327.

Synthesis of 3-(3-fluorophenyl)-1-methyl-6-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine, 2HCl (**Int-47**):

**Int-47**

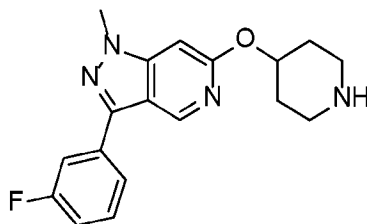
[0182] The title compound was prepared from 3-bromo-6-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine and tert-butyl 4-hydroxypiperidine-1-carboxylate following a similar procedure as described in the synthesis of **Int-43**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.50 (s, 1H), 8.77 (br s, 2H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.80 (dt, *J* = 10.2, 2.2 Hz, 1H), 7.57 (td, *J* = 8.1, 6.1 Hz, 1H), 7.30 (td, *J* = 8.6, 2.6 Hz, 1H), 5.36 (dt, *J* = 7.8, 4.1 Hz, 1H), 3.98 (s, 3H), 3.25 (dd, *J* = 12.2, 4.8 Hz, 2H), 3.15 (ddd, *J* = 12.5, 8.3, 3.7 Hz, 2H), 2.27 – 2.16 (m, 2H), 2.00 (dd, *J* = 13.3, 8.4 Hz, 2H). (including one salt NH); LC-MS (Method 1): *t*_R = 2.62 min, *m/z* (M+H)⁺ = 328.

Synthesis of 5-(3-fluorophenyl)-7-methyl-N-(piperidin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine, 2HCl (**Int-48**):

**Int-48**

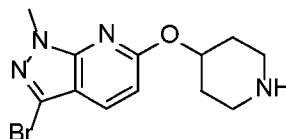
[0183] The title compound was prepared from 5-bromo-2-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidine and tert-butyl 4-aminopiperidine-1-carboxylate following a similar procedure as described in the synthesis of **Int-44**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.07 (s, 1H), 8.90 (br s, 1H), 8.75 (br s, 1H), 8.29 (br s, 1H), 7.92 (s, 1H), 7.55 – 7.42 (m, 3H), 7.16 – 7.07 (m, 1H), 4.15 (s, 1H), 3.70 (s, 3H), 3.31 (d, *J* = 12.8 Hz, 2H), 3.05 (d, *J* = 11.0 Hz, 2H), 2.17 – 2.06 (m, 2H), 1.85 – 1.71 (m, 2H). (including one salt NH); LC-MS (Method 1): *t*_R = 2.36 min, *m/z* (M+H)⁺ = 326.

Synthesis of 3-(3-fluorophenyl)-1-methyl-6-(piperidin-4-yloxy)-1H-pyrazolo[4,3-c]pyridine, 2HCl (**Int-49**):

**Int-49**

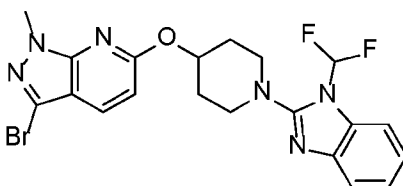
[0184] The title compound was prepared from 3-bromo-6-chloro-1-methyl-1H-pyrazolo[4,3-c]pyridine and tert-butyl 4-hydroxypiperidine-1-carboxylate following a similar procedure as described in the synthesis of **Int-43**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.10 (s, 1H), 8.89 (br s, 2H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.75 (dt, *J* = 10.2, 2.2 Hz, 1H), 7.56 (td, *J* = 8.1, 6.1 Hz, 1H), 7.28 (td, *J* = 8.6, 2.6 Hz, 1H), 7.08 (s, 1H), 5.29 (dt, *J* = 8.0, 4.2 Hz, 1H), 4.01 (s, 3H), 3.28 – 3.05 (m, 4H), 2.21 – 2.12 (m, 2H), 1.93 (dd, *J* = 13.1, 8.8 Hz, 2H). (including one salt NH); LC-MS (Method 1): *t*_R = 2.56 min, *m/z* (M+H)⁺ = 327.

Synthesis of 3-bromo-1-methyl-6-(piperidin-4-yloxy)-1H-pyrazolo[3,4-b]pyridine, 2HCl (**Int-50**):

**Int-50**

[0185] The title compound was prepared from 3-bromo-6-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine and tert-butyl 4-hydroxypiperidine-1-carboxylate following a similar procedure as described in the synthesis of **Int-43** (STEP 1 and STEP 3).

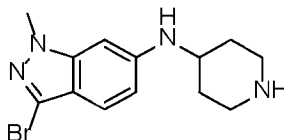
Synthesis of 3-bromo-6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-1-methyl-1H-pyrazolo[3,4-b]pyridine (**Int-51**):



Int-51

[0186] To a mixture of 3-bromo-1-methyl-6-(piperidin-4-yloxy)-1H-pyrazolo[3,4-b]pyridine, 2HCl (0.257 g, 0.669 mmol) in DMSO (2 ml) was added 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole (0.170 g, 0.84 mmol) and Hunig's base (0.467 ml, 2.68 mmol). The mixture was sealed and heated at 150 °C for 2 hr. After cooling to rt, the mixture was diluted with EtOAc (6 mL) and washed with H₂O (6 mL x 3). The organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-35% EtOAc/hexane as the eluent to give 3-bromo-6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-1-methyl-1H-pyrazolo[3,4-b]pyridine (270 mg, 0.57 mmol, 85 % yield). LC-MS (Method 1): *t*_R = 3.55 min, *m/z* (M+H)⁺ = 477, 479.

Synthesis of 3-bromo-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl (**Int-52**):



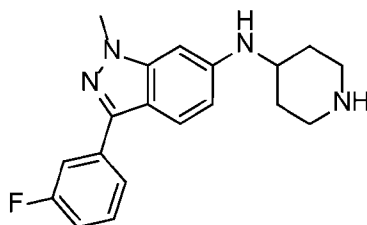
Int-52

[0187] STEP 1: To a mixture of 3-bromo-1-methyl-1H-indazol-6-amine (4.97 g, 22 mmol) and tert-butyl 4-oxopiperidine-1-carboxylate (4.82 g, 24.20 mmol) was added CH₂Cl₂ (50 ml). The mixture was stirred at rt for 5-10 min and then sodium triacetoxyborohydride (18.65 g, 88 mmol) was added portion wise. The mixture was then stirred at rt for overnight. The mixture was diluted with CH₂Cl₂ (100 mL) and then H₂O (70 mL) and saturated Na₂CO₃ (aq) (30 mL) were added slowly. The mixture was stirred for 10 min. The organic layer was separated, dried (Na₂SO₄) and filtered. After removal of solvent, to the crude product was added CH₂Cl₂ (40 mL) and then hexane (400 mL). The resulting solid was filtered, washed with 5% CH₂Cl₂/hexane, and dried to

give tert-butyl 4-((3-bromo-1-methyl-1H-indazol-6-yl)amino)piperidine-1-carboxylate (8.96 g, 21.89 mmol, 99 % yield). This product was pure and used for next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 7.15 (d, *J* = 8.8 Hz, 1H), 6.60 (dd, *J* = 8.9, 1.8 Hz, 1H), 6.45 (d, *J* = 1.8 Hz, 1H), 6.02 (d, *J* = 8.0 Hz, 1H), 3.87 (d, *J* = 12.8 Hz, 2H), 3.83 (s, 3H), 3.51 (d, *J* = 8.6 Hz, 1H), 2.93 (br s, 2H), 1.97 – 1.88 (m, 2H), 1.39 (s, 9H), 1.31 – 1.17 (m, 2H); LC-MS (Method 1): *t*_R = 3.55 min, *m/z* (M+H)⁺ = 409, 411.

[0188] STEP 2: To a solution of tert-butyl 4-((3-bromo-1-methyl-1H-indazol-6-yl)amino)piperidine-1-carboxylate (0.82 g, 2 mmol) in CH₂Cl₂ (6 ml) was added HCl (4M in dioxane, 16 mmol, 4 mL, 8 equiv). The mixture was stirred at rt for 2 hr. Then, hexane (30 mL) was added slowly and was stirred for 10 min. The solid was filtered and washed with hexane 5 mL x 2). The solid was dried in vacuo to give 3-bromo-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl (755 mg, 1.976 mmol, 99 % yield). The product was used for next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 8.97 (s, 1H), 8.88 (s, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 6.67 (dd, *J* = 8.8, 1.7 Hz, 1H), 6.55 (s, 1H), 3.85 (s, 3H), 3.62 (dt, *J* = 9.8, 5.7 Hz, 1H), 3.29 (d, *J* = 12.5 Hz, 2H), 2.99 (q, *J* = 11.2 Hz, 2H), 2.09 (dd, *J* = 13.5, 3.8 Hz, 2H), 1.63 (qd, *J* = 12.0, 3.6 Hz, 2H); LC-MS (Method 1): *t*_R = 2.41 min, *m/z* (M+H)⁺ = 309, 311.

Synthesis of 3-(3-fluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl (**Int-53**):



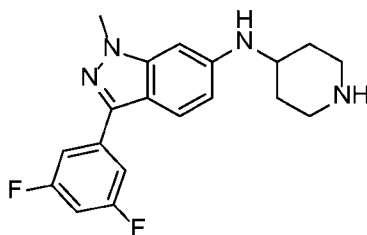
Int-53

[0189] STEP 1: In a flask was placed tert-butyl 4-((3-bromo-1-methyl-1H-indazol-6-yl)amino)piperidine-1-carboxylate (2.456 g, 6 mmol), (3-fluorophenyl)boronic acid (1.091 g, 7.80 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (0.490 g, 0.60 mmol), and K₂CO₃ (3.23 g, 23.40 mmol). The air was removed and re-filled with N₂ (repeat for 3 times). Then, 1,4-dioxane (24 ml)/water (12 ml) was added and the mixture was stirred at 90 °C for 2 hr. After cooling to rt, the organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layer was dried (Na₂SO₄), filtered through celite, and eluted with EtOAc. After removal of solvent, the product was purified by silica gel chromatography using 10-50% EtOAc/hexane as the eluent to give tert-butyl 4-((3-(3-fluorophenyl)-1-methyl-1H-indazol-6-

yl)amino)piperidine-1-carboxylate (2.23 g, 5.25 mmol, 88 % yield). LC-MS (Method 1): t_R = 3.63 min, m/z (M+H)⁺ = 425.

[0190] STEP 2: To a solution of tert-butyl 4-((3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)amino)piperidine-1-carboxylate (1220 mg, 2.87 mmol) in CH₂Cl₂ (10 ml) was added HCl (4M in dioxane, 23 mmol, 5.75 mL, 8 equiv). The mixture was stirred at rt for 2 hr. Then, hexane (35 mL) was added slowly and was stirred for 10 min. The solvent was carefully removed, and addition/removal of hexane was repeated 3 times. The residue was dried *in vacuo* to give 3-(3-fluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl (1050 mg, 2.64 mmol, 92 % yield). The product was pure and was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 9.02 (br s, 1H), 8.90 (br s, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.62 (dt, J = 10.3, 2.1 Hz, 1H), 7.50 (td, J = 8.0, 6.2 Hz, 1H), 7.17 (td, J = 8.6, 2.6 Hz, 1H), 6.78 (d, J = 8.9 Hz, 1H), 6.73 (s, 1H), 3.96 (s, 3H), 3.68 (tt, J = 10.0, 3.9 Hz, 1H), 3.31 (d, J = 12.5 Hz, 2H), 3.00 (q, J = 11.2 Hz, 2H), 2.11 (dd, J = 14.0, 3.8 Hz, 2H), 1.69 (q, J = 11.8 Hz, 2H); LC-MS (Method 1): t_R = 2.65 min, m/z (M+H)⁺ = 325.

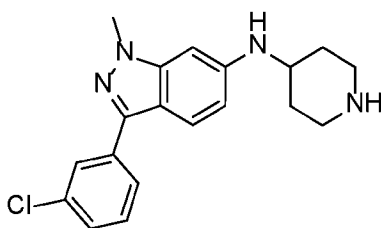
Synthesis of 3-(3,5-difluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl (**Int-54**):



Int-54

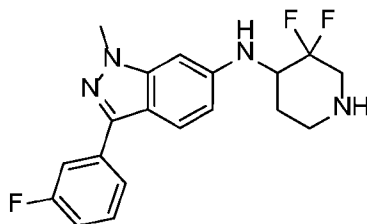
[0191] The title compound was prepared from tert-butyl 4-((3-bromo-1-methyl-1H-indazol-6-yl)amino)piperidine-1-carboxylate and (3,5-difluorophenyl)boronic acid following a similar procedure as described in the synthesis of **Int-53**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.08 (br s, 1H), 8.96 (br s, 1H), 7.88 – 7.80 (m, 1H), 7.59 – 7.48 (m, 2H), 7.20 (tt, J = 9.3, 2.4 Hz, 1H), 6.88 – 6.77 (m, 1H), 6.74 (d, J = 11.5 Hz, 1H), 3.97 (s, 3H), 3.68 (td, J = 9.3, 5.7 Hz, 1H), 3.31 (dt, J = 13.0, 3.5 Hz, 2H), 2.99 (q, J = 11.2 Hz, 2H), 2.11 (dd, J = 13.7, 3.8 Hz, 2H), 1.70 (ddt, J = 15.1, 11.0, 5.9 Hz, 2H); LC-MS (Method 1): t_R = 2.80 min, m/z (M+H)⁺ = 343.

Synthesis of 3-(3-chlorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl (**Int-55**):

**Int-55**

[0192] The title compound was prepared from tert-butyl 4-((3-bromo-1-methyl-1H-indazol-6-yl)amino)piperidine-1-carboxylate and (3-chlorophenyl)boronic acid following a similar procedure as described in the synthesis of **Int-53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.94 (s, 1H), 8.84 (s, 1H), 7.87–7.85 (m, 2H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.49 (t, *J* = 8.1 Hz, 1H), 7.42–7.37 (m, 1H), 6.74 (dd, *J* = 8.9, 1.8 Hz, 1H), 6.64 (s, 1H), 3.95 (s, 3H), 3.66 (tt, *J* = 9.6, 3.8 Hz, 1H), 3.31 (d, *J* = 12.5 Hz, 2H), 3.01 (q, *J* = 11.1 Hz, 2H), 2.11 (dd, *J* = 13.7, 3.8 Hz, 2H), 1.73–1.59 (m, 2H); LC-MS (Method 1): *t*_R = 2.85 min, *m/z* (M+H)⁺ = 341, 343.

Synthesis of N-(3,3-difluoropiperidin-4-yl)-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine, 2HCl (**Int-56**):

**Int-56**

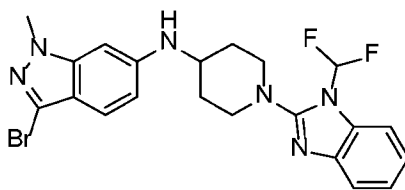
[0193] STEP 1: To a mixture of 3-bromo-1-methyl-1H-indazol-6-amine (0.904 g, 4 mmol), tert-butyl 3,3-difluoro-4-oxopiperidine-1-carboxylate (1.035 g, 4.40 mmol), and decaborane (0.489 g, 4.0 mmol) was added MeOH (8 mL). The mixture was stirred at rt for 7 hr. The mixture was concentrated by blowing air to remove most of MeOH solvent. Then, EtOAc/H₂O/Na₂CO₃ (aq) (25 mL/20 mL/5 mL) were added and stirred for another 1 hr. The organic layer was separated and the aqueous was extracted with EtOAc (20 mL). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 5–40% EtOAc/hexane as the eluent to give tert-butyl 4-((3-bromo-1-methyl-1H-indazol-6-yl)amino)-3,3-difluoropiperidine-1-carboxylate (1.41 g, 3.17 mmol, 79 % yield).

[0194] STEP 2: In a flask was placed tert-butyl 4-((3-bromo-1-methyl-1H-indazol-6-yl)amino)-3,3-difluoropiperidine-1-carboxylate (668 mg, 1.5 mmol), (3-fluorophenyl)boronic acid (315 mg, 2.250 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (306 mg, 0.375 mmol), and K₂CO₃ (933 mg, 6.75

mmol). The air was removed and re-filled with N₂ (repeat for 3 times). Then, 1,4-Dioxane (8 ml)/Water (4 ml) was added and the mixture was stirred at 90 °C for 2 hr. After cooling to rt, the organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layer was dried (Na₂SO₄), filtered through celite, and eluted with EtOAc. After removal of solvent, the product was purified by silica gel chromatography using 5-40% EtOAc/hexane as the eluent to give tert-butyl 3,3-difluoro-4-((3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)amino)piperidine-1-carboxylate (200 mg, 0.434 mmol, 29.0 % yield). LC-MS (Method 1): *t*_R = 3.72 min, *m/z* (M+H)⁺ = 461.

[0195] STEP 3: To a solution of tert-butyl 3,3-difluoro-4-((3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)amino)piperidine-1-carboxylate (200 mg, 0.434 mmol) in CH₂Cl₂ (2 ml) was added HCl (4M in dioxane, 3.48 mmol, 0.87 mL, 8 equiv). The mixture was stirred at rt for 2 hr. Then, hexane (20 mL) was added slowly and was stirred for 10 min. Carefully remove the solvent and repeat adding/removing of hexane step for 2-3 times. The product was then dried in vacuo to give N-(3,3-difluoropiperidin-4-yl)-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine, 2HCl (168 mg, 0.388 mmol, 89 % yield). The product was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.95 (br s, 1H), 9.38 (br s, 1H), 7.76 (t, *J* = 8.0 Hz, 2H), 7.62 (dt, *J* = 10.5, 2.2 Hz, 1H), 7.50 (td, *J* = 8.0, 6.2 Hz, 1H), 7.17 (td, *J* = 8.7, 2.6 Hz, 1H), 6.79 (dd, *J* = 8.9, 1.9 Hz, 1H), 6.69 (d, *J* = 1.9 Hz, 1H), 6.35 (br s, 1H), 4.35 (d, *J* = 10.2 Hz, 1H), 3.92 (s, 3H), 3.63 – 3.55 (m, 2H), 3.33 (d, *J* = 13.0 Hz, 1H), 3.13 (d, *J* = 10.5 Hz, 1H), 2.15 (dd, *J* = 11.8, 7.1 Hz, 1H), 1.89 (q, *J* = 12.1 Hz, 1H) (including one salt NH); LC-MS (Method 1): *t*_R = 2.77 min, *m/z* (M+H)⁺ = 261.

Synthesis of 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine (Int-57):

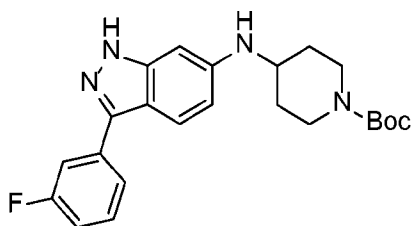


Int-57

[0196] The title compound was prepared from 3-bromo-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in the synthesis of **Int-51**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.70 (t, *J* = 57.9 Hz, 1H), 7.49 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.26 – 7.14 (m, 3H), 6.66 (dd, *J* = 8.8, 1.8 Hz, 1H),

6.52 (d, $J = 1.8$ Hz, 1H), 6.16 (d, $J = 7.9$ Hz, 1H), 3.85 (s, 3H), 3.65 – 3.55 (m, 3H), 3.27 – 3.15 (m, 2H), 2.12 – 2.00 (m, 2H), 1.75 – 1.61 (m, 2H); LC-MS (Method 1): $t_R = 3.29$ min, m/z (M+H)⁺ = 475, 477.

Synthesis of tert-butyl 4-((3-(3-fluorophenyl)-1H-indazol-6-yl)amino)piperidine-1-carboxylate (Int-58):



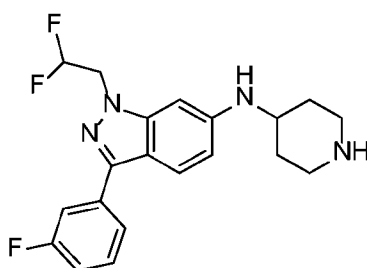
Int-58

[0197] STEP 1: To a mixture of 3-bromo-1H-indazol-6-amine (4.67 g, 22 mmol) and tert-butyl 4-oxopiperidine-1-carboxylate (4.82 g, 24.20 mmol) was added CH₂Cl₂ (50 ml). The mixture was stirred at rt for 5-10 min and then sodium triacetoxyborohydride (18.65 g, 88 mmol) was added portion wise. The mixture was then stirred at rt for overnight. The mixture was diluted with CH₂Cl₂ (50 mL) and H₂O (70 mL). Then, saturated Na₂CO₃ (aq) (30 mL) were added slowly until the pH of aqueous layer is ca. 7. The mixture was stirred for 10 min. The organic layer was separated, dried (Na₂SO₄) and filtered. After removal of solvent, to the crude product was added CH₂Cl₂ (40 mL) and then hexane (400 mL). The resulting solid was filtered, washed with 5% CH₂Cl₂/hexane, and dried to give tert-butyl 4-((3-bromo-1H-indazol-6-yl)amino)piperidine-1-carboxylate (8.89 g, 22.49 mmol, 102 % yield). This product was pure and used for next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 12.58 (s, 1H), 7.17 (d, $J = 8.8$ Hz, 1H), 6.60 (dd, $J = 8.9, 1.8$ Hz, 1H), 6.37 (d, $J = 1.8$ Hz, 1H), 5.96 (d, $J = 7.9$ Hz, 1H), 3.86 (d, $J = 13.2$ Hz, 2H), 3.45–3.43 (m, 1H), 2.93 (br s, 2H), 1.90 (dd, $J = 13.0, 3.6$ Hz, 2H), 1.39 (s, 9H), 1.31 – 1.17 (m, 2H); LC-MS (Method 1): $t_R = 3.28$ min, m/z (M+H)⁺ = 395, 397.

[0198] STEP 2: In a flask was placed tert-butyl 4-((3-bromo-1H-indazol-6-yl)amino)piperidine-1-carboxylate (2.372 g, 6 mmol), (3-fluorophenyl)boronic acid (1.679 g, 12.00 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (0.490 g, 0.60 mmol), and K₂CO₃ (5.80 g, 42.0 mmol). The air was removed and re-filled with N₂ (repeat for 3 times). Then, 1,4-dioxane (40 ml)/water (18 ml) was added and the mixture was stirred at 90 °C for overnight. After cooling to rt, the layers were separated. The aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layer was dried (Na₂SO₄) and filtered through celite. After removal of solvent, the product was purified by silica

gel chromatography using 20-70% EtOAc/hexane as the eluent to give tert-butyl 4-((3-(3-fluorophenyl)-1H-indazol-6-yl)amino)piperidine-1-carboxylate (1.615 g, 3.93 mmol, 65.6 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.58 (s, 1H), 7.76 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.64 (ddd, *J* = 10.6, 2.7, 1.5 Hz, 1H), 7.50 (td, *J* = 8.0, 6.3 Hz, 1H), 7.16 (td, *J* = 8.7, 2.6 Hz, 1H), 6.63 (dd, *J* = 8.9, 1.9 Hz, 1H), 6.45 (d, *J* = 1.9 Hz, 1H), 5.83 (d, *J* = 8.0 Hz, 1H), 3.87 (d, *J* = 13.2 Hz, 2H), 3.52 – 3.39 (m, 1H), 2.95 (br s, 2H), 1.99 – 1.88 (m, 2H), 1.38 (s, 9H), 1.33 – 1.19 (m, 2H); LC-MS (Method 1): *t*_R = 3.37 min, *m/z* (M+H)⁺ = 411.

Synthesis of 1-(2,2-difluoroethyl)-3-(3-fluorophenyl)-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl (Int-59):



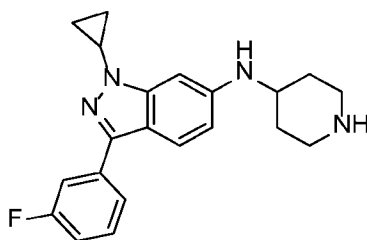
Int-59

[0199] STEP 1: To a mixture of tert-butyl 4-((3-(3-fluorophenyl)-1H-indazol-6-yl)amino)piperidine-1-carboxylate (0.205 g, 0.5 mmol) and Cs₂CO₃ (0.244 g, 0.75 mmol) was added DMF (1.5 mL). The mixture was stirred at rt for 5 min and 1,1-difluoro-2-iodoethane (0.288 g, 1.50 mmol) was added. The mixture was sealed and stirred at rt for overnight. After cooling to rt, the mixture was diluted with EtOAc (80 mL) and the mixture was washed with H₂O (8 mL x 3). The organic layer was dried (Na₂SO₄) and filtrated. After removal of solvent, the product purified by silica gel chromatography using 5-25% EtOAc/hexane as the eluent to give tert-butyl 4-((1-(2,2-difluoroethyl)-3-(3-fluorophenyl)-1H-indazol-6-yl)amino)piperidine-1-carboxylate (210 mg, 0.443 mmol, 89 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.78 – 7.68 (m, 2H), 7.62 (ddd, *J* = 10.4, 2.6, 1.5 Hz, 1H), 7.52 (td, *J* = 8.0, 6.2 Hz, 1H), 7.25 – 7.15 (m, 1H), 6.70 – 6.62 (m, 2H), 6.43 (tt, *J* = 56.0, 4.0 Hz, 1H), 5.98 (d, *J* = 8.1 Hz, 1H), 4.80 (td, *J* = 15.0, 3.9 Hz, 2H), 3.88 (d, *J* = 13.1 Hz, 2H), 3.62 – 3.46 (m, 1H), 2.96 (br s, 2H), 1.99 – 1.90 (m, 2H), 1.40 (s, 9H), 1.32 – 1.20 (m, 2H); LC-MS (Method 1): *t*_R = 3.70 min, *m/z* (M+H)⁺ = 475.

[0200] STEP 2: To a solution of tert-butyl 4-((1-(2,2-difluoroethyl)-3-(3-fluorophenyl)-1H-indazol-6-yl)amino)piperidine-1-carboxylate (0.2 g, 0.421 mmol) in CH₂Cl₂ (2 mL) was added HCl (4M in dioxane, 3.38 mmol, 0.85 mL, 8 equiv). The mixture was stirred at rt for 2 hr. Then, hexane (20 mL) was added and stirred for 5 min. The solvent was carefully removed. Repeat

adding/removing of hexane for 3 times. The left solid was dried in vacuo to give 1-(2,2-difluoroethyl)-3-(3-fluorophenyl)-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl (180 mg, 0.402 mmol, 95 % yield). The material was used for next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 8.86 (br s, 1H), 8.77 (br s, 1H), 7.79 – 7.72 (m, 2H), 7.63 (dt, *J* = 10.2, 2.2 Hz, 1H), 7.52 (td, *J* = 8.0, 6.2 Hz, 1H), 7.21 (td, *J* = 8.6, 2.7 Hz, 1H), 6.76 – 6.67 (m, 2H), 6.44 (tt, *J* = 55.1, 4.0 Hz, 1H), 4.81 (td, *J* = 14.9, 4.0 Hz, 2H), 3.63 (td, *J* = 9.5, 4.6 Hz, 1H), 3.31 (d, *J* = 12.4 Hz, 2H), 3.01 (q, *J* = 11.2 Hz, 2H), 2.11 (dd, *J* = 14.1, 3.8 Hz, 2H), 1.63 (ddt, *J* = 13.7, 10.0, 5.1 Hz, 2H); LC-MS (Method 1): *t*_R = 2.78 min, *m/z* (M+H)⁺ = 375.

Synthesis of 1-cyclopropyl-3-(3-fluorophenyl)-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl (Int-60):



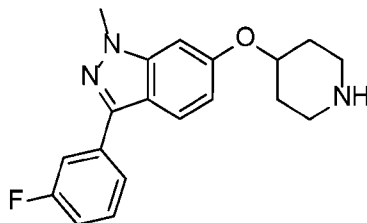
Int-60

[0201] STEP 1: To a mixture of tert-butyl 4-((3-(3-fluorophenyl)-1H-indazol-6-yl)amino)piperidine-1-carboxylate (0.308 g, 0.75 mmol), cyclopropylboronic acid (0.129 g, 1.50 mmol), copper (II) acetate (0.136 g, 0.75 mmol), 2,2'-bipyridine (0.117 g, 0.750 mmol), and Na₂CO₃ (0.159 g, 1.50 mmol) was added 1,2-dichloroethane (4 ml). The mixture was opened to air and stirred at 65 °C for overnight. After cooling to rt, the mixture was filter through celite and eluted with CH₂Cl₂. The filtrate was concentrated and then purified by silica gel chromatography using 20-40% EtOAc/hexane as the eluent to give tert-butyl 4-((1-cyclopropyl-3-(3-fluorophenyl)-1H-indazol-6-yl)amino)piperidine-1-carboxylate (293 mg, 0.650 mmol, 87 % yield). LC-MS (Method 1): *t*_R = 3.75 min, *m/z* (M+H)⁺ = 451.

[0202] STEP 2: To a solution of tert-butyl 4-((1-cyclopropyl-3-(3-fluorophenyl)-1H-indazol-6-yl)amino)piperidine-1-carboxylate (0.293 g, 0.65 mmol) in CH₂Cl₂ (2 ml) was added HCl (4M in dioxane, 5.20 mmol, 1.3 mL, 8 equiv). The mixture was stirred at rt for 2 hr. Then, hexane (20 mL) was added and stirred for 5 min. The solvent was carefully removed. Repeat adding/removing of hexane for 3 times. The left solid was dried *in vacuo* to give 1-cyclopropyl-3-(3-fluorophenyl)-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl (268 mg, 0.633 mmol, 97 % yield). The material was used in the next step without further purification. ¹H NMR (400 MHz,

DMSO- d_6) δ 8.97 (br s, 1H), 8.87 (br s, 1H), 7.78 (d, J = 9.2 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.60 (dt, J = 10.3, 2.2 Hz, 1H), 7.50 (td, J = 8.0, 6.2 Hz, 1H), 7.18 (td, J = 8.6, 2.6 Hz, 1H), 6.79 – 6.77 (m, 2H), 3.75 – 3.61 (m, 2H), 3.31 (d, J = 12.4 Hz, 2H), 3.02 (q, J = 11.0 Hz, 2H), 2.11 (dd, J = 14.1, 3.8 Hz, 2H), 1.76 – 1.62 (m, 2H), 1.16 – 1.05 (m, 4H); LC-MS (Method 1): t_R = 2.83 min, m/z ($M+H$) $^+$ = 351.

Synthesis of 3-(3-fluorophenyl)-1-methyl-6-(piperidin-4-yloxy)-1H-indazole, HCl (Int-61):



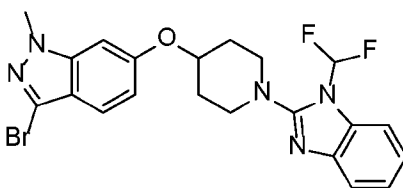
Int-61

[0203] STEP 1: In a microwave vial was placed 3-bromo-1-methyl-1H-indazol-6-ol (0.91 g, 4 mmol), tert-butyl 4-hydroxypiperidine-1-carboxylate (0.886 g, 4.40 mmol), DTBAD (1.382 g, 6.0 mmol), triphenylphosphine (1.574 g, 6.0 mmol). The vial was sealed and the air was removed and refilled with N_2 (repeat for 2 times). Then, THF (8 ml) was added and the mixture was stirred at rt for 3 hr. The mixture was concentrated and the mixture was purified by silica gel chromatography using 5-45% EtOAc/hexane as the eluent to give tert-butyl 4-((3-bromo-1-methyl-1H-indazol-6-yl)oxy)piperidine-1-carboxylate (2.095 g (ca. 70% purity), 3.57 mmol, 89 % yield). LC-MS (Method 1): t_R = 3.76 min, m/z ($M+H$) $^+$ = 410, 412.

[0204] STEP 2: In a flask was placed tert-butyl 4-((3-bromo-1-methyl-1H-indazol-6-yl)oxy)piperidine-1-carboxylate (2.095 g, 3.57 mmol), (3-fluorophenyl)boronic acid (0.750 g, 5.36 mmol), $PdCl_2(dppf)-CH_2Cl_2$ adduct (0.292 g, 0.357 mmol), and K_2CO_3 (2.223 g, 16.08 mmol). The air was removed and re-filled with N_2 (repeat for 3 times). Then, 1,4-dioxane (16 ml)/water (8 ml) was added and the mixture was stirred at 92 °C for 2 hr. After cooling to rt, the organic layer was separated and the aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layer was dried (Na_2SO_4), filtered through celite, and eluted with EtOAc. After removal of solvent, the product was purified by silica gel chromatography using 5-45% EtOAc/hexane as the eluent to give tert-butyl 4-((3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)oxy)piperidine-1-carboxylate (1.342 g (ca. 80% purity), 2.52 mmol, 70.6 % yield). LC-MS (Method 1): t_R = 3.78 min, m/z ($M+H$) $^+$ = 426.

[0205] STEP 3: To a solution of tert-butyl 4-((3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)oxy)piperidine-1-carboxylate (1342 mg, 2.52 mmol) in CH₂Cl₂ (4 mL) was added HCl (4M in dioxane, 15.24 mmol, 3.81 mL, 6 equiv). The mixture was stirred at rt for 2 hr. Then, hexane (25 mL) was added slowly and was stirred for 10 min. Carefully removed the solvent and repeated adding/removal of hexane for 3 times. The residue was dried in vacuo to give 3-(3-fluorophenyl)-1-methyl-6-(piperidin-4-yloxy)-1H-indazole, HCl (1.01 g, 2.51 mmol, 100 % yield). The product is pure and was used for next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 8.86 (br s, 1H), 8.57 (br s, 1H), 8.00 (s, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.54–7.49 (m, 1H), 7.34–7.13 (m, 3H), 7.10 (d, *J* = 8.8 Hz, 1H), 4.63 (dt, *J* = 6.6, 3.3 Hz, 1H), 3.36 (s, 3H), 2.99–2.83 (m, 2H), 2.78–2.64 (m, 2H), 1.99–1.86 (m, 2H), 1.71–1.57 (m, 2H) (including 1 salt NH); LC-MS (Method 1): *t*_R = 2.67 min, *m/z* (M+H)⁺ = 326.

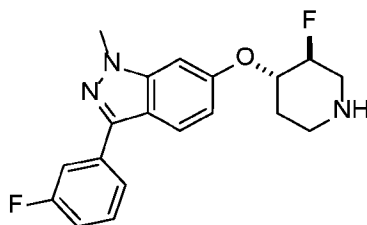
Synthesis of 3-bromo-6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-1-methyl-1H-indazole (Int-62):



Int-62

[0206] The title compound was prepared from 3-bromo-1-methyl-6-(piperidin-4-yloxy)-1H-indazole, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in the synthesis of **Int-51**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.01 (s, 1H), 7.72 (t, *J* = 57.4 Hz, 1H), 7.75–7.69 (m, 1H), 7.55–7.46 (m, 2H), 7.27–7.11 (m, 3H), 4.85 (dt, *J* = 7.0, 3.6 Hz, 1H), 4.29 (s, 3H), 3.55 (ddd, *J* = 12.0, 8.0, 3.3 Hz, 2H), 3.30–3.20 (m, 2H), 2.13 (ddt, *J* = 11.9, 7.6, 3.5 Hz, 2H), 2.00–1.88 (m, 2H); LC-MS (Method 1): *t*_R = 3.37 min, *m/z* (M+H)⁺ = 476, 478.

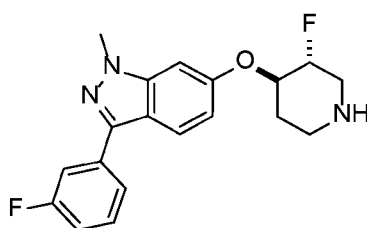
Synthesis of 3-(3-fluorophenyl)-6-(((3*S*,4*S*)-3-fluoropiperidin-4-yl)oxy)-1-methyl-1H-indazole, 2HCl (Int-63):



Int-63

[0207] The title compound was prepared from 3-bromo-1-methyl-1H-indazol-6-ol and tert-butyl (3S,4R)-3-fluoro-4-hydroxypiperidine-1-carboxylate following a similar procedure as described in the synthesis of **Int-61**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.42 (br s, 1H), 9.18 (br s, 1H), 8.02 (s, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.52 (q, *J* = 7.4 Hz, 1H), 7.34 – 7.20 (m, 3H), 7.17 (d, *J* = 8.9 Hz, 1H), 4.88 – 4.57 (m, 2H), 3.37 (s, 3H), 3.19 (br s, 1H), 2.92 (br s, 2H), 2.72 (br s, 1H), 2.02 (d, *J* = 9.4 Hz, 1H), 1.71 (br s, 1H). (including one salt NH); LC-MS (Method 1): *t*_R = 2.55 min, *m/z* (M+H)⁺ = 344.

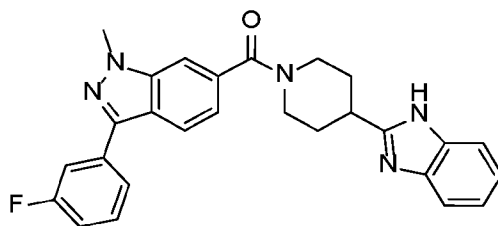
Synthesis of 3-(3-fluorophenyl)-6-(((3R,4R)-3-fluoropiperidin-4-yl)oxy)-1-methyl-1H-indazole, 2HCl (**Int-64**):



Int-64

[0208] The title compound was prepared from 3-bromo-1-methyl-1H-indazol-6-ol and tert-butyl (3R,4S)-3-fluoro-4-hydroxypiperidine-1-carboxylate following a similar procedure as described in the synthesis of **Int-61**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.50 (s, 1H), 9.24 (s, 1H), 8.02 (s, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.52 (q, *J* = 7.5 Hz, 1H), 7.34 – 7.19 (m, 3H), 7.17 (d, *J* = 8.9 Hz, 1H), 4.85 – 4.58 (m, 2H), 3.36 (s, 3H), 3.19 (br s, 1H), 2.92 (br s, 2H), 2.72 (br s, 1H), 2.07 – 1.97 (m, 1H), 1.74 – 1.68 (m, 1H). (including one salt NH); LC-MS (Method 1): *t*_R = 2.55 min, *m/z* (M+H)⁺ = 344.

Synthesis of (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (**Int-65**):

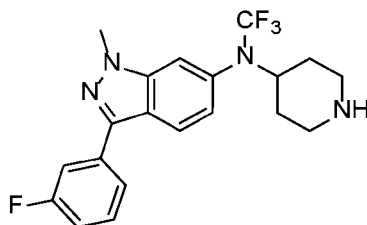


Int-65

[0209] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 2-(piperidin-4-yl)-1H-benzo[d]imidazole following a similar procedure as described in the synthesis of **Int-28**. ¹H NMR (400 MHz, DMSO-d₆) δ 12.70 (br s, 1H), 8.16 (d,

$J = 8.3$ Hz, 1H), 7.87 – 7.81 (m, 1H), 7.80 (s, 1H), 7.72 (ddd, $J = 10.4, 2.7, 1.5$ Hz, 1H), 7.61 – 7.45 (m, 3H), 7.27 – 7.21 (m, 2H), 7.15 (dd, $J = 6.0, 3.2$ Hz, 2H), 4.56 (br s, 1H), 4.14 (s, 3H), 3.72 (br s, 1H), 3.60 (tt, $J = 10.1, 5.0$ Hz, 1H), 3.28 – 2.98 (m, 2H), 2.24 – 1.67 (m, 4H); LC-MS (Method 1): $t_R = 2.86$ min, m/z ($M+H$) $^+ = 454$.

Synthesis of 3-(3-fluorophenyl)-1-methyl-N-(piperidin-4-yl)-N-(trifluoromethyl)-1H-indazol-6-amine, 2HCl (Int-66):



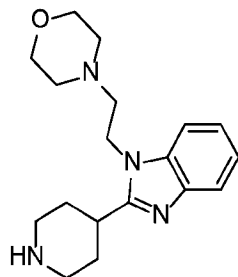
Int-66

[0210] STEP 1: To a mixture of tert-butyl 4-((3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)amino)piperidine-1-carboxylate (0.212 g, 0.5 mmol) and tetramethylammonium trifluoromethanethiolate (0.131 g, 0.75 mmol) was added MeCN (2.5 mL). The mixture was stirred at rt for overnight. Then, silver(I) fluoride (0.222 g, 1.75 mmol) was added and stirred at rt for another 4 hr. The mixture was poured into EtOAc/H₂O (25 mL/25 mL). The organic layer was washed with H₂O (25 mL), dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 5-65% EtOAc/hexane as the eluent to give tert-butyl 4-((3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(trifluoromethyl)amino)piperidine-1-carboxylate (135 mg, 0.274 mmol, 54.8 % yield) and recover SM (50 mg). LC-MS (Method 1): $t_R = 4.03$ min, m/z ($M+H$) $^+ = 493$.

[0211] STEP 2: To a solution of tert-butyl 4-((3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(trifluoromethyl)amino)piperidine-1-carboxylate (135 mg, 0.274 mmol) in CH₂Cl₂ (1.5 mL) was added HCl (4M in dioxane, 2.2 mmol, 0.55 mL, 8 equiv). The mixture was stirred at rt for 1.5 hr. Then, hexane (20 mL) was added slowly and was stirred for 10 min. Carefully remove the solvent and repeat adding/removing of hexane steps for 2-3 times. The product was then dried *in vacuo* to give 3-(3-fluorophenyl)-1-methyl-N-(piperidin-4-yl)-N-(trifluoromethyl)-1H-indazol-6-amine, 2HCl (122 mg, 0.262 mmol, 96 % yield). The product was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.80 (d, $J = 11.6$ Hz, 1H), 8.18 (d, $J = 8.7$ Hz, 1H), 7.87 (s, 1H), 7.83 (d, $J = 7.8$ Hz, 1H), 7.77 – 7.67 (m, 1H), 7.57 (td, $J = 8.0, 6.2$ Hz, 1H), 7.30 – 7.19 (m, 2H), 4.32 (td, $J = 10.2, 5.9$ Hz, 1H), 4.13 (s, 3H), 3.28 (d, $J = 13.1$ Hz, 2H),

3.02 (q, $J = 12.0$ Hz, 2H), 2.16 (d, $J = 13.5$ Hz, 2H), 1.75 – 1.62 (m, 2H); LC-MS (Method 1): $t_R = 3.05$ min, m/z (M+H) $^+ = 393$.

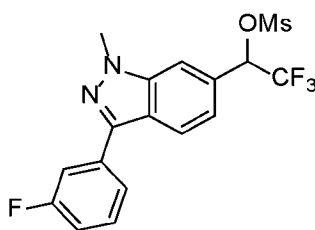
Synthesis of 4-(2-(2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)ethyl)morpholine, 3HCl (**Int-67**):



Int-67

[0212] The title compound was prepared from tert-butyl 4-(1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate and 4-(2-chloroethyl)morpholine, HCl following a similar procedure as described in the synthesis of **Int-5**. ^1H NMR (400 MHz, DMSO- d_6) δ 12.43 (s, 1H), 9.18 (s, 1H), 9.07 (s, 1H), 8.03 (d, $J = 7.8$ Hz, 1H), 7.76 (d, $J = 7.7$ Hz, 1H), 7.48 (p, $J = 7.5$ Hz, 2H), 4.94 (t, $J = 7.9$ Hz, 2H), 4.02 (d, $J = 12.8$ Hz, 2H), 3.96 – 3.77 (m, 3H), 3.62 – 3.34 (m, 6H), 3.24 – 3.14 (m, 4H), 2.24 – 2.05 (m, 4H). (including two salt NH); LC-MS (Method 1): $t_R = 0.70$ min, m/z (M+H) $^+ = 315$.

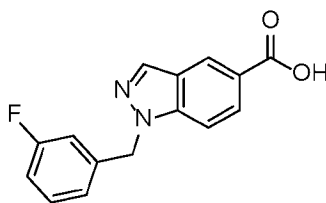
Synthesis of 2,2,2-trifluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethyl methanesulfonate (**Int-68**):



Int-68

[0213] The title compound was prepared from 2,2,2-trifluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethan-1-ol and methanesulfonyl chloride following a similar procedure as described in the synthesis of **Int-40**. LC-MS (Method 1): $t_R = 3.98$ min, m/z (M+H) $^+ = 403$.

Synthesis of 1-(3-fluorobenzyl)-1H-indazole-5-carboxylic acid (**Int-69**):

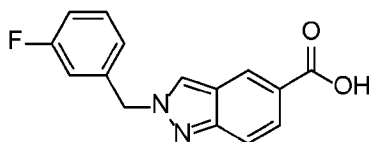


Int-69

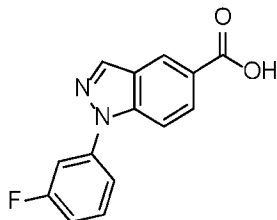
[0214] STEP 1: In a microwave tube was placed methyl 1H-indazole-5-carboxylate (0.400g, 2.27 mmol) and potassium carbonate (0.949 g, 6.87 mmol) and then N,N-dimethylformamide (7.6 ml) was added. 1-(Bromomethyl)-3-fluorobenzene (0.729 g, 0.47 ml 3.86 mmol) was added into the reaction mixture at room temperature. The reaction mixture was sealed and heated up to 90 °C and then stirred for overnight. After cooling to rt, the mixture was diluted with EtOAc (20 mL) and washed with H₂O (20 mL x3). The organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 10-80% EtOAc/hexane to give methyl 1-(3-fluorobenzyl)-1H-indazole-5-carboxylate (276.8 mg, 0.975 mmol; LC-MS (Method 1): *t_R* = 3.13 min, *m/z* (M+H)⁺ = 284) and methyl 2-(3-fluorobenzyl)-2H-indazole-5-carboxylate (155.1 mg, 0.546 mmol; LC-MS (Method 1): *t_R* = 3.25 min, *m/z* (M+H)⁺ = 285).

[0215] STEP 2: The title compound was prepared from methyl 1-(3-fluorobenzyl)-1H-indazole-5-carboxylate following a similar procedure as described in the synthesis of **Int-15** (STEP-2). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.79 (s, 1H), 8.44 (s, 1H), 8.28 (s, 1H), 7.92 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.33 (td, *J* = 7.9, 6.0 Hz, 1H), 7.08 (td, *J* = 9.2, 3.2 Hz, 1H), 7.07 – 6.98 (m, 2H), 5.71 (s, 2H); LC-MS (Method 1): *t_R* = 3.21 min, *m/z* (M+H)⁺ = 271.

Synthesis of 2-(3-fluorobenzyl)-2H-indazole-5-carboxylic acid (**Int-70**):

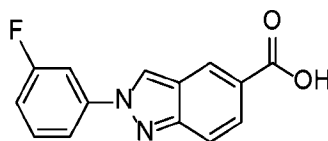
**Int-70**

[0216] The title compound was prepared from methyl 2-(3-fluorobenzyl)-2H-indazole-5-carboxylate following a similar procedure as described in the synthesis of **Int-15** (STEP-2). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.70 (s, 1H), 8.71 (s, 1H), 8.45 (d, *J* = 1.4 Hz, 1H), 7.73 (dd, *J* = 9.1, 1.5 Hz, 1H), 7.61 (d, *J* = 9.1 Hz, 1H), 7.39 (td, *J* = 7.9, 6.2 Hz, 1H), 7.15 (qd, *J* = 8.7, 2.2 Hz, 3H), 5.69 (s, 2H); LC-MS (Method 1): *t_R* = 3.10 min, *m/z* (M+H)⁺ = 271.

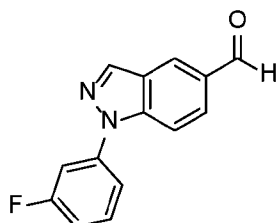
Synthesis of 1-(3-fluorophenyl)-1H-indazole-5-carboxylic acid (**Int-71**):**Int-71**

[0217] STEP 1: In a microwave tube was placed methyl 1H-indazole-5-carboxylate (300 mg, 1.70 mmol), 1-bromo-3-fluorobenzene (0.571 ml, 5.11 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (145 mg, 1.02 mmol), cesium carbonate (555 mg, 1.70 mmol) and copper(I) iodide (32.4 mg, 0.17 mmol) and then 1,4-dioxane (10 ml) was added. The mixture was sealed and then stirred at 100 °C for overnight. The mixture was poured into EtOAc (20 mL). The organic layer was washed with H₂O (20 mL x 3), dried (Na₂SO₄), and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-30% EtOAc/hexane to give methyl 1-(3-fluorophenyl)-1H-indazole-5-carboxylate (46 mg, 0.170 mmol; ¹H NMR (400 MHz, DMSO-d₆) δ 8.58 (t, *J* = 1.0 Hz, 2H), 8.05 (dd, *J* = 8.9, 1.5 Hz, 1H), 7.98 (d, *J* = 8.9 Hz, 1H), 7.70 – 7.59 (m, 3H), 7.29 (td, *J* = 8.9, 2.4 Hz, 1H), 3.88 (s, 3H); LC-MS (Method 1): *t*_R = 3.44 min, *m/z* (M+H)⁺ = 271) and methyl 2-(3-fluorophenyl)-2H-indazole-5-carboxylate (30 mg, 0.111 mmol; ¹H NMR (400 MHz, DMSO-d₆) δ 9.39 (s, 1H), 8.52 (d, *J* = 1.3 Hz, 1H), 8.05 – 7.95 (m, 2H), 7.85 – 7.75 (m, 2H), 7.70 – 7.60 (m, 1H), 7.34 (td, *J* = 8.5, 2.5 Hz, 1H), 3.87 (s, 3H); LC-MS (Method 1): *t*_R = 3.35 min, *m/z* (M+H)⁺ = 271).

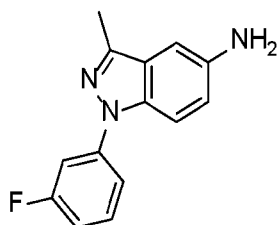
[0218] STEP 2: The title compound was prepared from methyl 1-(3-fluorophenyl)-1H-indazole-5-carboxylate following a similar procedure as described in the synthesis of **Int-15** (STEP-2). LC-MS (Method 1): *t*_R = 2.39 min *m/z* (M+H)⁺ = 257.

Synthesis of 2-(3-fluorophenyl)-2H-indazole-5-carboxylic acid (**Int-72**):**Int-72**

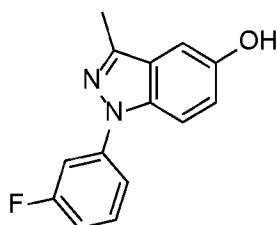
[0219] The title compound was prepared from methyl 2-(3-fluorophenyl)-2H-indazole-5-carboxylate following a similar procedure as described in the synthesis of **Int-15** (STEP-2). LC-MS (Method 1): *t*_R = 2.39 min *m/z* (M+H)⁺ = 257.

Synthesis of 1-(3-fluorophenyl)-1H-indazole-5-carbaldehyde (**Int-73**):**Int-73**

[0220] The title compound was prepared from methyl 1-(3-fluorophenyl)-1H-indazole-5-carboxylate following a similar procedure as described in the synthesis of **Int-30**. LC-MS (Method 1): $t_R = 3.37$ min, m/z ($M+H$)⁺ = 241.

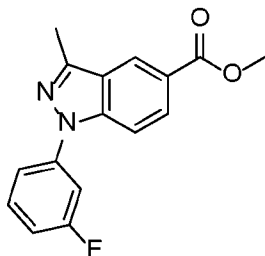
Synthesis of 1-(3-fluorophenyl)-3-methyl-1H-indazol-5-amine (**Int-74**):**Int-74**

[0221] The title compound was prepared from 3-methyl-1H-indazol-5-amine following a similar procedure as described in the synthesis of **Int-71** (STEP-1). LC-MS (Method 1): $t_R = 2.34$ min, m/z ($M+H$)⁺ = 242.

Synthesis of 1-(3-fluorophenyl)-3-methyl-1H-indazol-5-ol (**Int-75**):**Int-75**

[0222] The title compound was prepared from 3-methyl-1H-indazol-5-ol (2 g, 13.50 mmol) following a similar procedure as described in the synthesis of **Int-71** (STEP-1). LC-MS (Method 1): $t_R = 3.12$ min, m/z ($M+H$)⁺ = 243.

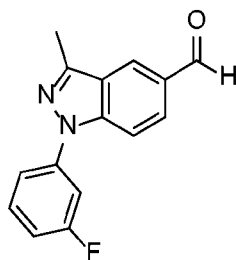
Synthesis of methyl 1-(3-fluorophenyl)-3-methyl-1H-indazole-5-carboxylate (**Int-76**):



Int-76

[0223] The title compound was prepared from methyl 3-methyl-1H-indazole-5-carboxylate following a similar procedure as described in the synthesis of **Int-71** (STEP-1). LC-MS (Method 1): t_R = 3.68 min, m/z ($M+H$)⁺ = 285.

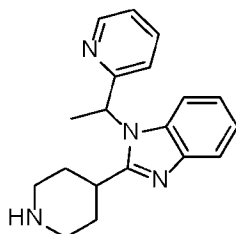
Synthesis of 1-(3-fluorophenyl)-3-methyl-1H-indazole-5-carbaldehyde (**Int-77**):



Int-77

[0224] The title compound was prepared from methyl 1-(3-fluorophenyl)-3-methyl-1H-indazole-5-carboxylate following a similar procedure as described in the synthesis of **Int-30**. LC-MS (Method 1): t_R = 3.49 min, m/z ($M+H$)⁺ = 255.

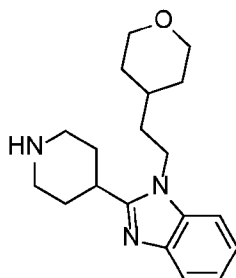
Synthesis of 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 2HCl (**Int-78**):



Int-78

[0225] The title compound was prepared from tert-butyl 4-(1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate and 2-(1-bromoethyl)pyridine following a similar procedure as described in the synthesis of **Int-5**. LC-MS (Method 1): t_R = 2.65 min, m/z ($M+H$)⁺ = 307.

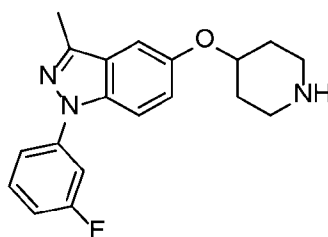
Synthesis of 2-(piperidin-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-benzo[d]imidazole, 2HCl (**Int-79**):



Int-79

[0226] The title compound was prepared from tert-butyl 4-(1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate and 4-(2-bromoethyl)tetrahydro-2H-pyran following a similar procedure as described in the synthesis of **Int-5**. LC-MS (Method 1): $t_R = 2.21$ min, m/z ($M+H$)⁺=314.

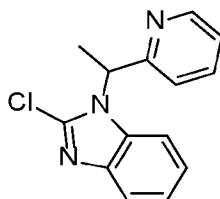
Synthesis of 1-(3-fluorophenyl)-3-methyl-5-(piperidin-4-yloxy)-1H-indazole, 2HCl (**Int-80**):



Int-80

[0227] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-1H-indazol-5-ol and tert-butyl 4-hydroxypiperidine-1-carboxylate following a similar procedure as described in the synthesis of **Int-61** (STEP 1 and STEP 3). LC-MS (Method 1): $t_R = 2.74$ min, m/z ($M+H$)⁺= 326.

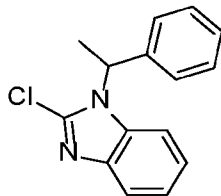
Synthesis of 2-chloro-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole (**Int-81**):



Int-81

[0228] The title compound was prepared from 2-chloro-1H-benzo[d]imidazole and 2-(1-bromoethyl)pyridine following a similar procedure as described in the synthesis of **Int-1**. LC-MS (Method 1): $t_R = 3.20$ min, m/z ($M+H$)⁺= 258.

Synthesis of 2-chloro-1-(1-phenylethyl)-1H-benzo[d]imidazole (**Int-82**):

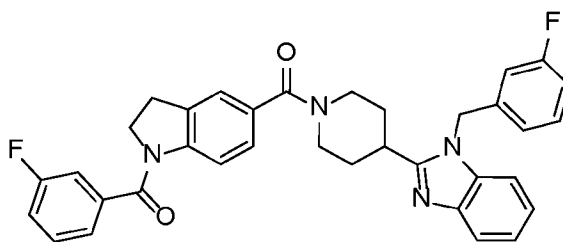


Int-82

[0229] The title compound was prepared from 2-chloro-1H-benzo[d]imidazole and (1-bromoethyl)benzene following a similar procedure as described in the synthesis of **Int-1**. LC-MS (Method 1): $t_R = 3.42$ min, m/z ($M+H$)⁺ = 257.

Synthesis of Test Compounds

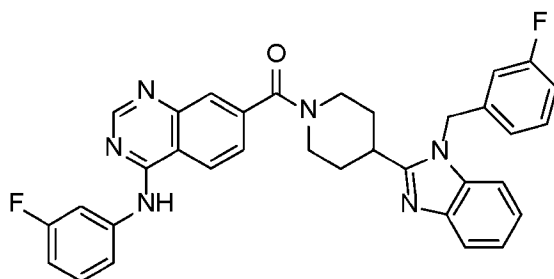
Example 1. (1-(3-fluorobenzoyl)indolin-5-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, TFA (Cpd 1)



Cpd 1

[0230] To a mixture of 1-(3-fluorobenzoyl)indoline-5-carboxylic acid (28.5 mg, 0.1 mmol), 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (38.2 mg, 0.10 mmol), and HATU (76 mg, 0.20 mmol) was added DMF (1 ml) and then Hunig's base (0.052 ml, 0.30 mmol). The mixture was stirred at rt for 2 hr. The mixture was filtered and submitted for purification by semi-preparative HPLC to give (1-(3-fluorobenzoyl)indolin-5-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, TFA (30.8 mg, 0.045 mmol, 44.6 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.08 (s, 1H), 7.75 (d, $J = 7.5$ Hz, 1H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.55 (td, $J = 7.9, 5.8$ Hz, 1H), 7.47 – 7.34 (m, 7H), 7.27 (s, 1H), 7.20 – 7.05 (m, 2H), 7.00 (d, $J = 7.8$ Hz, 1H), 5.76 (s, 2H), 4.51 (s, 1H), 4.02 (t, $J = 8.2$ Hz, 2H), 3.83 (s, 1H), 3.67 (s, 1H), 3.25 – 2.80 (m, 4H), 1.97 – 1.75 (m, 4H); LC-MS (Method 2): $t_R = 4.66$ min, m/z ($M+H$)⁺ = 577.

Example 2. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(4-((3-fluorophenyl)amino)quinazolin-7-yl)methanone, TFA (Cpd 2)

**Cpd 2****STEP 1: Synthesis of methyl 4-((3-fluorophenyl)amino)quinazoline-7-carboxylate**

[0231] To a suspension of methyl 4-chloroquinazoline-7-carboxylate (0.668 g, 3 mmol) in 2-propanol (6 ml) was added 3-fluoroaniline (0.367 g, 3.30 mmol) and then Hunig's base (0.786 ml, 4.50 mmol). Then, the microwave vial was sealed and heated at 90 °C for 5 hr. After cooling to rt, the mixture was concentrated and then H₂O/hexane (10 mL/10 mL) was added. The solid was filtered and triturated with 5% CH₂Cl₂/hexane and then dried in vacuo to give crude methyl 4-((3-fluorophenyl)amino)quinazoline-7-carboxylate (875 mg (ca. 85% purity), 2.502 mmol, 83 % yield). LC-MS (Method 1): *t*_R = 2.61 min, *m/z* (M+H)⁺ = 298.

STEP 2: Synthesis of 4-((3-fluorophenyl)amino)quinazoline-7-carboxylic acid

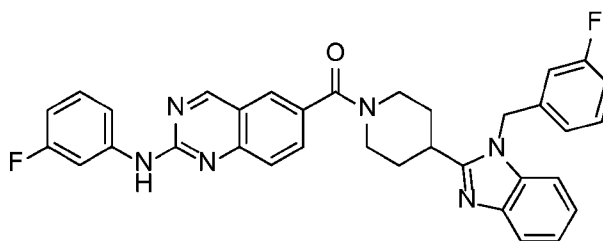
[0232] To a suspension of methyl 4-((3-fluorophenyl)amino)quinazoline-7-carboxylate (700 mg, 2.0 mmol) in THF (8 ml)/MeOH (2 ml) was added 1 N NaOH_(aq) (8 mL, 8 mmol, 4 equiv). The mixture was stirred at 50 °C for 1.5 hr. After cooling to rt, 1N HCl (aq) was added dropwise until the pH of aqueous layer was ca 5. Then, hexane (20 mL) was added and the solid was filtered, triturated with H₂O (5 mL x 2), hexane (5 mL x 2), and then dried to give 4-((3-fluorophenyl)amino)quinazoline-7-carboxylic acid (470 mg, 1.66 mmol, 83 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.51 (s, 1H), 10.06 (s, 1H), 8.72 (s, 1H), 8.66 (d, *J* = 8.7 Hz, 1H), 8.29 (d, *J* = 1.7 Hz, 1H), 8.09 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.94 (dt, *J* = 11.9, 2.3 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.42 (q, *J* = 7.9 Hz, 1H), 6.96 (td, *J* = 8.4, 2.5 Hz, 1H); LC-MS (Method 1): *t*_R = 2.42 min, *m/z* (M+H)⁺ = 284.

STEP 3: Synthesis of (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(4-((3-fluorophenyl)amino)quinazolin-7-yl)methanone, TFA (Cpd 2)

[0233] The title compound was prepared from 4-((3-fluorophenyl)amino)quinazoline-7-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.69 (s, 1H), 8.85 (s, 1H), 8.74 (d, *J* = 8.5 Hz, 1H), 7.90 – 7.81 (m, 2H), 7.77 (t, *J* = 8.5 Hz,

2H), 7.62 (t, $J = 8.3$ Hz, 2H), 7.51–7.36 (m, 4H), 7.20–7.02 (m, 3H), 7.00 (d, $J = 7.7$ Hz, 1H), 5.76 (br s, 2H), 4.64 (d, $J = 12.9$ Hz, 1H), 3.79–3.53 (m, 2H), 3.27 (br s, 1H), 3.00 (br s, 1H), 2.08–1.68 (m, 4H); LC-MS (Method 2): $t_R = 3.99$ min, m/z (M+H) $^+ = 575$.

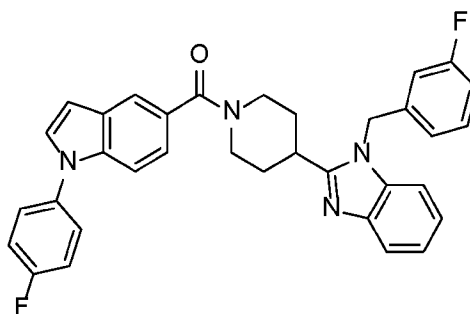
Example 3. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(2-((3-fluorophenyl)amino)quinazolin-6-yl)methanone, TFA (Cpd 3)



Cpd 3

[0234] The title compound was prepared from methyl 2-chloroquinazoline-6-carboxylate and 3-fluoroaniline following a similar procedure as described in **Example 2**. ^1H NMR (400 MHz, DMSO- d_6) δ 10.26 (s, 1H), 9.40 (s, 1H), 8.10–8.02 (m, 2H), 7.85 (dd, $J = 8.6, 1.9$ Hz, 1H), 7.80–7.72 (m, 2H), 7.70–7.60 (m, 2H), 7.36–7.31 (m, 4H), 7.14 (td, $J = 10.0, 4.4$ Hz, 2H), 7.01 (d, $J = 7.7$ Hz, 1H), 6.80 (td, $J = 8.4, 2.5$ Hz, 1H), 5.78 (s, 2H), 4.59 (br s, 1H), 3.85 (br s, 1H), 3.71 (br s, 1H), 3.11 (br s, 2H), 1.92 (s, 4H); LC-MS (Method 2): $t_R = 4.80$ min, m/z (M+H) $^+ = 575$.

Example 4. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(4-fluorophenyl)-1H-indol-5-yl)methanone (Cpd 4)

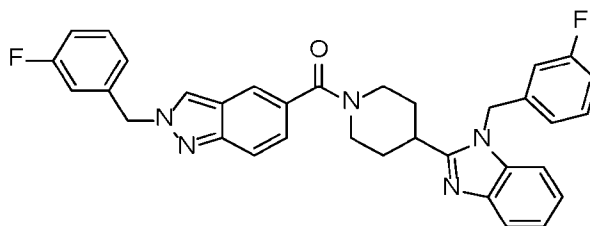


Cpd 4

[0235] The title compound was prepared from 1-(4-fluorophenyl)-1H-indole-5-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.74 (d, $J = 1.5$ Hz, 1H), 7.70 (d, $J = 3.3$ Hz, 1H), 7.63 (td, $J = 8.8, 5.0$ Hz, 3H), 7.51 (d, $J = 8.5$ Hz, 1H), 7.42 (t, $J = 8.5$ Hz, 3H), 7.34 (q, $J = 7.6$ Hz, 1H), 7.25 (dd, $J = 8.6, 1.6$ Hz, 1H), 7.22–7.13 (m, 2H), 7.08 (td, $J = 8.6, 2.5$ Hz, 1H), 6.95 (d, $J = 9.9$ Hz, 1H), 6.85 (d, $J = 7.7$ Hz, 1H), 6.77 (d, $J = 3.3$ Hz,

1H), 5.59 (s, 2H), 3.31 (s, 3H), 3.08 (s, 2H), 1.83 (d, $J = 14.3$ Hz, 4H); LC-MS (Method 2): $t_R = 5.05$ min, m/z (M+H)⁺ = 547.

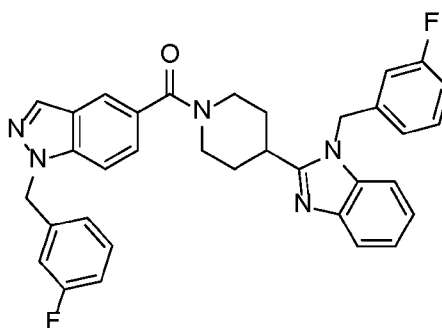
Example 5. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(2-(3-fluorobenzyl)-2H-indazol-5-yl)methanone, TFA (Cpd 5)



Cpd 5

[0236] The title compound was prepared from 2-(3-fluorobenzyl)-2H-indazole-5-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.61 (d, $J = 1.0$ Hz, 1H), 7.83 (t, $J = 1.3$ Hz, 1H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.66 (dd, $J = 8.9, 1.0$ Hz, 1H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.39 (tdd, $J = 8.4, 6.0, 2.8$ Hz, 3H), 7.27 (dd, $J = 8.9, 1.5$ Hz, 1H), 7.19 – 7.11 (m, 3H), 7.11 (s, 1H), 6.99 (d, $J = 7.7$ Hz, 1H), 5.72 (d, $J = 26.8$ Hz, 4H), 3.66 (s, 4H), 3.11 (d, $J = 30.6$ Hz, 3H), 1.87 (s, 4H); LC-MS (Method 2): $t_R = 4.59$ min, m/z (M+H)⁺ = 562.

Example 6. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorobenzyl)-1H-indazol-5-yl)methanone, TFA (Cpd 6)

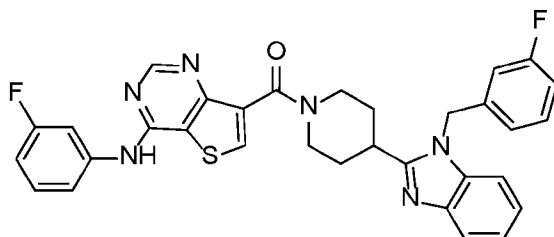


Cpd 6

[0237] The title compound was prepared from 1-(3-fluorobenzyl)-1H-indazole-5-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ : 8.22 (d, $J = 0.9$ Hz, 1H), 7.89 (dd, $J = 1.5, 0.8$ Hz, 1H), 7.87 – 7.74 (m, 2H), 7.63 (d, $J = 7.8$ Hz, 1H), 7.49 – 7.30 (m, 5H), 7.20 – 7.14 (m, 1H), 7.14 – 7.08 (m, 2H), 7.08 – 7.03 (m, 2H), 7.01 (d, $J = 7.7$ Hz, 1H),

5.79 – 5.70 (m, 4H), 3.68 (s, 1H), 2.50 (p, $J = 1.8$ Hz, 6H), 1.89 (s, 2H); LC-MS (Method 2): $t_R = 4.65$ min, m/z (M+H)⁺ = 562.

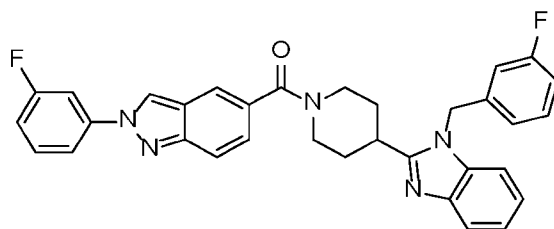
Example 7. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(4-((3-fluorophenyl)amino)thieno[3,2-d]pyrimidin-7-yl)methanone, TFA (Cpd 7)



Cpd 7

[0238] The title compound was prepared from methyl 4-chlorothieno[3,2-d]pyrimidine-7-carboxylate and 3-fluoroaniline following a similar procedure as described in **Example 2**. ¹H NMR (400 MHz, DMSO-d₆) δ 10.02 (s, 1H), 8.67 (s, 1H), 8.40 (s, 1H), 7.90 – 7.81 (m, 1H), 7.76 (d, $J = 7.7$ Hz, 1H), 7.61 (dd, $J = 13.4, 8.0$ Hz, 2H), 7.49 – 7.33 (m, 4H), 7.13 (t, $J = 9.2$ Hz, 2H), 7.01 (d, $J = 7.7$ Hz, 1H), 6.92 (td, $J = 8.6, 2.5$ Hz, 1H), 5.76 (s, 2H), 4.70 (d, $J = 13.0$ Hz, 1H), 3.67 (s, 1H), 3.50 (d, $J = 13.3$ Hz, 1H), 3.19 (t, $J = 12.9$ Hz, 1H), 2.97 (t, $J = 12.4$ Hz, 1H), 2.12 – 1.65 (m, 4H); LC-MS (Method 2): $t_R = 4.57$ min, m/z (M+H)⁺ = 581.

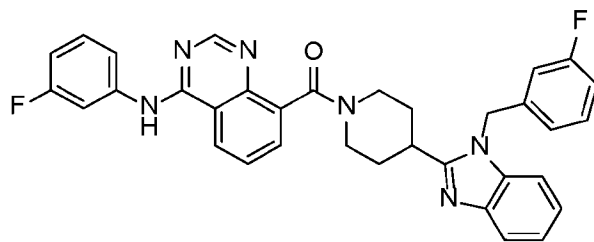
Example 8. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(2-(3-fluorophenyl)-2H-indazol-5-yl)methanone, TFA (Cpd 8)



Cpd 8

[0239] The title compound was prepared from 2-(3-fluorophenyl)-2H-indazole-5-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.26 (d, $J = 1.0$ Hz, 1H), 8.02 – 7.96 (m, 2H), 7.87 (t, $J = 1.3$ Hz, 1H), 7.79 (dd, $J = 9.0, 1.0$ Hz, 1H), 7.74 (d, $J = 7.5$ Hz, 1H), 7.64 (td, $J = 8.5, 6.4$ Hz, 1H), 7.60 (d, $J = 7.8$ Hz, 1H), 7.42 – 7.35 (m, 4H), 7.34 – 7.29 (m, 1H), 7.13 (td, $J = 8.7, 2.6$ Hz, 1H), 7.08 (d, $J = 10.2$ Hz, 1H), 6.98 (d, $J = 7.8$ Hz, 1H), 5.74 (s, 2H), 4.50 (s, 1H), 3.64 (s, 1H), 2.99 (s, 2H), 1.89 (s, 5H); LC-MS (Method 2): $t_R = 4.70$ min, m/z (M+H)⁺ = 548.

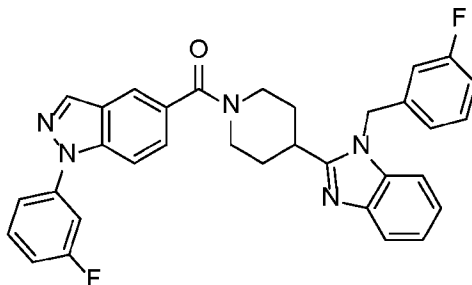
Example 9. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(4-((3-fluorophenyl)amino)quinazolin-8-yl)methanone, TFA (Cpd 9)



Cpd 9

[0240] The title compound was prepared from methyl 4-chloroquinazoline-8-carboxylate and 3-fluoroaniline following a similar procedure as described in **Example 2**. ^1H NMR (400 MHz, DMSO- d_6) δ 10.09 (s, 1H), 8.69 (s, 1H), 8.61 (d, J = 8.3 Hz, 1H), 7.92 (d, J = 11.7 Hz, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.74 (dt, J = 15.4, 7.7 Hz, 2H), 7.66 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.45 – 7.34 (m, 4H), 7.18 – 7.05 (m, 2H), 6.98 (dt, J = 11.0, 8.0 Hz, 2H), 5.75 (s, 2H), 4.76 (d, J = 13.0 Hz, 1H), 3.65 (s, 1H), 3.25 (d, J = 13.4 Hz, 1H), 3.11 (t, J = 12.4 Hz, 1H), 2.98 (td, J = 12.4, 3.4 Hz, 1H), 2.09 – 1.56 (m, 4H); LC-MS (Method 2): t_R = 4.25 min, m/z ($M+H$) $^+$ = 575.

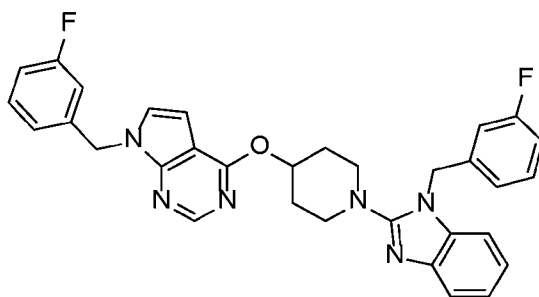
Example 10. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-5-yl)methanone, TFA (Cpd 10)



Cpd 10

[0241] The title compound was prepared from 1-(3-fluorophenyl)-1H-indazole-5-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.49 (d, J = 0.9 Hz, 1H), 8.03 – 7.93 (m, 2H), 7.75 – 7.51 (m, 7H), 7.49 – 7.19 (m, 3H), 7.12 (td, J = 8.6, 2.5 Hz, 1H), 7.01 (dd, J = 38.6, 8.9 Hz, 2H), 5.71 (s, 2H), 3.78 (s, 2H), 3.08 (s, 2H), 1.88 (s, 5H); LC-MS (Method 2): t_R = 4.79 min, m/z ($M+H$) $^+$ = 548.

Example 11. 7-(3-fluorobenzyl)-4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-7H-pyrrolo[2,3-d]pyrimidine, TFA (Cpd 11)



Cpd 11

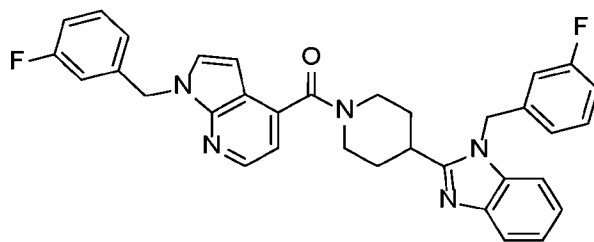
STEP 1: Synthesis of 4-chloro-7-(3-fluorobenzyl)-7H-pyrrolo[2,3-d]pyrimidine

[0242] The material, 4-chloro-7-(3-fluorobenzyl)-7H-pyrrolo[2,3-d]pyrimidine, was prepared from 4-chloro-7H-pyrrolo[2,3-d]pyrimidine and 1-(bromomethyl)-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-69** (STEP 1).

STEP 2: Synthesis of 7-(3-fluorobenzyl)-4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-7H-pyrrolo[2,3-d]pyrimidine, TFA (**Cpd 11**)

[0243] In a microwave tube was placed 1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-ol (50mg, 0.154 mmol) and sodium hydride (18.44 mg, 0.461 mmol) were added in N,N-Dimethylformamide (2 ml) and stirred for 30 mins at room temperature. After deprotonation, 4-chloro-7-(3-fluorobenzyl)-7H-pyrrolo[2,3-d]pyrimidine (44.2 mg, 0.169 mmol) was added in the reaction mixture. After stirring for 4 hrs at room temperature, the mixture was poured into EtOAc (20 mL). The organic layer was washed with H₂O (20 mL x 3), dried (Na₂SO₄), and filtered. After removal of solvent, the product was submitted for purification by semi-preparative HPLC to give 7-(3-fluorobenzyl)-4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-7H-pyrrolo[2,3-d]pyrimidine, TFA (**Cpd 11**, 6.0 mg, 0.011 mmol, 10.8 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.40 (s, 1H), 7.56 – 7.49 (m, 2H), 7.46 – 7.36 (m, 1H), 7.30 (ddd, *J* = 8.3, 5.3, 2.3 Hz, 5H), 7.19 – 7.09 (m, 5H), 6.52 (d, *J* = 3.5 Hz, 1H), 5.54 (dq, *J* = 8.0, 4.0 Hz, 1H), 5.45 (s, 2H), 5.41 (s, 2H), 3.65 (s, 3H), 2.17 (s, 2H), 1.95 (qd, *J* = 8.7, 4.4 Hz, 3H); LC-MS (Method 2): *t*_R = 5.08 min, *m/z* (M+H)⁺ = 551.

Example 12. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorobenzyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)methanone, TFA (Cpd 12)



Cpd 12

STEP 1: Synthesis of (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1H-pyrrolo[2,3-b]pyridin-4-yl)methanone

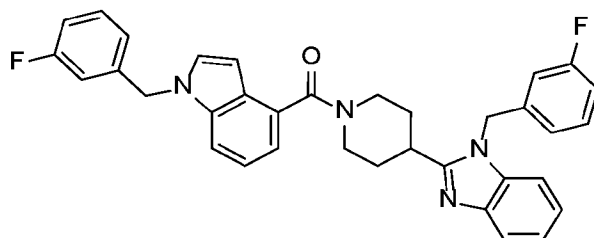
[0244] To a mixture of 1H-pyrrolo[2,3-b]pyridine-4-carboxylic acid (0.162 g, 1 mmol), 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (0.382 g, 1.00 mmol), and HATU (0.57 g, 1.50 mmol), was added DMF (3 mL) and then Hunig's base (0.517 g, 4.0 mmol). The mixture was stirred at rt for 3 hr. The mixture was then dropped into vigorously stirred H₂O (6 mL), and Na₂CO₃ (aq) was added until the pH was around 7-8. The solid was filtered, washed with H₂O (5 mL x 2), hexane (5 mL x 2), and then dried to give crude product. The product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent to give pure (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1H-pyrrolo[2,3-b]pyridin-4-yl)methanone (358 mg, 0.789 mmol, 79 % yield). LC-MS (Method 1): *t*_R = 2.64 min, *m/z* (M+H)⁺ = 454.

STEP 2: Synthesis of (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorobenzyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)methanone, TFA (Cpd 12)

[0245] To a mixture of (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1H-pyrrolo[2,3-b]pyridin-4-yl)methanone (45.4 mg, 0.1 mmol) and K₂CO₃ (27.6 mg, 0.20 mmol) was added a solution of 1-(bromomethyl)-3-fluorobenzene (56.7 mg, 0.30 mmol) in MeCN (1 mL). The mixture was heated at 80 °C for overnight. After cooling to rt, the mixture was filtered and submitted for purification using semi-preparative HPLC to give (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorobenzyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)methanone, TFA (5.5 mg, 8.14 μmol, 8.14 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.35 (d, *J* = 4.8 Hz, 1H), 7.78 (d, *J* = 3.5 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.42 – 7.28 (m, 4H), 7.15 – 7.02 (m, 6H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.51 (d, *J* = 3.5 Hz, 1H), 5.72 (s, 2H), 5.52 (s, 2H), 4.67 (d, *J* = 12.9 Hz, 1H), 3.62 (s, 1H), 3.50 (d, *J* = 13.3 Hz, 1H), 3.19 (s,

1H), 3.00 (t, $J = 12.3$ Hz, 1H), 2.06 – 1.69 (m, 4H); LC-MS (Method 2): $t_R = 4.60$ min, m/z (M+H)⁺ = 562.

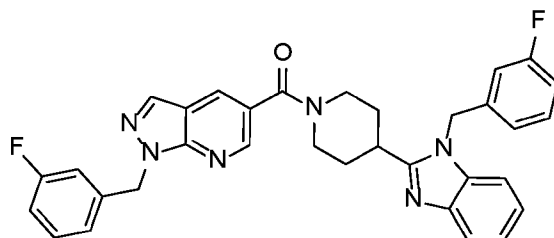
Example 13. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorobenzyl)-1H-indol-4-yl)methanone (Cpd 13)



Cpd 13

[0246] The title compound was prepared from (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1H-indol-4-yl)methanone and 1-(bromomethyl)-3-fluorobenzene (using NaH as the base and DMF as the solvent) following a similar procedure as described in **Example 12**. LC-MS (Method 2): $t_R = 5.03$ min, m/z (M+H)⁺ = 561.

Example 14. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-5-yl)methanone, TFA (Cpd 14)



Cpd 14

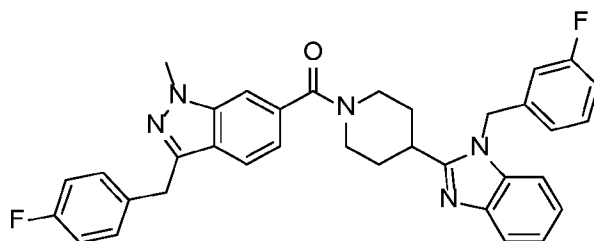
STEP 1: Synthesis of 1-(3-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid

[0247] The material, 1-(3-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, was prepared from methyl 1H-pyrazolo[3,4-b]pyridine-5-carboxylate and 1-(bromomethyl)-3-fluorobenzene following a similar procedure as described in **Int-69**. ¹H NMR (400 MHz, DMSO-d₆) δ 13.22 (s, 1H), 9.07 (d, $J = 2.0$ Hz, 1H), 8.82 (d, $J = 2.0$ Hz, 1H), 8.36 (s, 1H), 7.34 (td, $J = 8.0, 6.1$ Hz, 1H), 7.14 – 7.01 (m, 3H), 5.73 (s, 2H); LC-MS (Method 1): $t_R = 2.86$ min, m/z (M+H)⁺ = 272.

STEP 2: Synthesis of (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-5-yl)methanone (Cpd 14)

[0248] The title compound was prepared from 1-(3-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.66 (d, *J* = 2.0 Hz, 1H), 8.41 (d, *J* = 2.0 Hz, 1H), 8.30 (s, 1H), 7.66 – 7.57 (m, 1H), 7.45 – 7.31 (m, 3H), 7.23 – 7.04 (m, 6H), 6.95 (dt, *J* = 10.1, 2.0 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 5.73 (s, 2H), 5.60 (s, 2H), 4.52 (s, 1H), 3.80 (s, 1H), 3.68 – 3.56 (m, 1H), 3.20 – 3.09 (m, 1H), 1.89 (s, 1H), 1.87 (s, 4H); LC-MS (Method 2): *t*_R = 4.85 min, *m/z* (M+H)⁺ = 563.

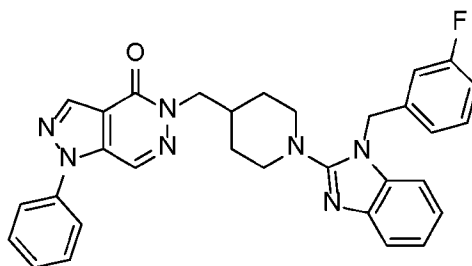
Example 15. (3-(4-fluorobenzyl)-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 15)



Cpd 15

[0249] In a microwave vial was placed (3-bromo-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (146 mg, 0.2 mmol), 2-(4-fluorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (70.8 mg, 0.30 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (16.33 mg, 0.02 mmol), and K₂CO₃ (124 mg, 0.90 mmol). The tube was sealed. The air was removed and re-filled with N₂ (repeat for 3 times). Then, 1,4-dioxane (1 ml)/water (0.5 ml) was added and the mixture was stirred at 95 °C for 4 hr. After cooling to rt, the layers were separated. The aqueous layer was extracted with EtOAc (1 mL x 2). The combined organic layer was dried (Na₂SO₄), filtered, and then concentrated. The product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent to give (3-(4-fluorobenzyl)-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (19.3 mg, 0.034 mmol, 16.76 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 7.68 (d, *J* = 8.3 Hz, 1H), 7.65 (s, 1H), 7.62 – 7.57 (m, 1H), 7.35 (ddt, *J* = 13.4, 9.7, 5.3 Hz, 4H), 7.20 – 7.11 (m, 2H), 7.11 – 7.02 (m, 4H), 6.93 (d, *J* = 10.0 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 5.57 (s, 2H), 4.54 (br s, 1H), 4.25 (s, 2H), 4.00 (s, 3H), 3.65 (br s, 1H), 3.40 – 2.89 (m, 3H), 1.94 – 1.62 (m, 4H); LC-MS (Method 2): *t*_R = 5.03 min, *m/z* (M+H)⁺ = 561.

Example 16. 5-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)methyl)-1-phenyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyridazin-4-one, TFA (Cpd 16)



Cpd 16

STEP 1: Synthesis of tert-butyl 4-((4-oxo-1-phenyl-1,4-dihydro-5H-pyrazolo[3,4-d]pyridazin-5-yl)methyl)piperidine-1-carboxylate

[0250] In a microwave was placed 1-phenyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyridazin-4-one (0.318 g, 1.5 mmol), tert-butyl 4-(bromomethyl)piperidine-1-carboxylate (0.709 g, 2.55 mmol), and Cs_2CO_3 (0.650 g, 2.0 mmol). Then, DMF (3 mL) was added and the tube was sealed and heated at 80 °C for 8 hr. After cooling to rt, the mixture was poured into EtOAc/ H_2O (40 mL/40 mL). The organic layer was washed with H_2O (40 mL x 2), dried (Na_2SO_4), and filtered. After removal of solvent, the product was purified by silica gel chromatography using 10-70% EtOAc/hexane as the eluent to give tert-butyl 4-((4-oxo-1-phenyl-1,4-dihydro-5H-pyrazolo[3,4-d]pyridazin-5-yl)methyl)piperidine-1-carboxylate (530 mg, 1.294 mmol, 86 % yield). LC-MS (Method 1): t_R = 3.43 min, m/z ($M+H$)⁺ = 410.

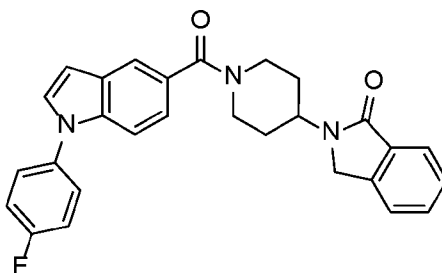
STEP 2: Synthesis of 1-phenyl-5-(piperidin-4-ylmethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyridazin-4-one, 2HCl

[0251] To a solution of tert-butyl 4-((4-oxo-1-phenyl-1,4-dihydro-5H-pyrazolo[3,4-d]pyridazin-5-yl)methyl)piperidine-1-carboxylate (530 mg, 1.294 mmol) in CH_2Cl_2 (4 mL) was added HCl (4M in dioxane, 10.32 mmol, 2.6 mL, 8 equiv). The mixture was stirred at rt for 2 hr. Then, hexane (30 mL) was added and the solid was filtered. The solid was triturated with hexane (5 mL x 2), and then dried in vacuo to give 1-phenyl-5-(piperidin-4-ylmethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyridazin-4-one, 2HCl (455 mg, 1.190 mmol, 92 % yield). LC-MS (Method 1): t_R = 2.45 min, m/z ($M+H$)⁺ = 310.

STEP 3: Synthesis of 5-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)methyl)-1-phenyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyridazin-4-one, TFA (Cpd 16)

[0252] In a microwave tube was placed 1-phenyl-5-(piperidin-4-ylmethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyridazin-4-one, 2HCl (38.2 mg, 0.1 mmol) and 2-chloro-1-(3-fluorobenzyl)-1H-benzo[d]imidazole (26.1 mg, 0.10 mmol) and then DMSO and Hunig's base (69.9 μ l, 0.40 mmol) were added. The tube was sealed and heated at 150 °C for overnight. After cooling to rt, the mixture was filtered and submitted for purification using semi-preparative HPLC to give 5-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)methyl)-1-phenyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyridazin-4-one, TFA (31.7 mg, 0.049 mmol, 48.9 % yield). ^1H NMR (400 MHz, DMSO- d_6) δ 8.59 (s, 1H), 8.53 (s, 1H), 7.78 (d, J = 7.9 Hz, 2H), 7.62 (t, J = 7.7 Hz, 2H), 7.53 (d, J = 7.3 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.40 (q, J = 7.7 Hz, 1H), 7.33 – 7.05 (m, 6H), 5.41 (s, 2H), 4.11 (d, J = 7.1 Hz, 2H), 3.64 (d, J = 12.7 Hz, 2H), 3.13 (s, 2H), 2.24 – 2.09 (m, 1H), 1.72 – 1.59 (m, 2H), 1.48 (tt, J = 13.1, 6.7 Hz, 2H); LC-MS (Method 2): t_R = 4.76 min, m/z ($M+H$) $^+$ = 534.

Example 17. 2-(1-(1-(4-fluorophenyl)-1H-indole-5-carbonyl)piperidin-4-yl)isoindolin-1-one (Cpd 17)

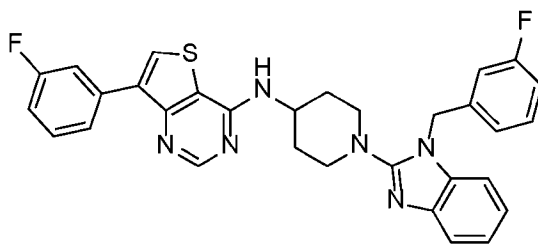


Cpd 17

[0253] The title compound was prepared from 1-(4-fluorophenyl)-1H-indole-5-carboxylic acid and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in

Example 1. ^1H NMR (400 MHz, DMSO- d_6) δ 7.76 (s, 1H), 7.71 (d, J = 3.4 Hz, 1H), 7.69 – 7.61 (m, 3H), 7.58 (d, J = 4.2 Hz, 2H), 7.51 (d, J = 8.6 Hz, 1H), 7.49 – 7.36 (m, 3H), 7.27 (d, J = 8.5 Hz, 1H), 6.76 (d, J = 3.3 Hz, 1H), 4.49 (s, 2H), 4.33 (p, J = 8.2 Hz, 1H), 4.19 – 3.65 (m, 2H), 3.07 (br s, 2H), 1.86 – 1.70 (m, 4H); LC-MS (Method 2): t_R = 5.53 min, m/z ($M+H$) $^+$ = 454.

Example 18. N-(1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-7-(3-fluorophenyl)thieno[3,2-d]pyrimidin-4-amine (Cpd 18)



Cpd 18

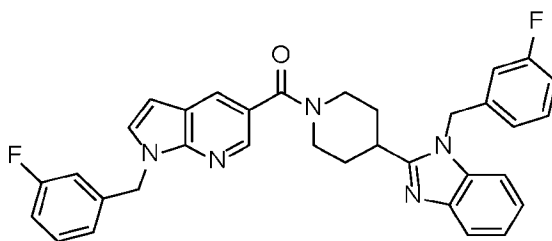
STEP 1: Synthesis of 7-bromo-N-(1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)thieno[3,2-d]pyrimidin-4-amine

[0254] The material, 7-bromo-N-(1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)thieno[3,2-d]pyrimidin-4-amine, was prepared from 7-bromo-4-chlorothieno[3,2-d]pyrimidine and 1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-amine, 2HCl following a similar procedure as described in the synthesis of **Int-42**. LC-MS (Method 1): $t_R = 2.81$ min, m/z ($M+H$) $^+ = 537, 539$.

STEP 2: Synthesis of N-(1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-7-(3-fluorophenyl)thieno[3,2-d]pyrimidin-4-amine (Cpd 18)

[0255] The title compound was prepared from 7-bromo-N-(1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)thieno[3,2-d]pyrimidin-4-amine and (3-fluorophenyl)boronic acid following a similar procedure as described in **Example 15**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.55 (s, 1H), 8.47 (s, 1H), 8.07 – 7.99 (m, 1H), 7.91 (dd, $J = 10.0, 7.7$ Hz, 2H), 7.49 (q, $J = 7.4$ Hz, 1H), 7.45 (d, $J = 7.8$ Hz, 1H), 7.37 (q, $J = 7.4$ Hz, 1H), 7.23 – 7.14 (m, 2H), 7.12 – 6.96 (m, 5H), 5.32 (s, 2H), 4.38 (q, $J = 7.5$ Hz, 1H), 3.57 (d, $J = 12.7$ Hz, 2H), 3.10 (t, $J = 12.2$ Hz, 2H), 1.99 (dd, $J = 12.4, 3.7$ Hz, 2H), 1.85 (qd, $J = 12.2, 3.8$ Hz, 2H); LC-MS (Method 2): $t_R = 4.61$ min, m/z ($M+H$) $^+ = 553$.

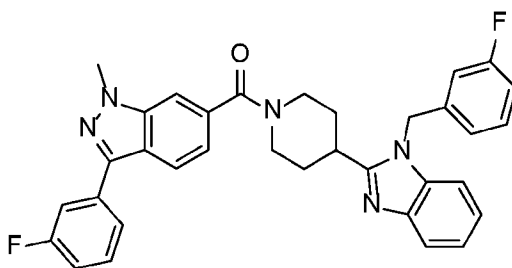
Example 19. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorobenzyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)methanone (Cpd 19)



Cpd 19

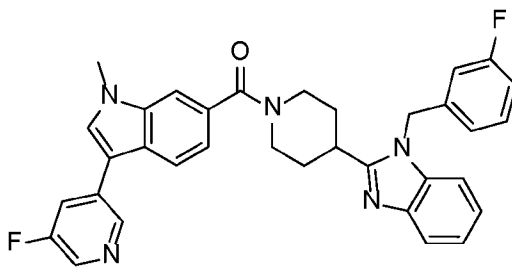
[0256] The title compound was prepared from 1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 12**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.34 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 7.75 (d, *J* = 3.5 Hz, 1H), 7.64 – 7.59 (m, 1H), 7.45 – 7.40 (m, 2H), 7.38 – 7.32 (m, 2H), 7.20 – 7.15 (m, 2H), 7.10 – 7.07 (m, 3H), 6.95 (dt, *J* = 9.8, 2.1 Hz, 1H), 6.86 (dt, *J* = 8.1, 1.1 Hz, 1H), 6.62 (d, *J* = 3.5 Hz, 1H), 5.60 (s, 2H), 5.53 (s, 2H), 4.09 (q, *J* = 5.3 Hz, 1H), 3.17 (d, *J* = 4.9 Hz, 3H), 1.84 (s, 5H); LC-MS (Method 2): *t*_R = 4.92 min, *m/z* (M+H)⁺ = 562.

Example 20. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone, TFA (Cpd 20)

**Cpd 20**

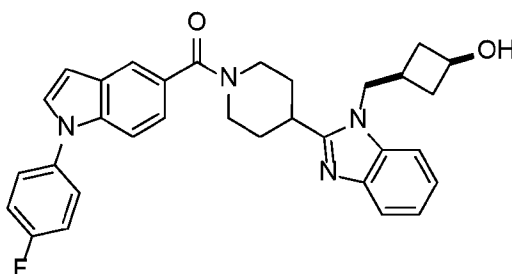
[0257] The title compound was prepared from (3-bromo-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone and (3-fluorophenyl)boronic acid following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.17 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.80 (s, 1H), 7.78 – 7.68 (m, 2H), 7.57 (dt, *J* = 14.7, 6.6 Hz, 2H), 7.38 (q, *J* = 7.5 Hz, 3H), 7.27 – 7.22 (m, 2H), 7.17 – 7.04 (m, 2H), 6.99 (d, *J* = 7.7 Hz, 1H), 5.74 (s, 2H), 4.64 (s, 1H), 4.15 (s, 3H), 3.92 – 3.47 (m, 2H), 3.25 (br s, 1H), 3.01 (br s, 1H), 1.89 (br s, 4H); LC-MS (Method 2): *t*_R = 5.15 min, *m/z* (M+H)⁺ = 562.

Example 21. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(5-fluoropyridin-3-yl)-1-methyl-1H-indol-6-yl)methanone, TFA (Cpd 21)

**Cpd 21**

[0258] The title compound was prepared from (3-bromo-1-methyl-1H-indol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone and (5-fluoropyridin-3-yl)boronic acid following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.81 (s, 1H), 8.43 (d, *J* = 2.6 Hz, 1H), 8.07 (s, 1H), 7.98 (t, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.67 – 7.64 (m, 2H), 7.53 – 7.34 (m, 3H), 7.24 (d, *J* = 8.3 Hz, 1H), 7.14 (t, *J* = 9.2 Hz, 2H), 7.03 (d, *J* = 7.8 Hz, 1H), 5.79 (s, 2H), 3.89 (s, 3H), 4.18 – 3.37 (m, 3H), 3.12 (s, 2H), 1.90 (s, 4H); LC-MS (Method 2): *t*_R = 4.81 min, *m/z* (M+H)⁺ = 562.

Example 22. (1-(4-fluorophenyl)-1H-indol-5-yl)(4-(1-(((1s,3s)-3-hydroxycyclobutyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, TFA (Cpd 22)



Cpd 22

STEP 1: Synthesis of (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(4-fluorophenyl)-1H-indol-5-yl)methanone

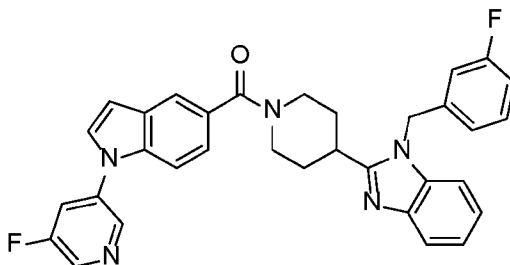
[0259] The material, (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(4-fluorophenyl)-1H-indol-5-yl)methanone, was prepared from 1-(4-fluorophenyl)-1H-indole-5-carboxylic acid and 2-(piperidin-4-yl)-1H-benzo[d]imidazole following a similar procedure as described in the synthesis of **Int-65**. LC-MS (Method 1): *t*_R = 2.97 min, *m/z* (M+H)⁺ = 439.

STEP 2: Synthesis of (1-(4-fluorophenyl)-1H-indol-5-yl)(4-(1-(((1s,3s)-3-hydroxycyclobutyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, TFA (Cpd 22)

[0260] To a mixture of (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(4-fluorophenyl)-1H-indol-5-yl)methanone (48.7 mg, 0.1 mmol) and Cs₂CO₃ (48.9 mg, 0.15 mmol) was added DMF (1 ml). The mixture was stirred at rt for 3-5 min and then (1s,3s)-3-(bromomethyl)cyclobutan-1-ol (33.0 mg, 0.20 mmol) was added. The mixture was stirred for another 2 hr at 50 °C. The mixture was filtered and then submitted for purification by semi-preparative HPLC to give (1-(4-fluorophenyl)-1H-indol-5-yl)(4-(1-(((1s,3s)-3-hydroxycyclobutyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, TFA (3.5 mg, 5.50 μmol, 5.50 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 7.85 (s, 1H), 7.77 (s, 1H), 7.72 (d, *J* = 3.5 Hz, 2H), 7.64 (dd, *J* = 8.7, 4.9 Hz, 2H),

7.54 (d, $J = 8.6$ Hz, 1H), 7.43 (t, $J = 8.6$ Hz, 4H), 7.29 (d, $J = 8.6$ Hz, 1H), 6.78 (d, $J = 3.2$ Hz, 1H), 4.49 (s, 2H), 3.86 (q, $J = 7.2$ Hz, 1H), 2.27 – 2.09 (m, 3H), 2.00 – 1.84 (m, 4H), 1.68 – 1.64 (m, 2H). (5 protons and OH are broad and not assigned; salt proton not shown); LC-MS (Method 2): $t_R = 4.65$ min, m/z ($M+H$)⁺ = 523.

Example 23. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(5-fluoropyridin-3-yl)-1H-indol-5-yl)methanone (Cpd 23)



Cpd 23

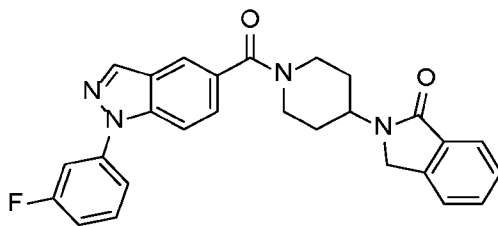
STEP 1: Synthesis of 1-(5-fluoropyridin-3-yl)-1H-indole-5-carboxylic acid

[0261] The material, 1-(5-fluoropyridin-3-yl)-1H-indole-5-carboxylic acid, was prepared from methyl 1H-indole-5-carboxylate and 3-bromo-5-fluoropyridine following a similar procedure as described in **Int-71**. LC-MS (Method 1): $t_R = 2.87$ min, m/z ($M+H$)⁺ = 257.

STEP 2: Synthesis of (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(5-fluoropyridin-3-yl)-1H-indol-5-yl)methanone (Cpd 23)

[0262] The title compound was prepared from 1-(5-fluoropyridin-3-yl)-1H-indole-5-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO- d_6) δ 8.80 (t, $J = 1.7$ Hz, 1H), 8.64 (d, $J = 2.7$ Hz, 1H), 8.17 (dt, $J = 10.0, 2.4$ Hz, 1H), 7.84 (d, $J = 3.3$ Hz, 1H), 7.76 (dd, $J = 1.6, 0.7$ Hz, 1H), 7.69 (dt, $J = 8.6, 0.8$ Hz, 1H), 7.65 – 7.55 (m, 1H), 7.44 – 7.26 (m, 3H), 7.21 – 7.11 (m, 2H), 7.11 – 7.03 (m, 1H), 6.94 (dt, $J = 10.1, 2.0$ Hz, 1H), 6.88 – 6.81 (m, 2H), 5.58 (s, 2H), 4.91 – 3.50 (m, 2H), 3.08 (qd, $J = 7.3, 4.7$ Hz, 3H), 1.83 (d, $J = 12.6$ Hz, 4H); LC-MS (Method 2): $t_R = 4.67$ min, m/z ($M+H$)⁺ = 548.

Example 24. 2-(1-(1-(3-fluorophenyl)-1H-indazole-5-carbonyl)piperidin-4-yl)isoindolin-1-one, TFA (Cpd 24)

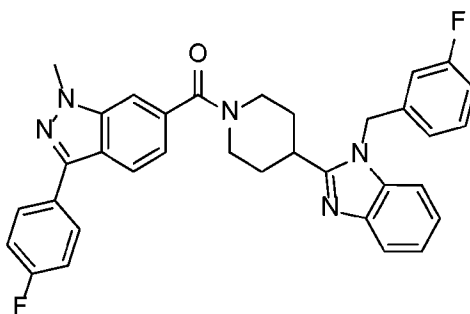


Cpd 24

[0263] The title compound was prepared from 1-(3-fluorophenyl)-1H-indazole-5-carboxylic acid and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in

Example 1. ^1H NMR (400 MHz, DMSO- d_6) δ 8.49 (d, $J = 0.9$ Hz, 1H), 8.01 (d, $J = 1.2$ Hz, 1H), 7.99 – 7.93 (m, 1H), 7.71 – 7.62 (m, 4H), 7.62 – 7.56 (m, 3H), 7.48 (dq, $J = 8.4, 4.2$ Hz, 1H), 7.31 – 7.22 (m, 1H), 4.49 (s, 2H), 4.34 (p, $J = 8.5$ Hz, 1H), 3.79 (s, 1H), 2.96 (m, 2H), 1.80 (s, 5H); LC-MS (Method 2): $t_R = 5.26$ min, m/z (M+H) $^+$ = 455.

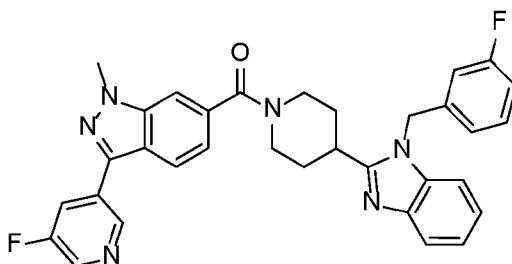
Example 25. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(4-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 25)



Cpd 25

[0264] The title compound was prepared from (3-bromo-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone and (4-fluorophenyl)boronic acid following a similar procedure as described in **Example 15.** ^1H NMR (400 MHz, DMSO- d_6) δ 8.09 (d, $J = 8.4$ Hz, 1H), 8.04 – 7.95 (m, 2H), 7.79 (s, 1H), 7.65 – 7.56 (m, 1H), 7.40 – 7.31 (m, 4H), 7.23 (d, $J = 8.4$ Hz, 1H), 7.18 – 7.13 (m, 2H), 7.08 (td, $J = 8.6, 2.6$ Hz, 1H), 6.98 – 6.90 (m, 1H), 6.84 (d, $J = 7.7$ Hz, 1H), 5.58 (s, 2H), 4.57 (br s, 1H), 4.13 (s, 3H), 3.71 (br s, 1H), 3.44 – 3.31 (m, 1H), 3.21 (br s, 1H), 3.01 (br s, 1H), 2.06 – 1.61 (m, 4H); LC-MS (Method 2): $t_R = 5.60$ min, m/z (M+H) $^+$ = 562.

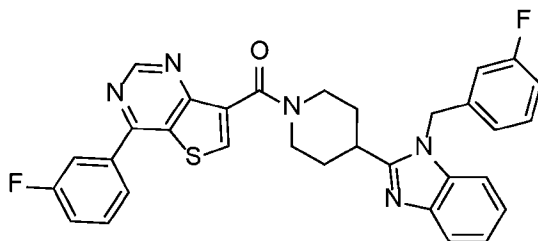
Example 26. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(5-fluoropyridin-3-yl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 26)



Cpd 26

[0265] The title compound was prepared from (3-bromo-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone and (5-fluoropyridin-3-yl)boronic acid following a similar procedure as described in **Example 15**. ^1H NMR (400 MHz, DMSO- d_6) δ 9.07 (d, J = 2.1 Hz, 1H), 8.62 (d, J = 2.7 Hz, 1H), 8.25 – 8.16 (m, 2H), 7.85 (s, 1H), 7.65 – 7.56 (m, 1H), 7.42 – 7.36 (m, 1H), 7.33 (dd, J = 8.0, 6.1 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.21 – 7.12 (m, 2H), 7.08 (td, J = 8.7, 2.6 Hz, 1H), 6.93 (dd, J = 9.9, 2.6 Hz, 1H), 6.84 (d, J = 7.7 Hz, 1H), 5.58 (s, 2H), 4.58 (br s, 1H), 4.17 (s, 3H), 3.69 (br s, 1H), 3.41 – 3.32 (m, 1H), 3.27 – 3.11 (m, 1H), 3.01 (brs, 1H), 1.97 – 1.63 (m, 4H); LC-MS (Method 2): t_R = 4.92 min, m/z ($M+H$) $^+$ = 563.

Example 27. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(4-(3-fluorophenyl)thieno[3,2-d]pyrimidin-7-yl)methanone (Cpd 27)



Cpd 27

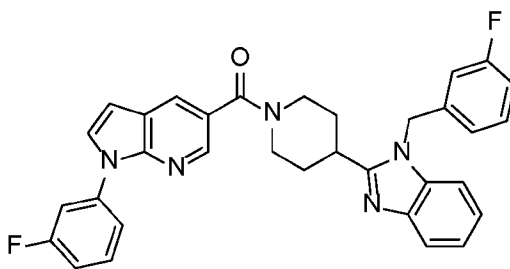
STEP 1: Synthesis of 4-(3-fluorophenyl)thieno[3,2-d]pyrimidine-7-carboxylic acid

[0266] The material, 4-(3-fluorophenyl)thieno[3,2-d]pyrimidine-7-carboxylic acid, was prepared from methyl 4-chlorothieno[3,2-d]pyrimidine-7-carboxylate and (3-fluorophenyl)boronic acid following a similar procedure as described in the synthesis of **Int-15**. LC-MS (Method 1): t_R = 3.39 min, m/z ($M+H$) $^+$ = 275.

STEP 2: Synthesis of (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(4-(3-fluorophenyl)thieno[3,2-d]pyrimidin-7-yl)methanone (Cpd 27)

[0267] The title compound was prepared from 4-(3-fluorophenyl)thieno[3,2-d]pyrimidine-7-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.34 (s, 1H), 8.74 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.93 (dd, *J* = 9.8, 2.4 Hz, 1H), 7.73 (td, *J* = 8.0, 5.8 Hz, 1H), 7.65 – 7.57 (m, 1H), 7.51 (td, *J* = 8.6, 2.6 Hz, 1H), 7.44 – 7.28 (m, 2H), 7.21 – 7.11 (m, 2H), 7.07 (td, *J* = 8.7, 2.6 Hz, 1H), 6.93 (dd, *J* = 10.2, 2.6 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 5.57 (s, 2H), 4.65 (d, *J* = 13.0 Hz, 1H), 3.49 (d, *J* = 13.5 Hz, 1H), 3.37 (q, *J* = 10.2 Hz, 1H), 3.18 (t, *J* = 12.6 Hz, 1H), 3.04 (td, *J* = 13.2, 4.1 Hz, 1H), 1.96 – 1.78 (m, 3H), 1.65 (d, *J* = 12.9 Hz, 1H); LC-MS (Method 2): *t*_R = 5.33 min, *m/z* (M+H)⁺ = 566.

Example 28. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)methanone (Cpd 28)



Cpd 28

STEP 1: Synthesis of 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid

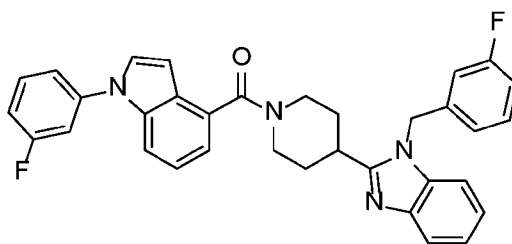
[0268] The material, 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid, was prepared from methyl 1H-pyrrolo[2,3-b]pyridine-5-carboxylate and 1-bromo-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-71**. LC-MS (Method 1): *t*_R = 3.28 min, *m/z* (M+H)⁺ = 257.

STEP 2: Synthesis of (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)methanone (Cpd 28)

[0269] The title compound was prepared from 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.41 (dd, *J* = 2.0, 0.4 Hz, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 8.10 (dd, *J* = 3.7, 0.4 Hz, 1H), 7.91 (dd, *J* = 2.5, 2.0 Hz, 1H), 7.83 (ddd, *J* = 8.2, 2.1, 0.9 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.42 – 7.31 (m, 2H),

7.22 – 7.13 (m, 3H), 7.08 (tdd, $J = 8.3, 2.7, 0.9$ Hz, 1H), 6.94 (dt, $J = 9.9, 2.1$ Hz, 1H), 6.85 (ddd, $J = 7.7, 1.7, 0.9$ Hz, 1H), 6.82 (d, $J = 3.7$ Hz, 1H), 5.59 (s, 2H), 4.57-3.82 (m, 2H), 3.37 (m, 1H), 1.85 (m, 6H); LC-MS (Method 2): $t_R = 5.53$ min, m/z (M+H)⁺ = 548.

Example 29. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indol-4-yl)methanone (Cpd 29)



Cpd 29

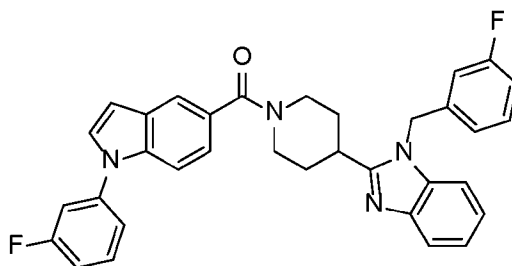
STEP 1: Synthesis of 1-(3-fluorophenyl)-1H-indole-4-carboxylic acid

[0270] The material, 1-(3-fluorophenyl)-1H-indole-4-carboxylic acid, was prepared from methyl 1H-indole-4-carboxylate and 1-bromo-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-71**. LC-MS (Method 1): $t_R = 3.20$ min, m/z (M+H)⁺ = 256.

STEP 2: Synthesis of (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indol-4-yl)methanone (**Cpd 29**)

[0271] The title compound was prepared from 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.79 (d, $J = 3.3$ Hz, 1H), 7.68 – 7.64 (m, 1H), 7.61 (ddt, $J = 6.4, 5.1, 2.5$ Hz, 2H), 7.53 (dt, $J = 10.2, 2.3$ Hz, 1H), 7.49 (ddd, $J = 8.0, 2.1, 0.9$ Hz, 1H), 7.41 – 7.37 (m, 1H), 7.34 (td, $J = 8.0, 6.1$ Hz, 1H), 7.29 – 7.24 (m, 2H), 7.18 – 7.13 (m, 3H), 7.08 (td, $J = 8.6, 2.5$ Hz, 1H), 6.96 – 6.81 (m, 2H), 6.64 (dd, $J = 3.3, 0.8$ Hz, 1H), 5.57 (s, 2H), 4.63 (s, 1H), 3.59 (s, 1H), 3.13 (m, 2H), 1.96 – 1.66 (m, 5H); LC-MS (Method 2): $t_R = 5.64$ min, m/z (M+H)⁺ = 547.

Example 30. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indol-5-yl)methanone (Cpd 30)



Cpd 30

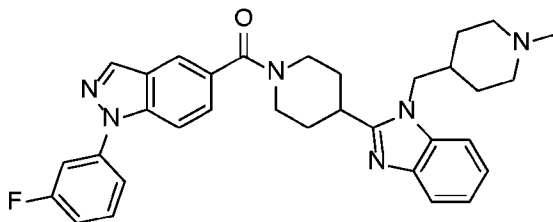
STEP 1: Synthesis of 1-(3-fluorophenyl)-1H-indole-5-carboxylic acid

[0272] The material, 1-(3-fluorophenyl)-1H-indole-5-carboxylic acid, was prepared from methyl 1H-indole-5-carboxylate and 1-bromo-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-71**. LC-MS (Method 1): $t_R = 3.30$ min, m/z (M+H)⁺ = 256.

STEP 2: Synthesis of (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indol-5-yl)methanone (Cpd 30)

[0273] The title compound was prepared from 1-(3-fluorophenyl)-1H-indole-5-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.77 (d, $J = 3.3$ Hz, 1H), 7.74 (dd, $J = 1.6, 0.7$ Hz, 1H), 7.68 – 7.56 (m, 4H), 7.52 (dt, $J = 10.1, 2.2$ Hz, 1H), 7.48 (ddd, $J = 8.0, 2.1, 0.9$ Hz, 1H), 7.41 – 7.37 (m, 1H), 7.34 (td, $J = 8.1, 6.2$ Hz, 1H), 7.30 – 7.23 (m, 2H), 7.19 – 7.12 (m, 2H), 7.11 – 7.05 (m, 1H), 6.94 (dt, $J = 10.1, 2.0$ Hz, 1H), 6.84 (ddd, $J = 7.7, 1.7, 0.9$ Hz, 1H), 6.80 (dd, $J = 3.3, 0.8$ Hz, 1H), 5.58 (s, 2H), 4.05 (m, 2H), 3.36 (m, 1H), 3.07 (s, 3H), 1.81 (s, 1H); LC-MS (Method 2): $t_R = 5.615$ min, m/z (M+H)⁺ = 547.

Example 31. (1-(3-fluorophenyl)-1H-indazol-5-yl)(4-(1-((1-methylpiperidin-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 31)

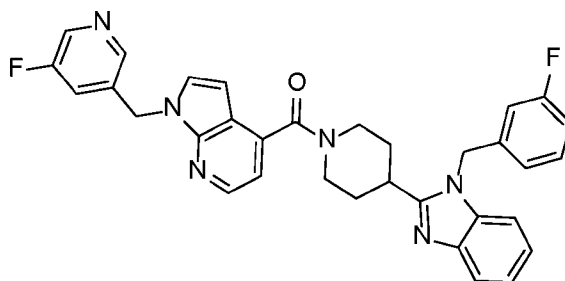


Cpd 31

[0274] The title compound was prepared from 1-(3-fluorophenyl)-1H-indazole-5-carboxylic acid and 1-((1-methylpiperidin-4-yl)methyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 3HCl

following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, $J = 0.9$ Hz, 1H), 7.98 (dt, $J = 8.6, 0.8$ Hz, 1H), 7.70 – 7.62 (m, 3H), 7.62 – 7.58 (m, 1H), 7.57 – 7.53 (m, 2H), 7.35 (dd, $J = 7.1, 0.7$ Hz, 1H), 7.31 – 7.24 (m, 1H), 7.20 – 7.11 (m, 2H), 4.16 (d, $J = 6.9$ Hz, 2H), 3.60 (pd, $J = 6.6, 3.9$ Hz, 2H), 3.12 (qd, $J = 7.4, 4.3$ Hz, 2H), 1.84 (s, 3H), 1.24 (dd, $J = 6.6, 5.4$ Hz, 10H), 0.51 – 0.48 (m, 2H), 0.43 (dd, $J = 4.9, 1.5$ Hz, 2H); LC-MS (Method 2): $t_R = 3.68$ min, m/z ($\text{M}+\text{H}$) $^+ = 551$.

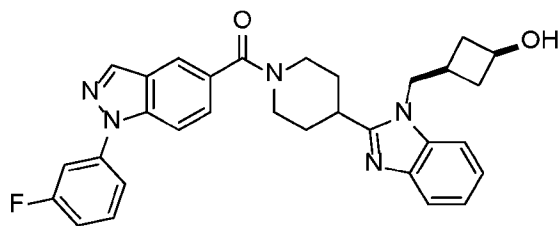
Example 32. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-((5-fluoropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)methanone, TFA (Cpd 32)



Cpd 32

[0275] The title compound was prepared from (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1H-pyrrolo[2,3-b]pyridin-4-yl)methanone and 3-(bromomethyl)-5-fluoropyridine, HBr following a similar procedure as described in **Example 12**. ^1H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, $J = 2.8$ Hz, 1H), 8.42 (t, $J = 1.8$ Hz, 1H), 8.36 (d, $J = 4.8$ Hz, 1H), 7.83 (d, $J = 3.6$ Hz, 1H), 7.80 – 7.74 (m, 1H), 7.66 – 7.58 (m, 2H), 7.46 – 7.36 (m, 3H), 7.17 – 7.09 (m, 3H), 6.99 (d, $J = 7.7$ Hz, 1H), 6.53 (d, $J = 3.5$ Hz, 1H), 5.75 (s, 2H), 5.58 (s, 2H), 4.67 (d, $J = 13.1$ Hz, 1H), 3.50 (d, $J = 13.5$ Hz, 1H), 2.98 (d, $J = 13.2$ Hz, 1H), 2.05 – 1.84 (m, 3H), 1.76 (s, 3H); LC-MS (Method 2): $t_R = 4.32$ min, m/z ($\text{M}+\text{H}$) $^+ = 563$.

Example 33. (1-(3-fluorophenyl)-1H-indazol-5-yl)(4-(1-(((1s,3s)-3-hydroxycyclobutyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 33)

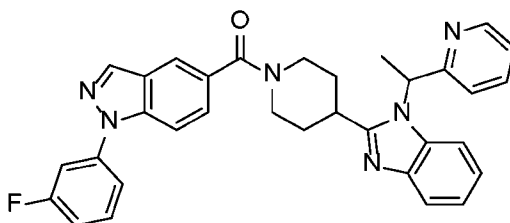


Cpd 33

[0276] The title compound was prepared from 1-(3-fluorophenyl)-1H-indazole-5-carboxylic acid and (1s,3s)-3-((2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol, 2HCl

following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.48 (d, $J = 2.8$ Hz, 1H), 8.42 (t, $J = 1.8$ Hz, 1H), 8.36 (d, $J = 4.8$ Hz, 1H), 7.83 (d, $J = 3.6$ Hz, 1H), 7.77 (d, $J = 7.6$ Hz, 1H), 7.67 – 7.59 (m, 2H), 7.49 – 7.37 (m, 3H), 7.37 – 7.33 (m, 1H), 7.18 – 7.04 (m, 3H), 6.99 (d, $J = 7.7$ Hz, 1H), 6.53 (d, $J = 3.5$ Hz, 1H), 5.75 (s, 2H), 5.58 (s, 2H), 4.67 (d, $J = 13.1$ Hz, 1H), 3.65 (s, 1H), 3.50 (d, $J = 13.4$ Hz, 1H), 3.19 (s, 1H), 2.99 (t, $J = 12.5$ Hz, 1H), 1.97 (d, $J = 20.0$ Hz, 2H), 1.76 (s, 3H); LC-MS (Method 2): $t_R = 4.09$ min, m/z ($M+H$) $^+ = 524$.

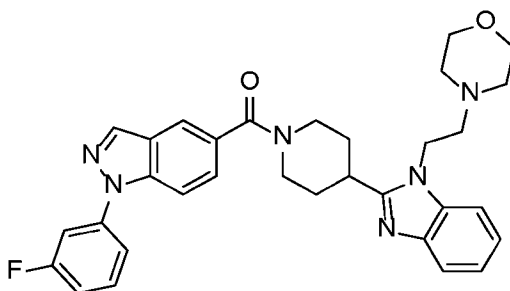
Example 34. (1-(3-fluorophenyl)-1H-indazol-5-yl)(4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 34)



Cpd 34

[0277] The title compound was prepared from 1-(3-fluorophenyl)-1H-indazole-5-carboxylic acid and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 3HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.60 – 8.54 (m, 1H), 8.49 (d, $J = 0.9$ Hz, 1H), 8.02 (t, $J = 1.1$ Hz, 1H), 7.97 (dt, $J = 8.7, 1.0$ Hz, 1H), 7.79 – 7.52 (m, 6H), 7.34 – 7.19 (m, 3H), 7.07 (ddd, $J = 10.7, 7.4, 2.0$ Hz, 2H), 6.98 (ddd, $J = 8.3, 6.9, 1.2$ Hz, 1H), 6.13 (q, $J = 7.0$ Hz, 1H), 4.55 (s, 1H), 3.83 (s, 1H), 3.14 (s, 3H), 1.98 – 1.88 (m, 6H), 1.24 – 1.12 (m, 1H); LC-MS (Method 2): $t_R = 4.63$ min, m/z ($M+H$) $^+ = 545$.

Example 35. (1-(3-fluorophenyl)-1H-indazol-5-yl)(4-(1-(2-morpholinoethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 35)

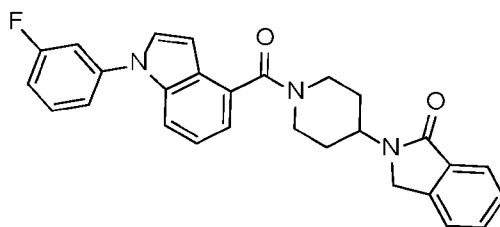


Cpd 35

[0278] The title compound was prepared from 1-(3-fluorophenyl)-1H-indazole-5-carboxylic acid and 4-(2-(2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)ethyl)morpholine, 3HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.51 (d, $J = 0.9$

Hz, 1H), 8.04 (t, $J = 1.1$ Hz, 1H), 8.02 – 7.95 (m, 1H), 7.74 – 7.48 (m, 6H), 7.28 (tt, $J = 8.3$, 2.0 Hz, 1H), 7.24 – 7.11 (m, 2H), 4.54 (s, 1H), 4.36 (t, $J = 6.3$ Hz, 2H), 4.03 (q, $J = 7.1$ Hz, 1H), 3.92 (s, 2H), 3.53 (t, $J = 4.6$ Hz, 4H), 3.10 (qd, $J = 7.3$, 4.8 Hz, 1H), 2.76 – 2.57 (m, 2H), 2.45 (s, 3H), 1.88 (q, $J = 11.7$ Hz, 2H), 1.17 (t, $J = 7.2$ Hz, 3H); LC-MS (Method 2): $t_R = 3.69$ min, m/z (M+H)⁺ = 553.

Example 36. 2-(1-(1-(3-fluorophenyl)-1H-indole-4-carbonyl)piperidin-4-yl)isoindolin-1-one (Cpd. 36)

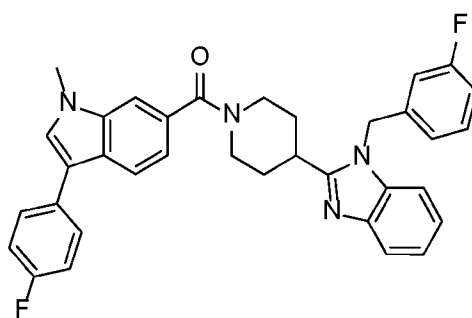


Cpd 36

[0279] The title compound was prepared from 1-(3-fluorophenyl)-1H-indole-4-carboxylic acid and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in

Example 1. ¹H NMR (400 MHz, DMSO- d_6) δ 7.79 (d, $J = 3.4$ Hz, 1H), 7.70 – 7.43 (m, 8H), 7.27 (dt, $J = 8.8$, 6.9 Hz, 2H), 7.17 (d, $J = 7.2$ Hz, 1H), 6.70 (d, $J = 3.3$ Hz, 1H), 4.72 (s, 1H), 4.49 (s, 2H), 4.32 (p, $J = 8.1$ Hz, 1H), 3.10 (d, $J = 83.6$ Hz, 2H), 1.77 (d, $J = 73.3$ Hz, 5H); LC-MS (Method 2): $t_R = 5.62$ min, m/z (M+H)⁺ = 454.

Example 37. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(4-fluorophenyl)-1-methyl-1H-indol-6-yl)methanone, TFA (Cpd 37)

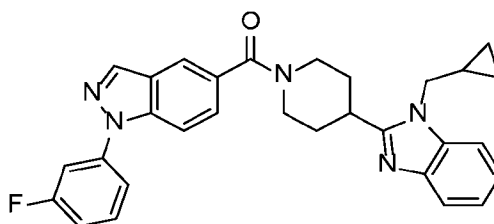


Cpd 37

[0280] The title compound was prepared from (3-bromo-1-methyl-1H-indol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone and (4-fluorophenyl)boronic acid following a similar procedure as described in **Example 15.** ¹H NMR (400 MHz, DMSO- d_6) δ 7.87 (d, $J = 8.2$ Hz, 1H), 7.79 (s, 1H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.70 – 7.56 (m, 4H), 7.38 (h, J

= 7.2 Hz, 3H), 7.26 (t, J = 8.7 Hz, 2H), 7.19 (d, J = 8.2 Hz, 1H), 7.12 (q, J = 9.9 Hz, 2H), 6.99 (d, J = 7.7 Hz, 1H), 5.75 (s, 2H), 3.87 (s, 3H), 3.72 (d, J = 43.6 Hz, 3H), 3.10 (br s, 2H), 2.06 – 1.73 (m, 4H); LC-MS (Method 2): t_R = 5.39 min, m/z ($M+H$)⁺ = 561.

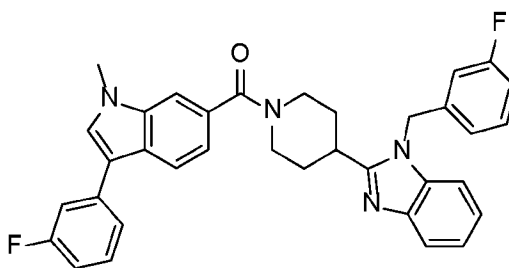
Example 38. (4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-5-yl)methanone (Cpd 38)



Cpd 38

[0281] The title compound was prepared from 1-(3-fluorophenyl)-1H-indazole-5-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO- d_6) δ 8.05 – 7.90 (m, 4H), 7.71 – 7.50 (m, 6H), 7.27 (t, J = 8.1 Hz, 1H), 7.19 – 7.11 (m, 1H), 4.16 (d, J = 6.9 Hz, 2H), 1.90 (s, 5H), 1.27 – 1.18 (m, 5H), 0.53 – 0.47 (m, 2H), 0.45 – 0.40 (m, 2H); LC-MS (Method 2): t_R = 4.57 min, m/z ($M+H$)⁺ = 494.

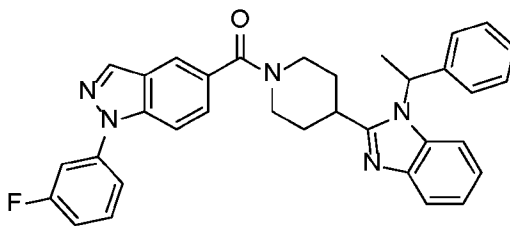
Example 39. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)methanone, TFA (Cpd 39)



Cpd 39

[0282] The title compound was prepared from (3-bromo-1-methyl-1H-indol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone and (3-fluorophenyl)boronic acid following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO- d_6) δ 7.94 (d, J = 8.3 Hz, 1H), 7.91 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.61 (s, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.50 – 7.32 (m, 5H), 7.21 (d, J = 8.3 Hz, 1H), 7.17 – 7.01 (m, 3H), 6.99 (d, J = 7.7 Hz, 1H), 5.75 (s, 2H), 3.87 (s, 3H), 3.80 – 3.50 (m, 3H), 3.10 (br s, 2H), 1.88 (br s, 4H); LC-MS (Method 2): t_R = 5.34 min, m/z ($M+H$)⁺ = 561.

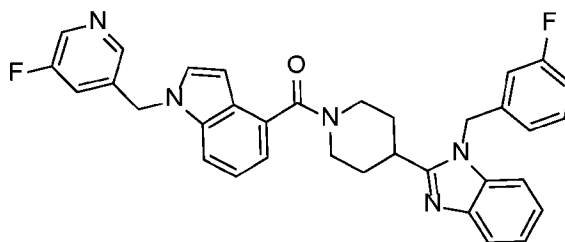
Example 40. (1-(3-fluorophenyl)-1H-indazol-5-yl)(4-(1-(1-phenylethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 40)



Cpd 40

[0283] The title compound was prepared from 1-(3-fluorophenyl)-1H-indazole-5-carboxylic acid and 1-(1-phenylethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.50 (d, *J* = 0.9 Hz, 1H), 8.05 – 7.91 (m, 2H), 7.70 – 7.52 (m, 6H), 7.30 – 7.10 (m, 3H), 4.57 (s, 1H), 4.19 (d, *J* = 6.9 Hz, 2H), 3.86 (s, 1H), 2.67 (s, 2H), 1.89 (d, *J* = 14.0 Hz, 4H), 1.23 (ddd, *J* = 10.9, 7.2, 4.6 Hz, 4H), 0.57 – 0.37 (m, 4H); LC-MS (Method 2): *t*_R = 4.96 min, *m/z* (M+H)⁺ = 544.

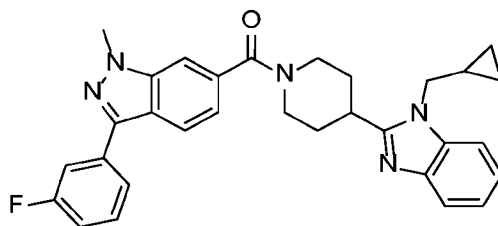
Example 41. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-((5-fluoropyridin-3-yl)methyl)-1H-indol-4-yl)methanone, TFA (Cpd 41)



Cpd 41

[0284] The title compound was prepared from (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1H-indol-4-yl)methanone and 3-(bromomethyl)-5-fluoropyridine, HBr following a similar procedure as described in **Example 12**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.47 (d, *J* = 2.8 Hz, 1H), 8.39 (d, *J* = 1.9 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 3.2 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.58 (dt, *J* = 9.5, 2.4 Hz, 2H), 7.37 (td, *J* = 8.0, 6.1 Hz, 3H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.15 – 7.01 (m, 3H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.48 (d, *J* = 3.2 Hz, 1H), 5.71 (s, 2H), 5.54 (s, 2H), 4.66 (s, 1H), 3.04 (m, 3H), 1.80 (s, 5H); LC-MS (Method 2): *t*_R = 4.59 min, *m/z* (M+H)⁺ = 562.

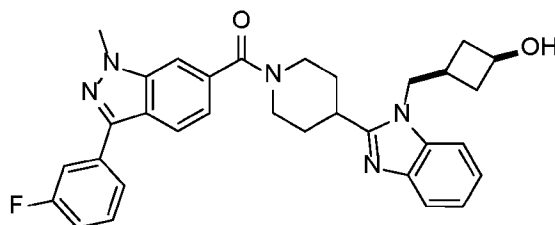
Example 42. (4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 42)



Cpd 42

[0285] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.85 – 7.83 (m, 2H), 7.76 – 7.68 (m, 1H), 7.61 – 7.52 (m, 3H), 7.30 – 7.09 (m, 4H), 4.62 (br s, 1H), 4.17 – 4.15 (m, 5H), 3.76 (br s, 1H), 3.40 – 3.22 (m, 2H), 3.09 (br s, 1H), 2.14 – 1.71 (m, 4H), 1.18 (p, *J* = 6.2 Hz, 1H), 0.54 – 0.38 (m, 4H); LC-MS (Method 2): *t*_R = 4.80 min, *m/z* (M+H)⁺ = 508.

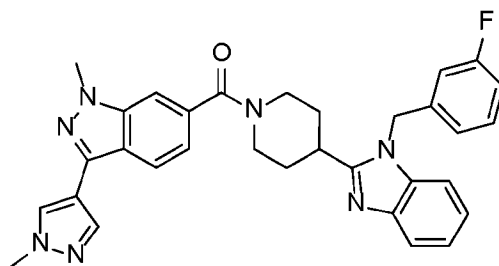
Example 43. (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-(((1s,3s)-3-hydroxycyclobutyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 43)



Cpd 43

[0286] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and (1s,3s)-3-((2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.85 – 7.83 (m, 2H), 7.76 – 7.68 (m, 1H), 7.59 – 7.50 (m, 3H), 7.30 – 7.08 (m, 4H), 5.00 (d, *J* = 6.1 Hz, 1H), 4.63 (br s, 1H), 4.27 (d, *J* = 6.3 Hz, 2H), 4.15 (s, 3H), 3.87 – 3.76 (m, 2H), 3.30 (s, 1H), 3.08 (s, 1H), 2.24 – 2.02 (m, 3H), 2.02 – 1.70 (m, 5H), 1.59 (q, *J* = 8.2 Hz, 2H); LC-MS (Method 2): *t*_R = 4.30 min, *m/z* (M+H)⁺ = 538.

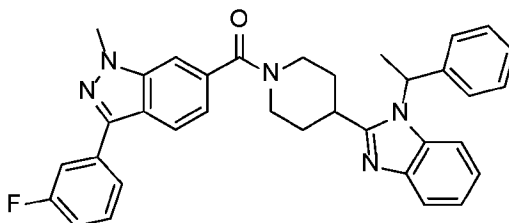
Example 44. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-methyl-3-(1-methyl-1H-pyrazol-4-yl)-1H-indazol-6-yl)methanone (Cpd 44)



Cpd 44

[0287] The title compound was prepared from (3-bromo-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.37 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.96 (s, 1H), 7.71 (s, 1H), 7.65 – 7.56 (m, 1H), 7.43 – 7.29 (m, 2H), 7.20 – 7.12 (m, 3H), 7.08 (td, *J* = 8.7, 2.6 Hz, 1H), 6.93 (dd, *J* = 10.1, 2.7 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 5.58 (s, 2H), 4.57 (br s, 1H), 4.05 (s, 3H), 3.91 (s, 3H), 3.72 (br s, 1H), 3.42 – 3.31 (m, 1H), 3.20 (br s, 1H), 3.00 (br s, 1H), 2.02 – 1.61 (m, 4H); LC-MS (Method 2): *t*_R = 4.21 min, *m/z* (M+H)⁺ = 548.

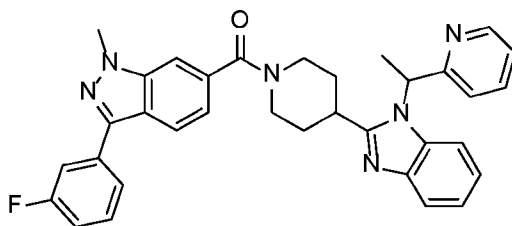
Example 45. (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-(1-phenylethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 45)



Cpd 45

[0288] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 1-(1-phenylethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.76 – 7.68 (m, 1H), 7.56 (q, *J* = 7.3 Hz, 2H), 7.37 – 7.18 (m, 7H), 7.10 – 6.96 (m, 3H), 6.09 (q, *J* = 7.0 Hz, 1H), 4.61 (br s, 1H), 4.15 (s, 3H), 3.73 (br s, 1H), 3.47 (s, 1H), 3.30 (br s, 1H), 3.03 (br s, 1H), 2.08 – 1.67 (m, 7H); LC-MS (Method 2): *t*_R = 5.11 min, *m/z* (M+H)⁺ = 558.

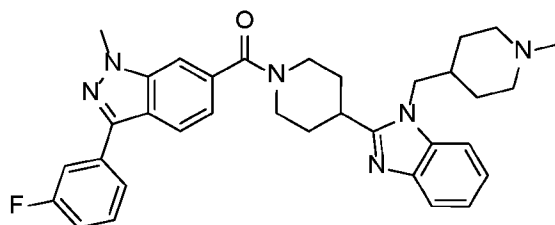
Example 46. (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 46)



Cpd 46

[0289] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 3HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.57 (d, J = 4.8 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.85 – 7.83 (m, 2H), 7.78 – 7.68 (m, 2H), 7.61 – 7.51 (m, 2H), 7.31 – 7.21 (m, 4H), 7.11 – 6.93 (m, 3H), 6.13 (q, J = 7.0 Hz, 1H), 4.62 (br s, 1H), 4.15 (s, 3H), 3.74 (br s, 1H), 3.57 – 3.43 (m, 1H), 3.30 (br s, 1H), 3.04 (br s, 1H), 2.20 – 1.66 (m, 7H); LC-MS (Method 2): t_R = 4.78 min, m/z ($M+H$) $^+$ = 559.

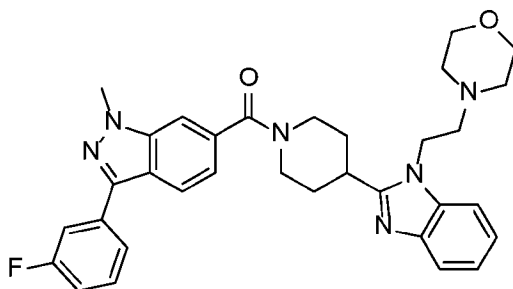
Example 47. (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-((1-methylpiperidin-4-yl)methyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 47)



Cpd 47

[0290] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 1-((1-methylpiperidin-4-yl)methyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 3HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, J = 8.4 Hz, 1H), 7.75 (dd, J = 8.4, 5.5 Hz, 2H), 7.69 – 7.62 (m, 1H), 7.59 (s, 1H), 7.47 (td, J = 7.9, 5.9 Hz, 1H), 7.35 – 7.22 (m, 4H), 7.09 (td, J = 8.4, 2.6 Hz, 1H), 4.91 (s, 1H), 4.16 (s, 3H), 4.05 (d, J = 7.5 Hz, 2H), 3.28 – 2.94 (m, 2H), 2.87 (d, J = 11.4 Hz, 2H), 2.19 (tt, J = 12.3, 6.5 Hz, 2H), 2.11 – 1.67 (m, 7H), 1.65 – 1.35 (m, 4H) (three protons were broad and not assigned); LC-MS (Method 2): t_R = 3.84 min, m/z ($M+H$) $^+$ = 565.

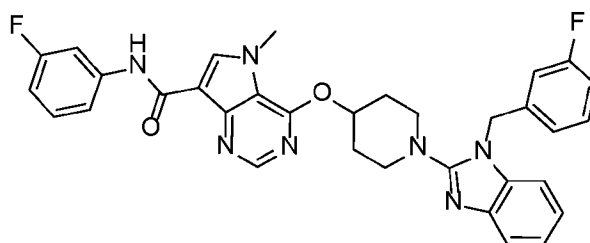
Example 48. (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-(2-morpholinoethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 48)



Cpd 48

[0291] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 4-(2-(2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)ethyl)morpholine, 3HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.16 (d, J = 8.4 Hz, 1H), 7.85 – 7.83 (m, 2H), 7.72 (dt, J = 10.4, 2.1 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.32 – 7.09 (m, 4H), 4.63 (br s, 1H), 4.34 (t, J = 6.4 Hz, 2H), 4.15 (s, 3H), 3.77 (br s, 1H), 3.51 (t, J = 4.5 Hz, 4H), 3.40 – 3.18 (m, 2H), 3.06 (br s, 1H), 2.60 (t, J = 6.3 Hz, 2H), 2.42 (t, J = 4.7 Hz, 4H), 2.15 – 1.75 (m, 4H); LC-MS (Method 2): t_R = 3.90 min, m/z ($M+H$) $^+$ = 567.

Example 49. 4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-N-(3-fluorophenyl)-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxamide (Cpd 49)



Cpd 49

STEP 1: Synthesis of 1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-ol

[0292] In a microwave tube was placed N-ethyl-N-isopropylpropan-2-amine (8.82 ml, 50.5 mmol), 2-chloro-1-(3-fluorobenzyl)-1H-benzo[d]imidazole (5 g, 16.83 mmol), piperidin-4-ol (6.81 g, 67.3 mmol), then N,N-dimethylformamide (20 ml) was added. The mixture was sealed and then stirred at room temperature for 24 hr. The mixture was poured into EtOAc (60 mL). The organic layer was washed with H₂O (60 mL x 3), dried with Na₂SO₄, and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-10%

EtOAc/DCM with 0.05% triethylamine to give 1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-ol (4.5 g, 13.83 mmol, 82 % yield); LC-MS (Method 1): t_R = 2.62 min, m/z (M+H)⁺ = 326.

STEP 2: Synthesis of methyl 4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylate

[0293] In a microwave tube was placed 1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-ol (300 mg, 0.922 mmol), methyl 4-chloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylate (229 mg, 1.014 mmol), and NaH (24.34 mg, 1.014 mmol) were added in N,N-Dimethylformamide (2 ml) then the reaction was heated up to 80 °C. After stirring for overnight, the mixture was cooled down to room temperature and poured into EtOAc (20 mL). The organic layer was washed with H₂O (20 mL x 3), dried (Na₂SO₄), and filtered. After removal of solvent, the product was purified with 10.0 % MeOH/DCM with 0.10 % triethylamine to give methyl 4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylate (155 mg, 0.301 mmol, 32.7 % yield); LC-MS (Method 1): t_R = 3.32 min, m/z (M+H)⁺ = 515.

STEP 3: Synthesis of 4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid

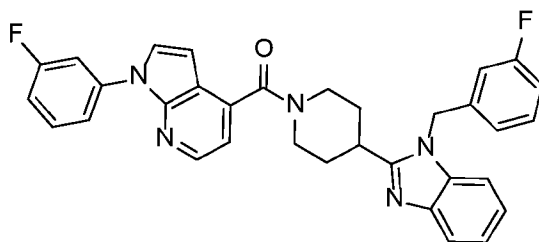
[0294] The material, 4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid, was prepared from methyl 4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylate following the similar procedure as described in the synthesis of **Int-71** (STEP-2). LC-MS (Method 1): t_R = 2.62 min, m/z (M+H)⁺ = 501.

STEP 4: Synthesis of 4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-N-(3-fluorophenyl)-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxamide (Cpd 49)

[0295] The title compound was prepared from 4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid and 3-fluoroaniline following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 10.64 (s, 1H), 8.63 (s, 1H), 8.36 (s, 1H), 7.79 (dt, J = 11.5, 2.2 Hz, 1H), 7.48 – 7.44 (m, 1H), 7.40 – 7.33 (m, 3H), 7.20 – 7.16 (m, 1H), 7.12 – 7.05 (m, 2H), 7.03 (dd, J = 7.3, 1.3 Hz, 1H), 7.01 – 6.95 (m, 1H), 6.95 – 6.88 (m, 1H), 5.62 (dd, J = 7.4, 3.9 Hz, 1H), 5.34 (s, 2H), 4.10

(s, 3H), 3.51 – 3.42 (m, 1H), 3.26 (m, 1H), 2.67 (s, 1H), 2.27 – 1.94 (m, 5H). LC-MS (Method 2): t_R = 5.365 min, m/z ($M+H$)⁺ = 594.

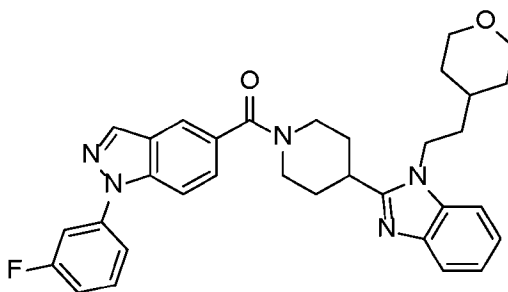
Example 50. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)methanone, TFA (Cpd 50)



Cpd 50

[0296] The title compound was prepared from (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1H-pyrrolo[2,3-b]pyridin-4-yl)methanone and 1-bromo-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-71** (STEP-1). ¹H NMR (400 MHz, DMSO-d₆) δ 8.43 (d, J = 4.8 Hz, 1H), 8.14 (d, J = 3.8 Hz, 1H), 7.92 (dt, J = 10.9, 2.3 Hz, 1H), 7.83 (dd, J = 8.1, 2.0 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.59 (td, J = 8.3, 6.6 Hz, 2H), 7.43 – 7.33 (m, 3H), 7.27 – 7.04 (m, 4H), 6.98 (d, J = 7.7 Hz, 1H), 6.73 (d, J = 3.7 Hz, 1H), 5.73 (s, 2H), 4.69 (d, J = 13.0 Hz, 1H), 3.23 (s, 4H), 1.97 (d, J = 27.5 Hz, 2H), 1.78 (s, 2H); LC-MS (Method 2): t_R = 5.01 min, m/z ($M+H$)⁺ = 548.

Example 51. (1-(3-fluorophenyl)-1H-indazol-5-yl)(4-(1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 51)

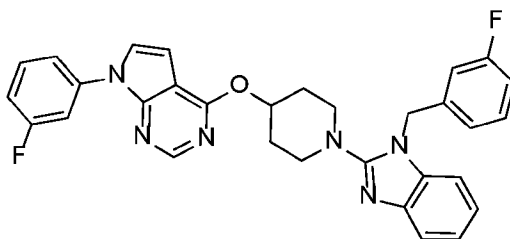


Cpd 51

[0297] The title compound was prepared from 1-(3-fluorophenyl)-1H-indazole-5-carboxylic acid and 2-(piperidin-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.51 (d, J = 0.9 Hz, 1H), 8.06 – 8.02 (m, 1H), 7.99 (dt, J = 8.7, 0.9 Hz, 1H), 7.73 – 7.64 (m, 3H), 7.64 – 7.54 (m, 2H), 7.50 (d, J = 7.7 Hz, 1H), 7.28 (tdd, J = 8.5, 2.6, 1.3 Hz, 1H), 7.18 (dtd, J = 17.4,

7.3, 1.2 Hz, 2H), 4.58 (s, 1H), 4.27 (t, $J = 7.5$ Hz, 2H), 3.88 – 3.80 (m, 2H), 3.68 – 3.55 (m, 1H), 3.32 – 3.22 (m, 2H), 3.14 (qd, $J = 7.3, 4.2$ Hz, 1H), 1.90 (s, 4H), 1.67 (d, $J = 13.5$ Hz, 5H), 1.26 (dd, $J = 6.6, 5.4$ Hz, 4H); LC-MS (Method 2): $t_R = 4.56$ min, m/z ($M+H$) $^+ = 552$.

Example 52. 4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-7-(3-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine (Cpd 52)



Cpd 52

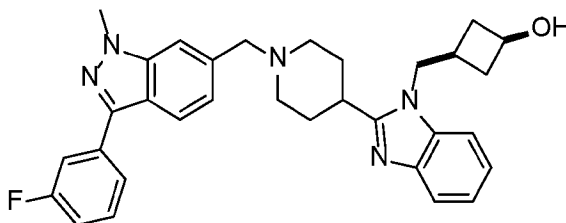
STEP 1: Synthesis of 4-chloro-7-(3-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine

[0298] The material, 4-chloro-7-(3-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine, was prepared from 4-chloro-7H-pyrrolo[2,3-d]pyrimidine and 1-bromo-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-71** (STEP 1).

STEP 2: Synthesis of 4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-7-(3-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine (Cpd 52)

[0299] The title compound was prepared from 4-chloro-7-(3-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine and 1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-ol following a similar procedure as described in **Example 49** (STEP-2). ^1H NMR (400 MHz, DMSO- d_6) δ 8.50 (s, 1H), 7.91 (d, $J = 3.8$ Hz, 1H), 7.85 (dt, $J = 10.7, 2.4$ Hz, 1H), 7.77 (dd, $J = 8.1, 2.0$ Hz, 1H), 7.59 (td, $J = 8.3, 6.6$ Hz, 1H), 7.46 (d, $J = 7.7$ Hz, 1H), 7.42 – 7.32 (m, 1H), 7.28 – 7.17 (m, 2H), 7.13 – 6.96 (m, 5H), 6.78 (d, $J = 3.7$ Hz, 1H), 5.61 – 5.46 (m, 1H), 5.35 (s, 2H), 3.49 (s, 1H), 3.27 – 3.09 (m, 3H), 2.33 – 1.78 (m, 4H). LC-MS (Method 2): $t_R = 5.41$ min, m/z ($M+H$) $^+ = 537$.

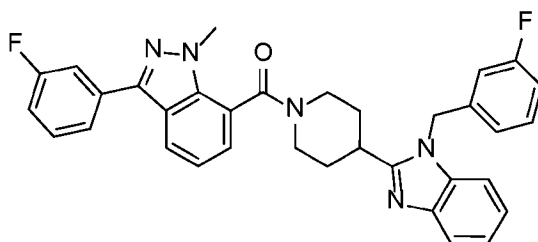
Example 53. (1s,3s)-3-((2-(1-((3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol (Cpd 53)



Cpd 53

[0300] To a mixture of 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde (38.1 mg, 0.15 mmol) and (1s,3s)-3-((2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol, 2HCl (53.7 mg, 0.15 mmol) in CH₂Cl₂ (1.5 mL) was added Et₃N (0.042 mL, 0.30 mmol) and stirred for 5 min. Then, sodium triacetoxyborohydride (95 mg, 0.45 mmol) was added and stirred at rt for 2 hr. The mixture was poured into EtOAc/2N Na₂CO₃ (aq) (10 mL/10 mL). The aqueous layer was extracted with EtOAc (5 mL x 2). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-15% MeOH/EtOAc as the eluent to give (1s,3s)-3-((2-(1-((3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol (59.1 mg, 0.113 mmol, 75 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.70 (dt, *J* = 10.6, 2.0 Hz, 1H), 7.62 (s, 1H), 7.59 – 7.49 (m, 2H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.21 (td, *J* = 8.7, 2.7 Hz, 1H), 7.18 – 7.08 (m, 2H), 4.98 (d, *J* = 6.3 Hz, 1H), 4.21 (d, *J* = 6.5 Hz, 2H), 4.11 (s, 3H), 3.82 (p, *J* = 7.1 Hz, 1H), 3.71 (s, 2H), 3.10 – 2.82 (m, 3H), 2.27 – 1.72 (m, 9H), 1.63 – 1.50 (m, 2H); LC-MS (Method 2): *t*_R = 3.92 min, *m/z* (M+H)⁺ = 524.

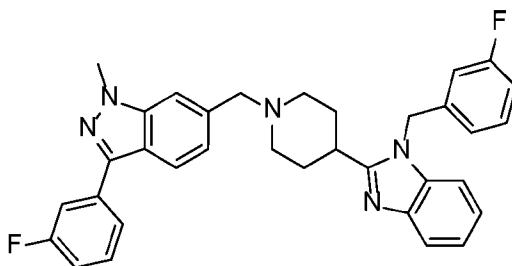
Example 54. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-7-yl)methanone (Cpd 54)



Cpd 54

[0301] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.14 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 10.3 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.46 – 7.21 (m, 5H), 7.16 (h, *J* = 6.9 Hz, 2H), 7.08 (td, *J* = 8.7, 2.6 Hz, 1H), 6.94 (d, *J* = 10.1 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 5.58 (s, 2H), 4.74 – 4.65 (m, 1H), 4.11 (s, 1.5H), 3.99 (s, 1.5H), 3.66 (d, *J* = 13.5 Hz, 0.5H), 3.49 (d, *J* = 13.4 Hz, 0.5H), 3.37 (br s, 1H), 3.20 (t, *J* = 12.6 Hz, 1H), 3.09 (br s, 1H), 2.03 – 1.61 (m, 4H). (s-cis and trans isomers of amide bond was observed; some peaks were split); LC-MS (Method 2): *t*_R = 5.16 min, *m/z* (M+H)⁺ = 562.

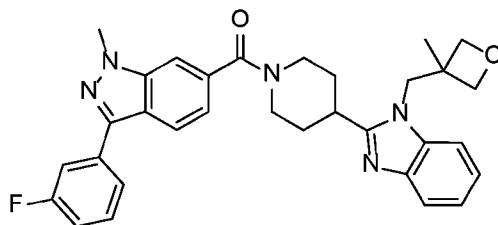
Example 55. 6-((4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 55)



Cpd 55

[0302] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.03 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.69 (dt, J = 10.5, 2.1 Hz, 1H), 7.63 – 7.49 (m, 3H), 7.43 – 7.29 (m, 2H), 7.28 – 7.11 (m, 4H), 7.07 (td, J = 8.6, 2.7 Hz, 1H), 6.90 (dd, J = 10.0, 2.6 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 5.54 (s, 2H), 4.09 (s, 3H), 3.66 (s, 2H), 2.98 – 2.91 (m, 3H), 2.10 (t, J = 12.2 Hz, 2H), 1.98 – 1.84 (m, 2H), 1.70 (d, J = 12.6 Hz, 2H); LC-MS (Method 2): t_R = 4.71 min, m/z ($M+H$) $^+$ = 548.

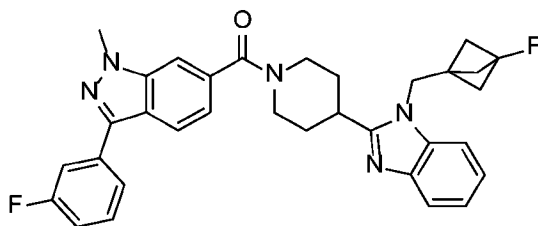
Example 56. (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-((3-methyloxetan-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 56)



Cpd 56

[0303] The title compound was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone and 3-(bromomethyl)-3-methyloxetane following a similar procedure as described in **Example 22** (STEP-2). ^1H NMR (400 MHz, DMSO- d_6) δ 8.16 (d, J = 8.4 Hz, 1H), 7.84 – 7.82 (m, 2H), 7.72 (dt, J = 10.5, 2.0 Hz, 1H), 7.61 – 7.50 (m, 3H), 7.30 – 7.11 (m, 4H), 4.60 (br s, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.43 (s, 2H), 4.16 – 4.14 (m, 5H), 3.75 (br s, 1H), 3.35 – 2.95 (m, 3H), 2.05 – 1.64 (m, 4H), 1.25 (s, 3H); LC-MS (Method 2): t_R = 4.52 min, m/z ($M+H$) $^+$ = 538.

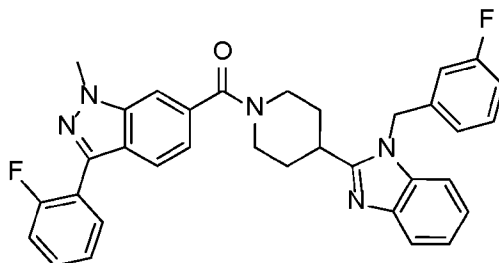
Example 57. (4-(1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 57)



Cpd 57

[0304] The title compound was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone and 1-(bromomethyl)-3-fluorobicyclo[1.1.1]pentane following a similar procedure as described in **Example 22** (STEP-2). ¹H NMR (400 MHz, DMSO-d₆) δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.85 – 7.83 (m, 2H), 7.76 – 7.68 (m, 1H), 7.59 – 7.53 (m, 2H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.30 – 7.10 (m, 4H), 4.62 (br s, 3H), 4.15 (s, 3H), 3.76 (br s, 1H), 3.27 – 2.93 (m, 3H), 2.05 – 1.72 (m, 10H); LC-MS (Method 2): *t*_R = 4.99 min, *m/z* (M+H)⁺ = 552.

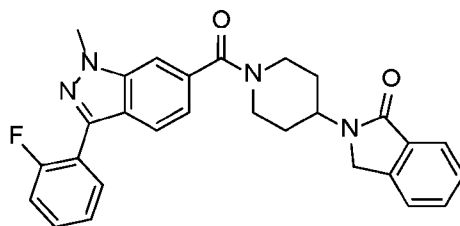
Example 58. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(2-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 58)



Cpd 58

[0305] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.83 – 7.72 (m, 3H), 7.65 – 7.56 (m, 1H), 7.55 – 7.45 (m, 1H), 7.44 – 7.29 (m, 4H), 7.23 – 7.12 (m, 3H), 7.08 (td, *J* = 8.7, 2.6 Hz, 1H), 6.94 (d, *J* = 9.9 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 5.58 (s, 2H), 4.57 (br s, 1H), 4.15 (s, 3H), 3.71 (br s, 1H), 3.37 (t, *J* = 10.3 Hz, 1H), 3.21 (br s, 1H), 3.00 (br s, 1H), 2.01 – 1.62 (m, 4H); LC-MS (Method 2): *t*_R = 4.95 min, *m/z* (M+H)⁺ = 562.

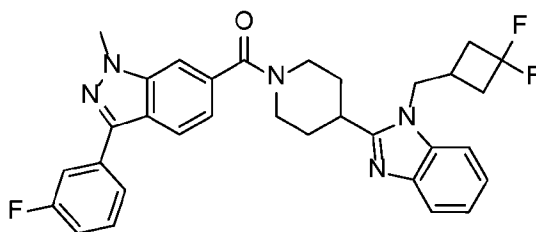
Example 59. 2-(1-(3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carbonyl)piperidin-4-yl)isoindolin-1-one (Cpd 59)



Cpd 59

[0306] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.83 – 7.73 (m, 3H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 4.2 Hz, 2H), 7.53 – 7.44 (m, 2H), 7.43 – 7.31 (m, 2H), 7.24 (d, *J* = 8.4 Hz, 1H), 4.67 (br s, 1H), 4.50 (s, 2H), 4.40 – 4.27 (m, 1H), 4.16 (s, 3H), 3.71 (br s, 1H), 3.32 (br s, 1H), 2.95 (br s, 1H), 1.98 – 1.60 (m, 4H); LC-MS (Method 2): *t*_R = 5.19 min, *m/z* (M+H)⁺ = 469.

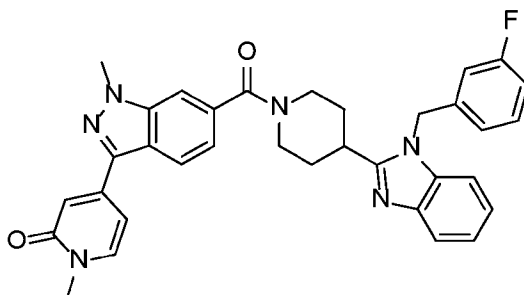
Example 60. (4-(1-((3,3-difluorocyclobutyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 60)



Cpd 60

[0307] The title compound was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone and 3-(bromomethyl)-1,1-difluorocyclobutane following a similar procedure as described in **Example 22** (STEP 2). ¹H NMR (400 MHz, DMSO-d₆) δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.87 – 7.80 (m, 2H), 7.72 (dt, *J* = 10.8, 2.0 Hz, 1H), 7.66 – 7.51 (m, 3H), 7.30 – 7.11 (m, 4H), 4.63 (br s, 1H), 4.42 (d, *J* = 6.0 Hz, 2H), 4.15 (s, 3H), 3.76 (br s, 1H), 3.42 – 3.22 (m, 2H), 3.08 (br s, 1H), 2.69 – 2.37 (m, 5H), 2.07 – 1.68 (m, 4H); LC-MS (Method 2): *t*_R = 4.98 min, *m/z* (M+H)⁺ = 558.

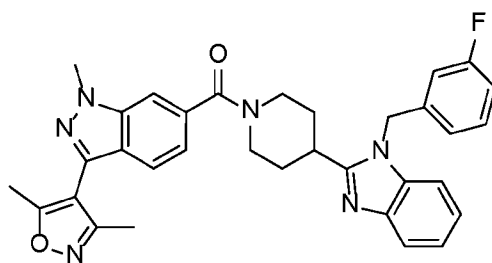
Example 61. 4-(6-(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidine-1-carbonyl)-1-methyl-1H-indazol-3-yl)-1-methylpyridin-2(1H)-one (Cpd 61)



Cpd 61

[0308] The title compound was prepared from (3-bromo-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.13 (d, *J* = 8.4 Hz, 1H), 7.84 (s, 1H), 7.77 (d, *J* = 7.1 Hz, 1H), 7.65 – 7.56 (m, 1H), 7.42 – 7.30 (m, 2H), 7.27 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.20 – 7.12 (m, 2H), 7.08 (td, *J* = 8.6, 2.6 Hz, 1H), 6.96 – 6.91 (m, 2H), 6.87 – 6.79 (m, 2H), 5.58 (s, 2H), 4.57 (br s, 1H), 4.15 (s, 3H), 3.69 (br s, 1H), 3.46 (s, 3H), 3.39 – 3.32 (m, 1H), 3.21 (br s, 1H), 3.01 (br s, 1H), 1.96 – 1.63 (m, 4H); LC-MS (Method 2): *t*_R = 4.07 min, *m/z* (M+H)⁺ = 575.

Example 62. (3-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 62)

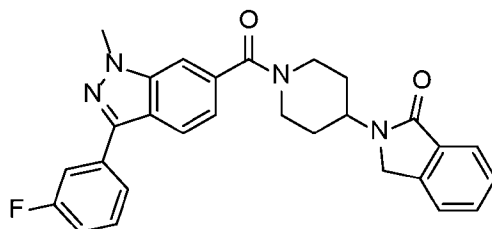


Cpd 62

[0309] The title compound was prepared from (3-bromo-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone and 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.81 (s, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.64 – 7.56 (m, 1H), 7.43 – 7.29 (m, 2H), 7.21 – 7.12 (m, 3H), 7.08 (td, *J* = 8.7, 2.6 Hz, 1H), 6.93 (dd, *J* = 10.1, 2.6 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 5.58 (s, 2H), 4.57 (br s, 1H), 4.13 (s, 3H), 3.70 (br

s, 1H), 3.39 – 3.30 (m, 1H), 3.21 (br s, 1H), 3.00 (br s, 1H), 2.44 (s, 3H), 2.24 (s, 3H), 1.97 – 1.61 (m, 4H); LC-MS (Method 2): t_R = 4.46 min, m/z ($M+H$)⁺ = 563.

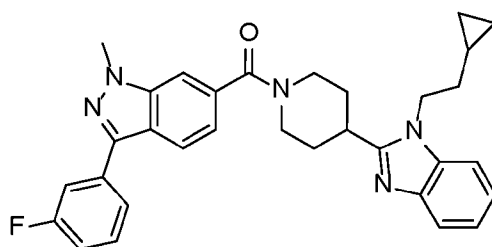
Example 63. 2-(1-(3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbonyl)piperidin-4-yl)isoindolin-1-one (Cpd 63)



Cpd 63

[0310] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.16 (d, J = 8.4 Hz, 1H), 7.87 – 7.79 (m, 2H), 7.72 (dt, J = 10.5, 2.1 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.61 – 7.51 (m, 3H), 7.47 (dt, J = 8.1, 4.2 Hz, 1H), 7.31 – 7.19 (m, 2H), 4.67 (br s, 1H), 4.50 (s, 2H), 4.41 – 4.29 (m, 1H), 4.15 (s, 3H), 3.70 (br s, 1H), 3.31 (br s, 1H), 2.96 (br s, 1H), 1.93 – 1.61 (m, 4H); LC-MS (Method 2): t_R = 5.41 min, m/z ($M+H$)⁺ = 469.

Example 64. (4-(1-(2-cyclopropylethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 64)

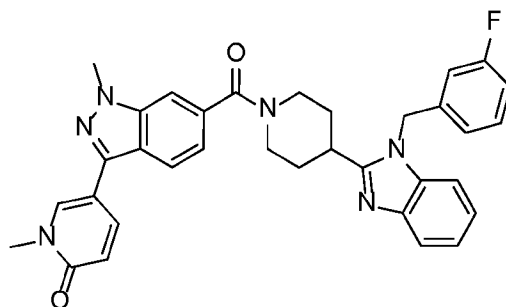


Cpd 64

[0311] The title compound was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone and (2-bromoethyl)cyclopropane following a similar procedure as described in **Example 22** (STEP 2). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.16 (d, J = 8.4 Hz, 1H), 7.85 – 7.83 (m, 2H), 7.76 – 7.68 (m, 1H), 7.60 – 7.52 (m, 2H), 7.49 (d, J = 7.6 Hz, 1H), 7.30 – 7.09 (m, 4H), 4.62 (br s, 1H), 4.31 (t, J = 7.1 Hz, 2H), 4.15 (s, 3H), 3.76 (br s, 1H), 3.41 – 3.21 (m, 2H), 3.09 (br s, 1H), 2.09 – 1.71 (m, 4H), 1.62 (q, J = 7.0

Hz, 2H), 0.63 (ddd, $J = 12.8, 8.3, 5.3$ Hz, 1H), 0.32 (dd, $J = 8.4, 4.4$ Hz, 2H), -0.04 (t, $J = 4.9$ Hz, 2H); LC-MS (Method 2): $t_R = 5.00$ min, m/z ($M+H$) $^+ = 522$.

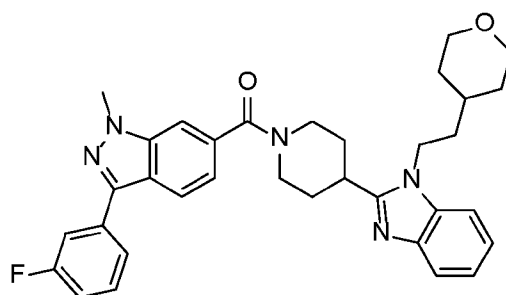
Example 65. 5-(6-(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidine-1-carbonyl)-1-methyl-1H-indazol-3-yl)-1-methylpyridin-2(1H)-one (Cpd 65)



Cpd 65

[0312] The title compound was prepared from (3-bromo-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one following a similar procedure as described in **Example 15**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.31 (d, $J = 2.6$ Hz, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 8.00 (dd, $J = 9.5, 2.5$ Hz, 1H), 7.75 (s, 1H), 7.62 – 7.57 (m, 1H), 7.43 – 7.29 (m, 2H), 7.23 – 7.12 (m, 3H), 7.08 (td, $J = 8.6, 2.6$ Hz, 1H), 6.93 (dt, $J = 10.1, 2.2$ Hz, 1H), 6.84 (d, $J = 7.7$ Hz, 1H), 6.53 (d, $J = 9.4$ Hz, 1H), 5.58 (s, 2H), 4.58 (br s, 1H), 4.08 (s, 3H), 3.69 (br s, 1H), 3.56 (s, 3H), 3.40 – 3.32 (m, 1H), 3.20 (br s, 1H), 3.00 (br s, 1H), 1.98 – 1.63 (m, 4H); LC-MS (Method 2): $t_R = 4.00$ min, m/z ($M+H$) $^+ = 575$.

Example 66. (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 66)

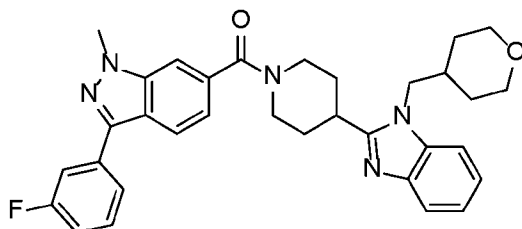


Cpd 66

[0313] The title compound was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone and 4-(2-bromoethyl)tetrahydro-2H-pyran following a similar procedure as described in **Example 22** (STEP 2). ^1H NMR (400 MHz,

DMSO- d_6) δ 8.16 (d, J = 8.4 Hz, 1H), 7.85 – 7.82 (m, 2H), 7.76 – 7.68 (m, 1H), 7.61 – 7.50 (m, 2H), 7.47 (d, J = 7.7 Hz, 1H), 7.30 – 7.09 (m, 4H), 4.62 (s, 1H), 4.25 (t, J = 7.5 Hz, 2H), 4.15 (s, 3H), 3.89 – 3.68 (m, 3H), 3.30 – 3.08 (s, 5H), 2.10 – 1.73 (m, 4H), 1.66 – 1.57 (m, 5H), 1.31 – 1.17 (m, 2H); LC-MS (Method 2): t_R = 4.74 min, m/z ($M+H$) $^+$ = 566.

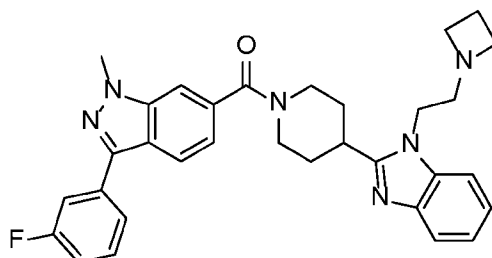
Example 67. (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 67)



Cpd 67

[0314] The title compound was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone and 4-(bromomethyl)tetrahydro-2H-pyran following a similar procedure as described in **Example 22** (STEP-2). ^1H NMR (400 MHz, DMSO- d_6) δ 8.16 (d, J = 8.4 Hz, 1H), 7.85 – 7.83 (m, 2H), 7.76 – 7.66 (m, 1H), 7.59 – 7.54 (m, 3H), 7.30 – 7.09 (m, 4H), 4.62 (br s, 1H), 4.15 – 4.13 (m, 5H), 3.87 – 3.64 (m, 3H), 3.42 – 2.97 (m, 5H), 2.11 – 1.72 (m, 5H), 1.44 – 1.34 (m, 4H); LC-MS (Method 2): t_R = 4.61 min, m/z ($M+H$) $^+$ = 552.

Example 68. (4-(1-(2-(azetidin-1-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 68)

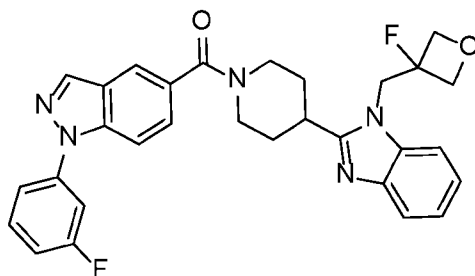


Cpd 68

[0315] The title compound was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone and 1-(2-chloroethyl)azetidine, HCl following a similar procedure as described in **Example 22** (STEP 2). ^1H NMR (400 MHz, DMSO- d_6) δ 8.17 (d, J = 8.4 Hz, 1H), 7.85 – 7.83 (m, 2H), 7.75 – 7.69 (m, 1H), 7.61 – 7.51 (m, 2H), 7.47 (d, J = 7.7 Hz, 1H), 7.30 – 7.09 (m, 4H), 4.63 (br s, 1H), 4.21 – 4.11 (m, 5H), 3.77 (br

s, 1H), 3.39 – 2.97 (m, 7H), 2.69 (br s, 2H), 2.14 – 1.76 (m, 6H); LC-MS (Method 2): t_R = 3.85 min, m/z (M+H)⁺ = 537.

Example 69. (4-(1-((3-fluorooxetan-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-5-yl)methanone (Cpd 69)



Cpd 69

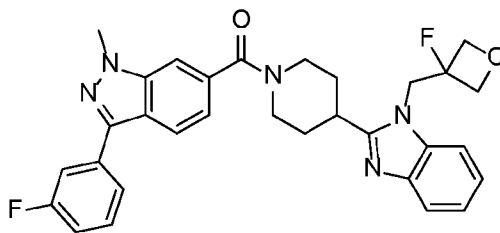
STEP 1: Synthesis of (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-5-yl)methanone

[0316] The material, (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-5-yl)methanone, was prepared from 1-(3-fluorophenyl)-1H-indazole-5-carboxylic acid and 2-(piperidin-4-yl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 1**. LC-MS (Method 2): t_R = 2.75 min, m/z (M+H)⁺ = 440.

STEP 2: Synthesis of (4-(1-((3-fluorooxetan-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-5-yl)methanone (Cpd 69)

[0317] The title compound was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-5-yl)methanone and 3-(bromomethyl)-3-fluorooxetane following a similar procedure as described in **Example 22** (STEP 2). ¹H NMR (400 MHz, DMSO-d₆) δ 8.51 (d, J = 0.9 Hz, 1H), 8.06 – 8.02 (m, 1H), 8.02 – 7.95 (m, 1H), 7.70 – 7.64 (m, 4H), 7.59 (ddd, J = 9.3, 8.2, 1.5 Hz, 2H), 7.32 – 7.25 (m, 1H), 7.20 (dtd, J = 18.3, 7.2, 1.3 Hz, 2H), 5.01 (s, 1H), 4.95 (s, 1H), 4.80 (d, J = 8.4 Hz, 1H), 4.74 (d, J = 8.5 Hz, 1H), 4.60 (dd, J = 21.1, 8.3 Hz, 2H), 3.16 (s, 3H), 1.99 (s, 1H), 1.88 (s, 5H); LC-MS (Method 2): t_R = 4.33 min, m/z (M+H)⁺ = 528.

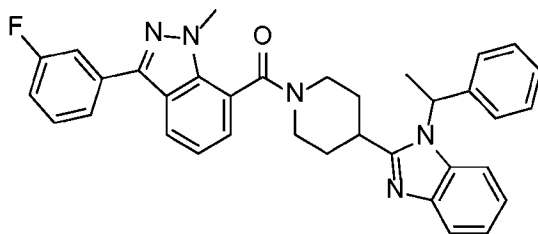
Example 70. (4-(1-((3-fluorooxetan-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 70)



Cpd 70

[0318] The title compound was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone and 3-(bromomethyl)-3-fluorooxetane following a similar procedure as described in **Example 22** (STEP 2). ^1H NMR (400 MHz, DMSO- d_6) δ 8.16 (d, J = 8.4 Hz, 1H), 7.87 – 7.80 (m, 2H), 7.72 (dt, J = 10.4, 2.0 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.27 (d, J = 8.4 Hz, 1H), 7.25 – 7.13 (m, 3H), 4.96 (d, J = 21.6 Hz, 2H), 4.75 (dd, J = 22.8, 8.2 Hz, 2H), 4.65 (s, 1H), 4.58 (dd, J = 21.1, 8.2 Hz, 2H), 4.15 (s, 3H), 3.76 (br s, 1H), 3.40 – 3.20 (m, 2H), 3.03 (br s, 1H), 2.09 – 1.67 (m, 4H); LC-MS (Method 2): t_R = 4.69 min, m/z ($M+H$) $^+$ = 542.

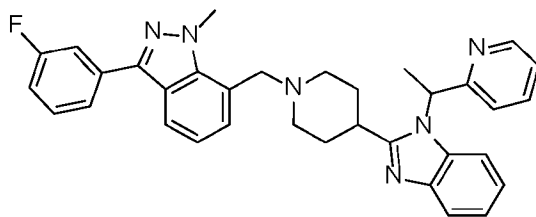
Example 71. (3-(3-fluorophenyl)-1-methyl-1H-indazol-7-yl)(4-(1-(1-phenylethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 71)



Cpd 71

[0319] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carboxylic acid and 1-(1-phenylethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.15 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 10.4 Hz, 1H), 7.57 (td, J = 8.0, 4.4 Hz, 2H), 7.48 – 7.16 (m, 8H), 7.10 – 6.94 (m, 3H), 6.08 (q, J = 7.1 Hz, 1H), 4.78 – 4.70 (m, 1H), 4.12 (s, 1.5H), 4.00 (s, 1.5H), 3.65 – 3.00 (m, 4H), 2.15 – 1.64 (m, 7H). (s-cis and trans isomers of the amide bond were observed; some peaks were split); LC-MS (Method 2): t_R = 5.34 min, m/z ($M+H$) $^+$ = 558.

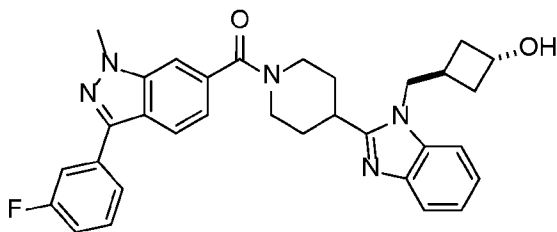
Example 72. 3-(3-fluorophenyl)-1-methyl-7-((4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1H-indazole (Cpd 72)



Cpd 72

[0320] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 3HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.57 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.73 (td, *J* = 7.7, 1.8 Hz, 1H), 7.67 (dt, *J* = 10.5, 2.1 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.30 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.27 – 7.11 (m, 4H), 7.11 – 7.01 (m, 2H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.08 (q, *J* = 7.0 Hz, 1H), 4.47 (s, 3H), 3.91 – 3.79 (m, 2H), 3.10 (br s, 1H), 2.94 (t, *J* = 12.9 Hz, 2H), 2.26 – 2.06 (m, 2H), 1.92 (d, *J* = 7.0 Hz, 3H), 1.88 – 1.64 (m, 4H); LC-MS (Method 2): *t*_R = 4.47 min, *m/z* (M+H)⁺ = 545.

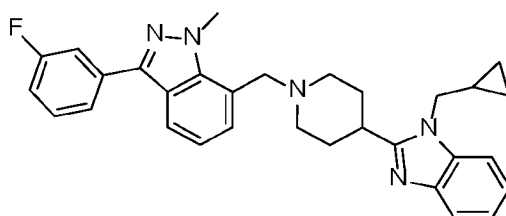
Example 73. (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-(((1*r*,3*r*)-3-hydroxycyclobutyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 73)



Cpd 73

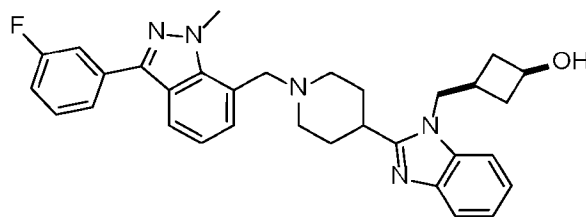
[0321] The title compound was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone and (1*r*,3*r*)-3-(bromomethyl)cyclobutan-1-ol following a similar procedure as described in **Example 22** (STEP 2). ¹H NMR (400 MHz, DMSO-d₆) δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.85 – 7.80 (m, 2H), 7.72 (dt, *J* = 10.3, 1.9 Hz, 1H), 7.59 – 7.53 (m, 3H), 7.30 – 7.08 (m, 4H), 5.00 (d, *J* = 6.2 Hz, 1H), 4.62 (br s, 1H), 4.43 (h, *J* = 6.8 Hz, 1H), 4.30 (d, *J* = 8.2 Hz, 2H), 4.15 (s, 3H), 3.75 (br s, 1H), 3.37 – 3.02 (m, 3H), 2.69 – 2.54 (m, 1H), 2.06 – 1.70 (m, 8H); LC-MS (Method 2): *t*_R = 4.46 min, *m/z* (M+H)⁺ = 538.

Example 74. 7-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 74)

**Cpd 74**

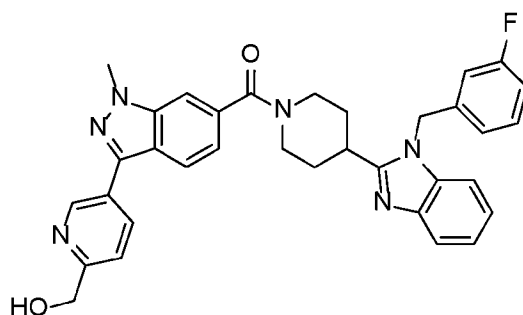
[0322] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.73 – 7.63 (m, 1H), 7.58 – 7.49 (m, 3H), 7.29 – 7.07 (m, 5H), 4.49 (s, 3H), 4.13 (d, *J* = 6.8 Hz, 2H), 3.88 (s, 2H), 3.03 – 2.93 (m, 3H), 2.26 – 2.20 (m, 2H), 1.92 – 1.83 (m, 4H), 1.16 (h, *J* = 5.9 Hz, 1H), 0.49 (dd, *J* = 7.1, 2.8 Hz, 2H), 0.41 (t, *J* = 4.8 Hz, 2H); LC-MS (Method 2): *t*_R = 4.46 min, *m/z* (M+H)⁺ = 494.

Example 75. (1s,3s)-3-((2-(1-((3-(3-fluorophenyl)-1-methyl-1H-indazol-7-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol (Cpd 75)

**Cpd 75**

[0323] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde and (1s,3s)-3-((2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.67 (dt, *J* = 10.6, 1.9 Hz, 1H), 7.57 – 7.45 (m, 3H), 7.29 – 7.06 (m, 5H), 4.99 (d, *J* = 6.3 Hz, 1H), 4.49 (s, 3H), 4.22 (d, *J* = 6.4 Hz, 2H), 3.92 – 3.78 (m, 3H), 3.00 – 2.88 (m, 3H), 2.27 – 2.13 (m, 4H), 2.13 – 2.02 (m, 1H), 1.91 – 1.77 (m, 4H), 1.63 – 1.51 (m, 2H); LC-MS (Method 2): *t*_R = 4.07 min, *m/z* (M+H)⁺ = 524.

Example 76. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(6-(hydroxymethyl)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 76)

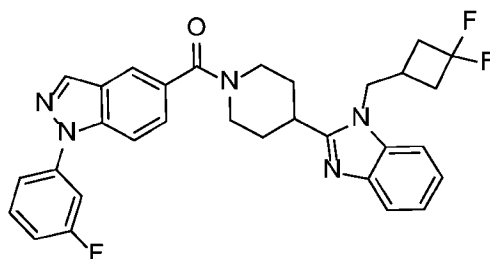


Cpd 76

[0324] The title compound was prepared from (3-bromo-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone and (6-(hydroxymethyl)pyridin-3-yl)boronic acid following a similar procedure as described in

Example 15. ^1H NMR (400 MHz, DMSO- d_6) δ 9.06 (d, $J = 2.1$ Hz, 1H), 8.35 (dd, $J = 8.2$, 2.3 Hz, 1H), 8.14 (d, $J = 8.4$ Hz, 1H), 7.82 (s, 1H), 7.63 – 7.57 (m, 2H), 7.42 – 7.29 (m, 2H), 7.25 (d, $J = 8.4$ Hz, 1H), 7.18 – 7.12 (m, 2H), 7.08 (td, $J = 8.6$, 2.6 Hz, 1H), 6.94 (d, $J = 9.6$ Hz, 1H), 6.84 (d, $J = 7.7$ Hz, 1H), 5.58 (s, 2H), 5.48 (t, $J = 5.8$ Hz, 1H), 4.62 (d, $J = 5.8$ Hz, 2H), 4.57 (br s, 1H), 4.15 (s, 3H), 3.70 (br s, 1H), 3.40 – 3.32 (m, 1H), 3.21 (br s, 1H), 3.01 (br s, 1H), 1.96 – 1.64 (m, 4H); LC-MS (Method 2): $t_R = 3.78$ min, m/z ($M+H$) $^+ = 575$.

Example 77. (4-(1-((3,3-difluorocyclobutyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-5-yl)methanone (Cpd 77)

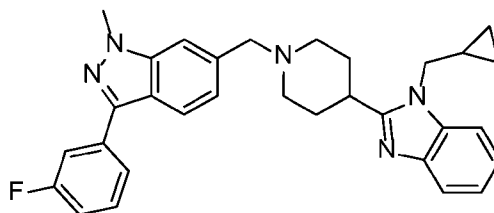


Cpd 77

[0325] The title compound was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-5-yl)methanone and 3-(bromomethyl)-1,1-difluorocyclobutane following a similar procedure as described in **Example 22** (STEP 2). ^1H NMR (400 MHz, DMSO- d_6) δ 8.49 (d, $J = 0.9$ Hz, 1H), 8.02 (dd, $J = 1.6$, 0.8 Hz, 1H), 7.97 (dt, $J = 8.8$, 1.0 Hz, 1H), 7.70 – 7.62 (m, 3H), 7.62 – 7.54 (m, 3H), 7.31 – 7.23 (m, 1H), 7.18 (dt, $J = 17.9$, 7.2 Hz,

2H), 4.60 (s, 1H), 4.43 (d, $J = 6.0$ Hz, 2H), 3.87 (s, 1H), 3.37 (s, 1H), 3.36 (m, 1H), 3.17 (m, 2H), 2.72 – 2.50 (m, 4H), 1.88 (s, 4H); LC-MS (Method 2): $t_R = 4.83$ min, m/z (M+H)⁺ = 544.

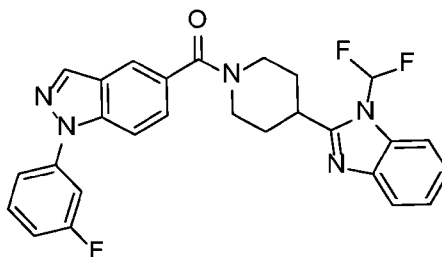
Example 78. 6-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 78)



Cpd 78

[0326] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO- d_6) δ 8.04 (d, $J = 8.4$ Hz, 1H), 7.82 (d, $J = 7.7$ Hz, 1H), 7.70 (dt, $J = 10.6, 2.0$ Hz, 1H), 7.62 (s, 1H), 7.57 – 7.51 (m, 3H), 7.27 (d, $J = 8.4$ Hz, 1H), 7.21 (td, $J = 8.6, 2.7$ Hz, 1H), 7.18 – 7.08 (m, 2H), 4.13 – 4.10 (m, 5H), 3.70 (s, 2H), 3.01 – 2.90 (m, 3H), 2.19 (t, $J = 11.5$ Hz, 2H), 1.96 (qd, $J = 12.3, 3.6$ Hz, 2H), 1.84 (dd, $J = 13.3, 3.7$ Hz, 2H), 1.14 (ddd, $J = 12.7, 7.4, 4.9$ Hz, 1H), 0.53 – 0.32 (m, 4H); LC-MS (Method 2): $t_R = 4.32$ min, m/z (M+H)⁺ = 494.

Example 79. (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-5-yl)methanone (Cpd 79)

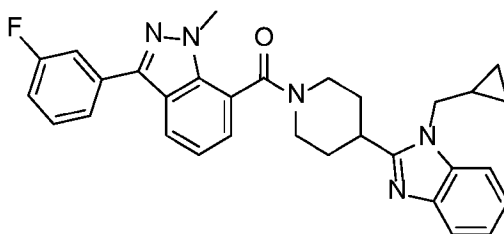


Cpd 79

[0327] In a microwave tube was placed cesium carbonate (44.5 mg, 0.137 mmol), (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-5-yl)methanone (30 mg, 0.068 mmol), diethyl (bromodifluoromethyl)phosphonate (0.018 ml, 0.102 mmol) and then N,N-dimethylformamide (1 ml) was added. The mixture was sealed and then stirred at rt for 24 hr. The mixture was poured into EtOAc (60 mL). The organic layer was washed with H₂O (60 mL x 3), dried (Na₂SO₄), and filtered. After removal of solvent, the product was purified by silica gel

chromatography using 0-10% MeOH/DCM with 0.05% triethylamine to give (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-5-yl)methanone (4.5 mg, 9.19 μ mol, 13.5 % yield). ^1H NMR (400 MHz, DMSO- d_6) δ 8.49 (d, J = 0.9 Hz, 1H), 8.22 (t, J = 57.4 Hz, 1H), 8.05 – 8.00 (m, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.67 (td, J = 8.4, 3.9 Hz, 5H), 7.58 (dd, J = 8.7, 1.6 Hz, 1H), 7.36 – 7.21 (m, 3H), 4.23 (d, J = 276.7 Hz, 2H), 3.49 (s, 1H), 3.16 (s, 2H), 1.97 (s, 2H), 1.88 (d, J = 10.5 Hz, 2H); LC-MS (Method 2): t_R = 5.77 min, m/z ($M+H$) $^{+}$ = 490.

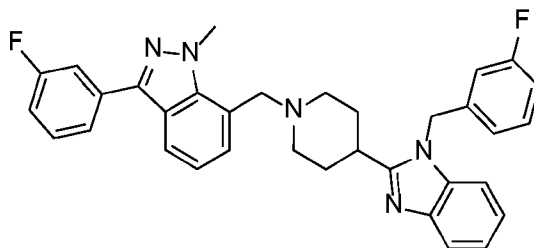
Example 80. (4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-7-yl)methanone (Cpd 80)



Cpd 80

[0328] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.15 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.71 (d, J = 10.2 Hz, 1H), 7.60 – 7.53 (m, 3H), 7.47 – 7.21 (m, 3H), 7.19 – 7.10 (m, 2H), 4.79 – 4.70 (m, 1H), 4.24 – 3.99 (m, 5H), 3.70 (d, J = 13.4 Hz, 0.5H), 3.52 (d, J = 13.4 Hz, 0.5H), 3.43 – 3.27 (m, 2H), 3.18 (t, J = 12.7 Hz, 1H), 2.13 – 1.64 (m, 4H), 1.23 – 1.13 (m, 1H), 0.52 – 0.40 (m, 4H) (s-cis and s-trans isomers of the amide bond were observed; some peaks were split); LC-MS (Method 2): t_R = 5.03 min, m/z ($M+H$) $^{+}$ = 508.

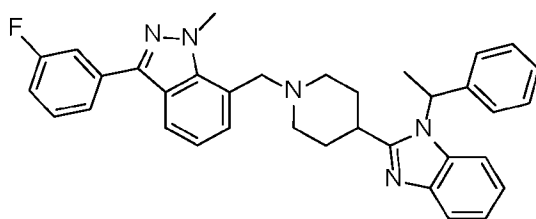
Example 81. 7-((4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 81)



Cpd 81

[0329] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.98 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.66 (dt, *J* = 10.6, 2.0 Hz, 1H), 7.60 – 7.50 (m, 2H), 7.40 (dt, *J* = 7.3, 3.6 Hz, 1H), 7.34 (td, *J* = 7.9, 5.9 Hz, 1H), 7.24 – 7.20 (m, 2H), 7.15 – 7.05 (m, 4H), 6.91 (dd, *J* = 10.0, 2.6 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 5.55 (s, 2H), 4.46 (s, 3H), 3.83 (s, 2H), 3.02 – 2.89 (m, 3H), 2.13 (t, *J* = 11.4 Hz, 2H), 1.80 (dd, *J* = 13.2, 9.7 Hz, 2H), 1.70 (d, *J* = 12.4 Hz, 2H); LC-MS (Method 2): *t*_R = 4.83 min, *m/z* (M+H)⁺ = 548.

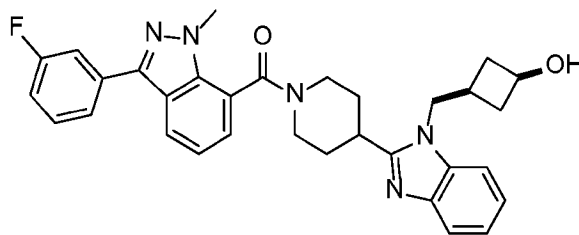
Example 82. 3-(3-fluorophenyl)-1-methyl-7-((4-(1-(1-phenylethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1H-indazole (Cpd 82)



Cpd 82

[0330] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde and 1-(1-phenylethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.98 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.66 (dt, *J* = 10.5, 2.1 Hz, 1H), 7.60 – 7.48 (m, 2H), 7.37 – 7.10 (m, 8H), 7.05 (dt, *J* = 7.6, 3.4 Hz, 2H), 6.97 (dd, *J* = 8.5, 6.6 Hz, 1H), 6.04 (q, *J* = 7.0 Hz, 1H), 4.47 (s, 3H), 3.90 – 3.78 (m, 2H), 3.08 – 2.99 (m, 3H), 2.23 – 2.07 (m, 2H), 1.99 – 1.65 (m, 7H); LC-MS (Method 2): *t*_R = 4.83 min, *m/z* (M+H)⁺ = 544.

Example 83. (3-(3-fluorophenyl)-1-methyl-1H-indazol-7-yl)(4-(1-(((1s,3s)-3-hydroxycyclobutyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 83)

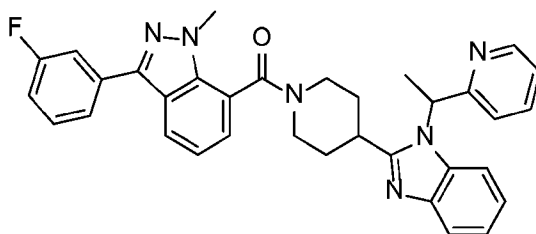


Cpd 83

[0331] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carboxylic acid and (1s,3s)-3-((2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-

1-ol, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.16 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 10.3 Hz, 1H), 7.61 – 7.36 (m, 4H), 7.36 – 7.22 (m, 2H), 7.16 (p, J = 7.3 Hz, 2H), 4.99 (d, J = 6.0 Hz, 1H), 4.79 – 4.70 (m, 1H), 4.26 (d, J = 6.3 Hz, 2H), 4.14 (s, 1.5H), 4.02 (s, 1.5H), 3.84 (q, J = 7.0 Hz, 1H), 3.71 (d, J = 13.6 Hz, 0.5H), 3.53 (d, J = 13.4 Hz, 0.5H), 3.42 – 3.24 (s, 2H), 3.17 (t, J = 12.7 Hz, 1H), 2.23 – 1.66 (m, 7H), 1.62 – 1.56 (m, 2H) (s-cis and s-trans isomers of the amide bond were observed; some peaks were split); LC-MS (Method 2): t_R = 4.54 min, m/z ($M+H$) $^+$ = 538.

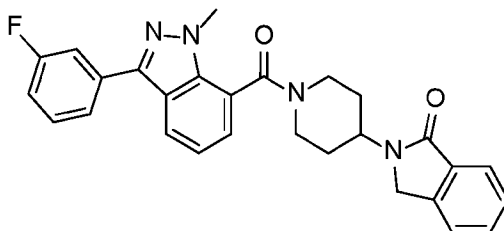
Example 84. (3-(3-fluorophenyl)-1-methyl-1H-indazol-7-yl)(4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 84)



Cpd 84

[0332] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carboxylic acid and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 3HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.61 – 8.51 (m, 1H), 8.15 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.79 – 7.65 (m, 2H), 7.59 – 7.54 (m, 2H), 7.49 – 7.16 (m, 5H), 7.10 – 6.95 (m, 3H), 6.12 (q, J = 7.3 Hz, 1H), 4.81 – 4.65 (m, 1H), 4.12 (s, 1.5H), 4.00 (s, 1.5H), 3.73 – 3.00 (m, 4H), 2.23 – 1.65 (m, 7H) (s-cis and s-trans isomers of the amide bond were observed; some peaks were split); LC-MS (Method 2): t_R = 4.97 min, m/z ($M+H$) $^+$ = 559.

Example 85. 2-(1-(3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carbonyl)piperidin-4-yl)isoindolin-1-one (Cpd 85)

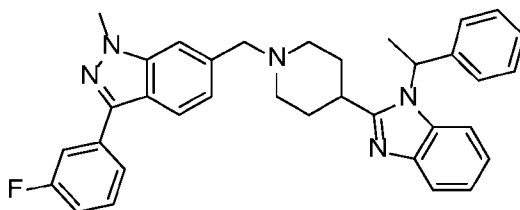


Cpd 85

[0333] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carboxylic acid and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as

described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.15 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.62 – 7.40 (m, 5H), 7.39 – 7.21 (m, 2H), 4.82 – 4.74 (m, 1H), 4.52 (s, 1H), 4.48 (s, 1H), 4.42 – 4.27 (m, 1H), 4.14 (s, 1.5H), 3.99 (s, 1.5H), 3.66 (d, J = 13.7 Hz, 0.5H), 3.46 (d, J = 13.4 Hz, 0.5H), 3.39 – 3.20 (., 1H), 3.10 – 2.98 (m, 1H), 1.99 – 1.58 (m, 4H) (s-cis and s-trans isomers of the amide bond were observed; some peaks were split); LC-MS (Method 2): t_R = 5.58 min, m/z ($M+H$) $^+$ = 469.

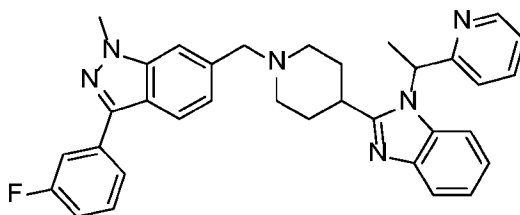
Example 86. 3-(3-fluorophenyl)-1-methyl-6-((4-(1-(1-phenylethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1H-indazole (Cpd 86)



Cpd 86

[0334] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 1-(1-phenylethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.03 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.69 (dt, J = 10.4, 2.1 Hz, 1H), 7.60 (s, 1H), 7.57 – 7.52 (m, 2H), 7.37 – 7.14 (m, 7H), 7.09 – 7.03 (m, 2H), 7.00 – 6.94 (m, 1H), 6.02 (q, J = 7.0 Hz, 1H), 4.10 (s, 3H), 3.67 (s, 2H), 3.10 – 2.87 (m, 3H), 2.22 – 1.65 (m, 6H), 1.89 (d, J = 7.1 Hz, 3H); LC-MS (Method 2): t_R = 4.81 min, m/z ($M+H$) $^+$ = 544.

Example 87. 3-(3-fluorophenyl)-1-methyl-6-((4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1H-indazole (Cpd 87)

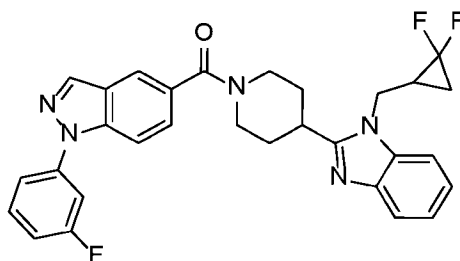


Cpd 87

[0335] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 3HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.56 (dd, J = 5.0, 1.6 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.75 – 7.68

(m, 2H), 7.61 (s, 1H), 7.57 – 7.51 (m, 2H), 7.33 – 7.15 (m, 4H), 7.11 – 7.01 (m, 2H), 6.97 (t, $J = 7.6$ Hz, 1H), 6.07 (q, $J = 7.0$ Hz, 1H), 4.10 (s, 3H), 3.68 (s, 2H), 3.07 (d, $J = 11.6$ Hz, 1H), 2.95 (t, $J = 10.4$ Hz, 2H), 2.23 – 1.63 (m, 6H), 1.92 (d, $J = 7.0$ Hz, 3H); LC-MS (Method 2): $t_R = 4.41$ min, m/z ($M+H$) $^+ = 545$.

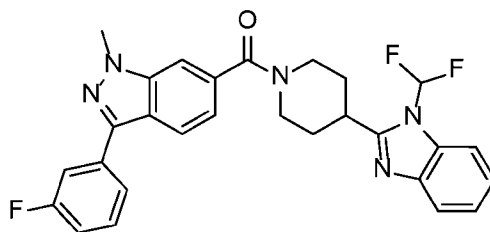
Example 88. (4-(1-((2,2-difluorocyclopropyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-5-yl)methanone (Cpd 88)



Cpd 88

[0336] The title compound was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-5-yl)methanone and 2-(bromomethyl)-1,1-difluorocyclopropane following a similar procedure as described in **Example 22** (STEP 2). ^1H NMR (400 MHz, DMSO- d_6) δ 8.49 (d, $J = 0.8$ Hz, 1H), 8.02 (d, $J = 1.5$ Hz, 1H), 7.97 (d, $J = 8.7$ Hz, 1H), 7.72 – 7.62 (m, 3H), 7.62 – 7.53 (m, 3H), 7.27 (tdd, $J = 8.6, 2.6, 1.3$ Hz, 1H), 7.19 (q, $J = 7.4$ Hz, 2H), 4.44 (d, $J = 7.0$ Hz, 2H), 3.87 (s, 1H), 3.38 (s, 1H), 3.21 (s, 2H), 2.23 (dp, $J = 20.0, 7.2$ Hz, 1H), 1.88 (t, $J = 12.5$ Hz, 5H), 1.69 (tdd, $J = 12.3, 7.9, 5.0$ Hz, 1H), 1.59 – 1.46 (m, 1H); LC-MS (Method 2): $t_R = 4.67$ min, m/z ($M+H$) $^+ = 530$.

Example 89. (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 89)

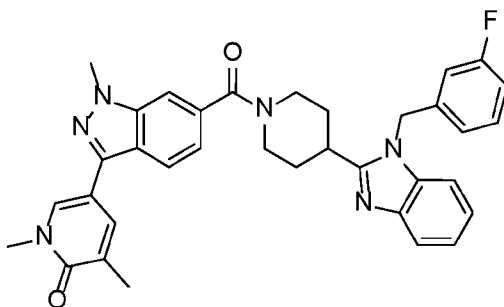


Cpd 89

[0337] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.22 (t, $J = 57.4$ Hz, 1H), 8.16 (d, $J = 8.4$ Hz, 1H), 7.85 – 7.83 (m, 2H), 7.76 – 7.63 (m, 3H), 7.56 (q,

$J = 7.7$ Hz, 1H), 7.37 – 7.19 (m, 4H), 4.63 (br s, 1H), 4.15 (s, 3H), 3.76 (br s, 1H), 3.53 – 3.43 (m, 1H), 3.38 – 2.97 (m, 2H), 2.17 – 1.80 (m, 4H); LC-MS (Method 2): $t_R = 6.00$ min, m/z (M+H)⁺ = 504.

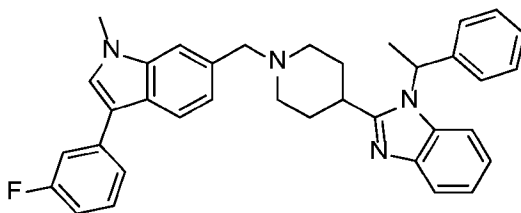
Example 90. 5-(6-(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidine-1-carbonyl)-1-methyl-1H-indazol-3-yl)-1,3-dimethylpyridin-2(1H)-one (Cpd 90)



Cpd 90

[0338] The title compound was prepared from (3-bromo-1-methyl-1H-indazol-6-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone and 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.18 (d, $J = 2.5$ Hz, 1H), 8.14 (d, $J = 8.4$ Hz, 1H), 7.94 – 7.89 (m, 1H), 7.75 (s, 1H), 7.62 – 7.57 (m, 1H), 7.43 – 7.29 (m, 2H), 7.23 – 7.11 (m, 3H), 7.08 (td, $J = 8.6, 2.6$ Hz, 1H), 6.97 – 6.89 (m, 1H), 6.84 (d, $J = 7.7$ Hz, 1H), 5.58 (s, 2H), 4.57 (s, 1H), 4.08 (s, 3H), 3.69 (br s, 1H), 3.57 (s, 3H), 3.40 – 3.32 (m, 1H), 3.21 (br s, 1H), 3.00 (br s, 1H), 2.10 (s, 3H), 1.96 – 1.61 (m, 4H); LC-MS (Method 2): $t_R = 4.33$ min, m/z (M+H)⁺ = 589.

Example 91. 2-(1-((3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)methyl)piperidin-4-yl)-1-(1-phenylethyl)-1H-benzo[d]imidazole (Cpd 91)

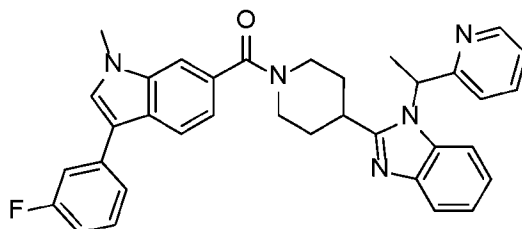


Cpd 91

[0339] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde and 1-(1-phenylethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.82 (d, $J = 8.2$ Hz, 1H), 7.75 (s, 1H), 7.55 (d, $J = 7.9$ Hz, 1H), 7.51 (d, $J = 7.8$ Hz, 1H), 7.48 – 7.38 (m, 3H),

7.32 (t, $J = 7.4$ Hz, 2H), 7.25 (t, $J = 7.2$ Hz, 1H), 7.17 (d, $J = 7.6$ Hz, 2H), 7.13 (d, $J = 8.2$ Hz, 1H), 7.10 – 6.93 (m, 4H), 6.02 (q, $J = 7.0$ Hz, 1H), 3.82 (s, 3H), 3.63 (s, 2H), 3.05 – 2.88 (m, 3H), 2.17 – 1.63 (m, 6H), 1.89 (d, $J = 6.9$ Hz, 3H); LC-MS (Method 2): $t_R = 5.04$ min, m/z (M+H)⁺ = 543.

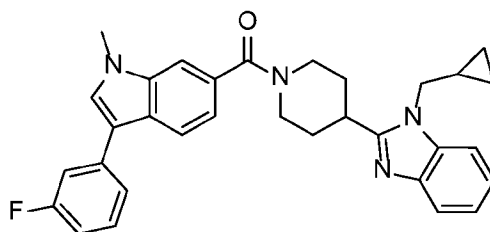
Example 92. (3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)(4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 92)



Cpd 92

[0340] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carboxylic acid and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 3HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO- d_6) δ 8.57 (d, $J = 4.8$ Hz, 1H), 7.93 (d, $J = 8.3$ Hz, 1H), 7.90 (s, 1H), 7.74 (dd, $J = 8.5, 6.7$ Hz, 1H), 7.62 (s, 1H), 7.54 (t, $J = 8.2$ Hz, 2H), 7.50 – 7.41 (m, 2H), 7.29 (dd, $J = 7.5, 4.9$ Hz, 1H), 7.21 (t, $J = 7.4$ Hz, 2H), 7.10 – 7.01 (m, 3H), 7.01 – 6.93 (m, 1H), 6.13 (q, $J = 7.0$ Hz, 1H), 4.54 (br s, 1H), 4.17 – 3.77 (br s, 1H), 3.88 (s, 3H), 3.54 – 3.45 (m, 1H), 3.13 (br s, 2H), 1.94 (d, $J = 6.9$ Hz, 3H), 2.09 – 1.78 (m, 4H); LC-MS (Method 2): $t_R = 5.11$ min, m/z (M+H)⁺ = 558.

Example 93. (4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)methanone (Cpd 93)

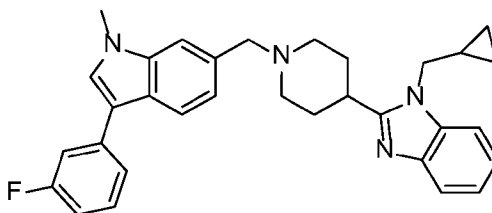


Cpd 93

[0341] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO- d_6) δ 7.94 (d, $J = 8.3$ Hz, 1H), 7.90 (s, 1H), 7.63 (s, 1H), 7.54 (t, $J = 8.1$ Hz, 3H), 7.50 – 7.41 (m, 2H), 7.24 – 7.09 (m, 3H), 7.04 (td, $J = 8.5, 2.6$ Hz, 1H), 4.54 (br s, 1H), 4.16 (d, $J = 6.8$ Hz, 2H), 4.04 –

3.78 (br s, 1H), 3.88 (s, 3H), 3.39–3.00 (m, 3H), 2.02–1.79 (m, 4H), 1.22–1.15 (m, 1H), 0.54–0.38 (m, 4H); LC-MS (Method 2): t_R = 5.20 min, m/z (M+H)⁺ = 507.

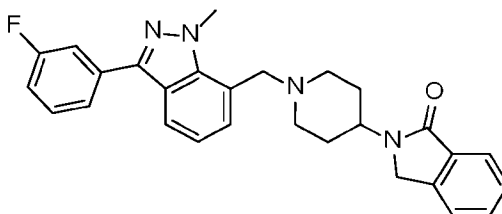
Example 94. 1-(cyclopropylmethyl)-2-(1-((3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazole (Cpd 94)



Cpd 94

[0342] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.84 (d, J = 8.2 Hz, 1H), 7.76 (s, 1H), 7.54–7.51 (m, 3H), 7.48–7.38 (m, 3H), 7.18–7.08 (m, 3H), 7.01 (td, J = 8.5, 2.6 Hz, 1H), 4.11 (d, J = 6.8 Hz, 2H), 3.83 (s, 3H), 3.66 (s, 2H), 3.00–2.91 (m, 3H), 2.16 (t, J = 11.2 Hz, 2H), 1.94 (qd, J = 12.1, 3.7 Hz, 2H), 1.83 (d, J = 12.5 Hz, 2H), 1.19–1.08 (m, 1H), 0.48 (dd, J = 7.0, 2.7 Hz, 2H), 0.39 (d, J = 4.9 Hz, 2H); LC-MS (Method 2): t_R = 4.66 min, m/z (M+H)⁺ = 493.

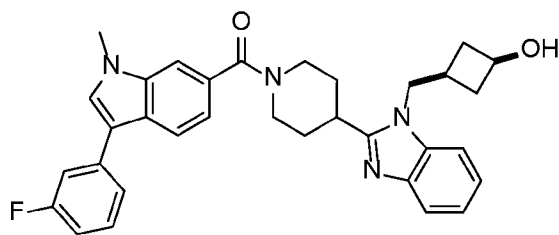
Example 95. 2-(1-((3-(3-fluorophenyl)-1-methyl-1H-indazol-7-yl)methyl)piperidin-4-yl)isoindolin-1-one (Cpd 95)



Cpd 95

[0343] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.98 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.70–7.61 (m, 2H), 7.58–7.52 (m, 3H), 7.47–7.41 (m, 1H), 7.29–7.18 (m, 2H), 7.15 (t, J = 7.6 Hz, 1H), 4.46 (s, 3H), 4.42 (s, 2H), 4.09–4.02 (m, 1H), 3.86 (s, 2H), 2.95 (d, J = 11.2 Hz, 2H), 2.18 (td, J = 11.5, 3.3 Hz, 2H), 1.79–1.67 (m, 4H); LC-MS (Method 2): t_R = 4.48 min, m/z (M+H)⁺ = 455.

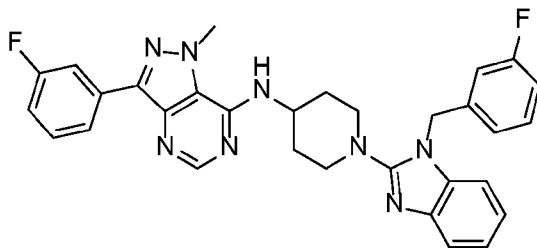
Example 96. (3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)(4-(1-(((1s,3s)-3-hydroxycyclobutyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 96)



Cpd 96

[0344] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carboxylic acid and (1s,3s)-3-((2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutanol, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.94 (d, *J* = 8.3 Hz, 1H), 7.90 (s, 1H), 7.63 (s, 1H), 7.56 – 7.41 (m, 5H), 7.24 – 7.10 (m, 3H), 7.04 (td, *J* = 8.6, 2.6 Hz, 1H), 5.00 (d, *J* = 6.1 Hz, 1H), 4.53 (br s, 1H), 4.26 (d, *J* = 6.3 Hz, 2H), 3.88 (s, 3H), 4.11 – 3.78 (m, 2H), 3.33 – 3.00 (m, 3H), 2.24 – 2.02 (m, 3H), 2.00 – 1.75 (m, 4H), 1.65 – 1.54 (m, 2H); LC-MS (Method 2): *t*_R = 4.70 min, *m/z* (M+H)⁺ = 537.

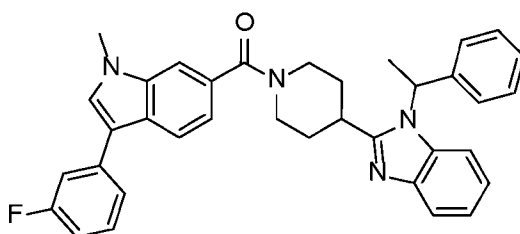
Example 97. N-(1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine (Cpd 97)



Cpd 97

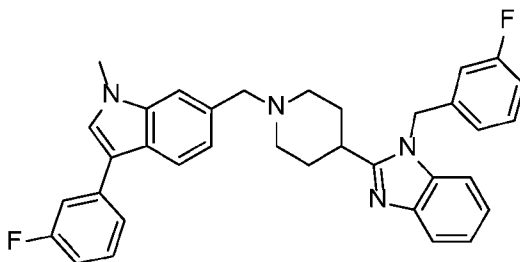
[0345] The title compound was prepared from 3-bromo-N-(1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine and (3-fluorophenyl)boronic acid following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.37 (s, 1H), 8.22 – 8.12 (m, 2H), 7.62 – 7.47 (m, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.37 (q, *J* = 7.4 Hz, 1H), 7.24 – 6.93 (m, 8H), 5.33 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 1H), 4.32 (s, 3H), 3.60 (d, *J* = 12.7 Hz, 2H), 3.12 (td, *J* = 11.7, 4.3 Hz, 2H), 2.05 – 1.91 (m, 4H); LC-MS (Method 2): *t*_R = 4.99 min, *m/z* (M+H)⁺ = 551.

Example 98. (3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)(4-(1-(1-phenylethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 98)

**Cpd 98**

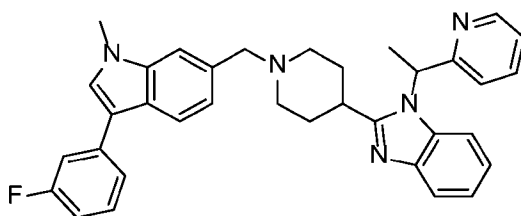
[0346] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carboxylic acid and 1-(1-phenylethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.93 (d, J = 8.3 Hz, 1H), 7.90 (s, 1H), 7.62 (s, 1H), 7.59 – 7.40 (m, 4H), 7.35 – 7.32 (m, 2H), 7.29 – 7.16 (m, 4H), 7.12 – 6.93 (m, 4H), 6.09 (q, J = 7.0 Hz, 1H), 4.53 (br s, 1H), 3.88 (s, 3H), 4.13 – 3.76 (br s, 1H), 3.45 (p, J = 7.5 Hz, 1H), 3.11 (br s, 2H), 1.92 (d, J = 7.0 Hz, 3H), 2.03 – 1.72 (m, 4H); LC-MS (Method 2): t_R = 5.47 min, m/z ($M+H$) $^+$ = 557.

Example 99. 1-(3-fluorobenzyl)-2-(1-((3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazole (Cpd 99)

**Cpd 99**

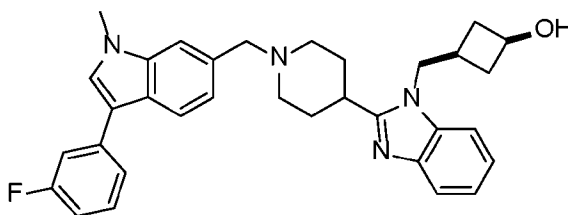
[0347] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.82 (d, J = 8.2 Hz, 1H), 7.75 (s, 1H), 7.61 – 7.56 (m, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.47 – 7.38 (m, 4H), 7.33 (td, J = 7.9, 6.0 Hz, 1H), 7.18 – 6.97 (m, 5H), 6.89 (dd, J = 10.1, 2.7 Hz, 1H), 6.81 (d, J = 7.7 Hz, 1H), 5.54 (s, 2H), 3.82 (s, 3H), 3.62 (s, 2H), 2.96 – 2.90 (m, 3H), 2.06 (t, J = 11.6 Hz, 2H), 1.96 – 1.81 (m, 2H), 1.68 (d, J = 11.2 Hz, 2H); LC-MS (Method 2): t_R = 4.90 min, m/z ($M+H$) $^+$ = 547.

Example 100. 2-(1-((3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)methyl)piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole (Cpd 100)

**Cpd 100**

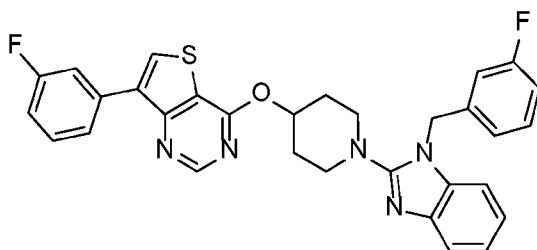
[0348] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 3HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.59 – 8.53 (m, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.52 (dd, J = 10.2, 7.7 Hz, 2H), 7.46 – 7.41 (m, 3H), 7.29 (dd, J = 7.5, 4.9 Hz, 1H), 7.18 (d, J = 7.9 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 7.10 – 6.92 (m, 4H), 6.06 (q, J = 7.0 Hz, 1H), 3.83 (s, 3H), 3.64 (s, 2H), 3.11 – 2.90 (m, 3H), 2.20 – 1.64 (m, 6H), 1.91 (d, J = 7.0 Hz, 3H); LC-MS (Method 2): t_R = 4.70 min, m/z ($M+H$) $^+$ = 544.

Example 101. (1s,3s)-3-((2-(1-((3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol (Cpd 101)

**Cpd 101**

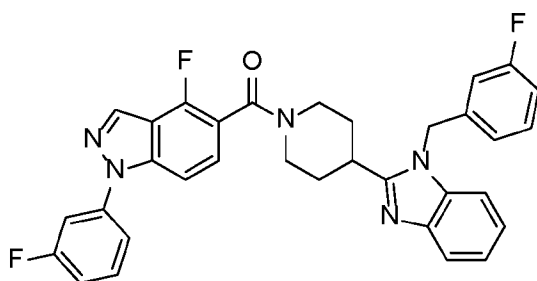
[0349] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde and (1s,3s)-3-((2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.84 (d, J = 8.2 Hz, 1H), 7.76 (s, 1H), 7.55 – 7.37 (m, 6H), 7.18 – 7.08 (m, 3H), 7.02 (td, J = 8.5, 2.6 Hz, 1H), 4.98 (d, J = 6.3 Hz, 1H), 4.21 (d, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.87 – 3.77 (m, 1H), 3.66 (s, 2H), 3.11 – 2.81 (m, 3H), 2.23 – 2.01 (m, 5H), 1.93 (q, J = 11.5 Hz, 2H), 1.80 (d, J = 12.8 Hz, 2H), 1.62 – 1.49 (m, 2H); LC-MS (Method 2): t_R = 4.29 min, m/z ($M+H$) $^+$ = 523.

Example 102. 4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-7-(3-fluorophenyl)thieno[3,2-d]pyrimidine (Cpd 102)

**Cpd 102**

[0350] To a mixture of 2-chloro-1-(3-fluorobenzyl)-1H-benzo[d]imidazole (43.0 mg, 0.165 mmol) and 7-(3-fluorophenyl)-4-(piperidin-4-yloxy)thieno[3,2-d]pyrimidine, 2HCl (60.3 mg, 0.15 mmol) was added DMSO (1 mL) and Hunig's base (0.092 mL, 0.525 mmol). The tube was sealed and heated at 150 °C for overnight. After cooled to rt, the mixture was diluted with EtOAc (5 mL) and washed with H₂O (5 mL x 3). The organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 10-60% EtOAc/hexane as the eluent to give 4-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-7-(3-fluorophenyl)thieno[3,2-d]pyrimidine (42.7 mg, 0.077 mmol, 51.4 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.88 (s, 1H), 8.72 (s, 1H), 8.03 (dd, *J* = 10.7, 2.4 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.53 (q, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.36 (td, *J* = 7.9, 5.9 Hz, 1H), 7.28 – 7.16 (m, 2H), 7.13 – 6.92 (m, 5H), 5.62 (tt, *J* = 8.0, 3.8 Hz, 1H), 5.34 (s, 2H), 3.48 (dd, *J* = 13.2, 5.8 Hz, 2H), 3.24 (ddd, *J* = 12.6, 8.7, 3.3 Hz, 2H), 2.26 – 2.15 (m, 2H), 2.04 – 1.96 (m, 2H); LC-MS (Method 2): *t*_R = 5.61 min, *m/z* (M+H)⁺ = 554.

Example 103. (4-fluoro-1-(3-fluorophenyl)-1H-indazol-5-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 103)

**Cpd 103**

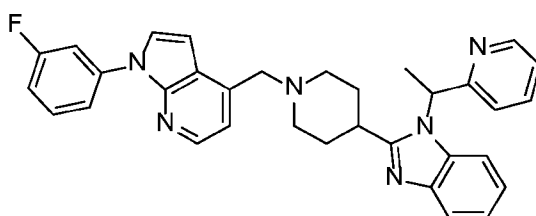
STEP 1: Synthesis of 4-fluoro-1-(3-fluorophenyl)-1H-indazole-5-carboxylic acid

[0351] The material, 4-fluoro-1-(3-fluorophenyl)-1H-indazole-5-carboxylic acid, was prepared from methyl 4-fluoro-1-(3-fluorophenyl)-1H-indazole-5-carboxylate and 1-bromo-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-71**.

STEP 2: Synthesis of (4-fluoro-1-(3-fluorophenyl)-1H-indazol-5-yl)(4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 103)

[0352] The title compound was prepared from 4-fluoro-1-(3-fluorophenyl)-1H-indazole-5-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. LC-MS (Method 2): $t_R = 4.92$ min, m/z (M+H)⁺ = 566.

Example 104. 2-(1-((1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)methyl)piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole (Cpd 104)



Cpd 104

STEP 1: Synthesis of methyl 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carboxylate

[0353] The material, methyl 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carboxylate, was prepared from methyl 1H-pyrrolo[2,3-b]pyridine-4-carboxylate and 1-bromo-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-71** (STEP 1).

STEP 2: Synthesis of 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carbaldehyde

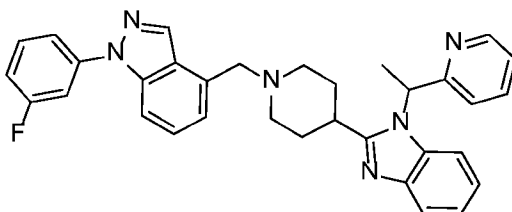
[0354] The material, 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carbaldehyde, was prepared from methyl 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carboxylate following a similar procedure as described in the synthesis of **Int-30**. LC-MS (Method 1): $t_R = 3.44$ min, m/z (M+H)⁺ = 241.

STEP 3: Synthesis of 2-(1-((1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)methyl)piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole (Cpd 104)

[0355] The title compound was prepared from 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carbaldehyde and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 3HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.62 (d, $J = 0.9$ Hz, 1H), 8.56 (ddd, $J = 4.8, 1.8, 0.9$ Hz, 1H), 7.80 (dt, $J = 8.5, 0.8$ Hz, 1H), 7.73 (ddd, $J = 8.0, 7.5, 1.8$ Hz, 1H), 7.69 – 7.57 (m, 3H), 7.57 – 7.50 (m, 1H), 7.46 (dd, $J = 8.5, 7.0$ Hz, 1H), 7.31 – 7.16 (m, 4H), 7.11 – 7.02 (m, 2H), 6.97 (ddd, $J = 8.0, 7.3, 1.2$ Hz, 1H), 6.07

(q, $J = 7.0$ Hz, 1H), 3.88 (s, 2H), 3.13 – 3.03 (m, 1H), 2.96 (t, $J = 10.4$ Hz, 2H), 2.23 – 2.09 (m, 2H), 1.97 (s, 1H), 1.95 – 1.88 (m, 5H), 1.76 – 1.68 (m, 1H); LC-MS (Method 2): $t_R = 4.20$ min, m/z (M+H)⁺ = 531.

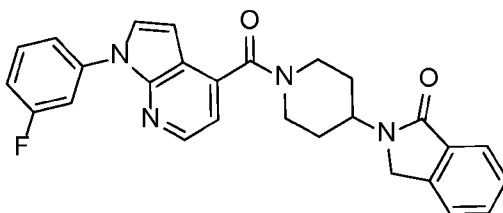
Example 105. 1-(3-fluorophenyl)-4-((4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1H-indazole (Cpd 105)



Cpd 105

[0356] The title compound was prepared from methyl 1H-indazole-4-carboxylate and 1-bromo-3-fluorobenzene following a similar procedure as described in **Example 104**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.56 (ddd, $J = 4.8, 1.9, 0.9$ Hz, 1H), 8.30 (d, $J = 4.8$ Hz, 1H), 8.01 (d, $J = 3.8$ Hz, 1H), 7.95 (dt, $J = 11.1, 2.3$ Hz, 1H), 7.84 (ddd, $J = 8.2, 2.1, 0.9$ Hz, 1H), 7.73 (td, $J = 7.7, 1.8$ Hz, 1H), 7.62 – 7.51 (m, 2H), 7.33 – 7.25 (m, 1H), 7.25 – 7.11 (m, 3H), 7.06 (ddd, $J = 8.7, 7.3, 1.5$ Hz, 2H), 7.02 – 6.93 (m, 2H), 6.07 (q, $J = 7.0$ Hz, 1H), 3.86 (s, 2H), 3.02 (d, $J = 49.6$ Hz, 3H), 2.18 (q, $J = 12.3$ Hz, 2H), 1.91 (d, $J = 7.1$ Hz, 6H), 1.73 (d, $J = 12.9$ Hz, 1H); LC-MS (Method 2): $t_R = 4.11$ min, m/z (M+H)⁺ = 531.

Example 106. 2-(1-(1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carbonyl)piperidin-4-yl)isoindolin-1-one (Cpd 106)



Cpd 106

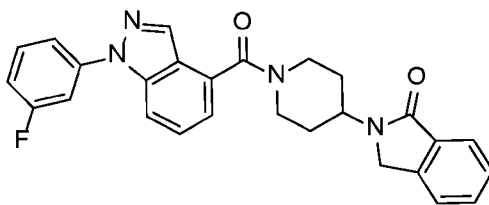
STEP 1: Synthesis of 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carboxylic acid

[0357] The material, 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carboxylic acid, was prepared from methyl 1H-pyrrolo[2,3-b]pyridine-4-carboxylate and 1-bromo-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-71**. LC-MS (Method 1): $t_R = 3.15$ min, m/z (M+H)⁺ = 257.

STEP 2: Synthesis of 2-(1-(1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carbonyl)piperidin-4-yl)isoindolin-1-one (Cpd 106)

[0358] The title compound was prepared from 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carboxylic acid and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.42 (d, *J* = 4.8 Hz, 1H), 8.13 (d, *J* = 3.8 Hz, 1H), 7.92 (dt, *J* = 10.9, 2.3 Hz, 1H), 7.83 (ddd, *J* = 8.2, 2.1, 0.9 Hz, 1H), 7.67 (dt, *J* = 7.5, 1.1 Hz, 1H), 7.64 – 7.54 (m, 3H), 7.47 (ddd, *J* = 7.6, 4.7, 3.7 Hz, 1H), 7.26 (d, *J* = 4.8 Hz, 1H), 7.20 (tdd, *J* = 8.5, 2.5, 0.9 Hz, 1H), 6.76 (d, *J* = 3.8 Hz, 1H), 4.72 (d, *J* = 13.2 Hz, 1H), 4.50 (d, *J* = 10.5 Hz, 2H), 4.33 (p, *J* = 8.0 Hz, 1H), 3.49 (d, *J* = 13.5 Hz, 1H), 3.15 (s, 1H), 3.01 (s, 1H), 1.79 (d, *J* = 83.7 Hz, 4H); LC-MS (Method 2): *t*_R = 5.31 min, *m/z* (M+H)⁺ = 455.

Example 107. 2-(1-(1-(3-fluorophenyl)-1H-indazole-4-carbonyl)piperidin-4-yl)isoindolin-1-one (Cpd 107)



Cpd 107

STEP 1: Synthesis of 1-(3-fluorophenyl)-1H-indazole-4-carboxylic acid

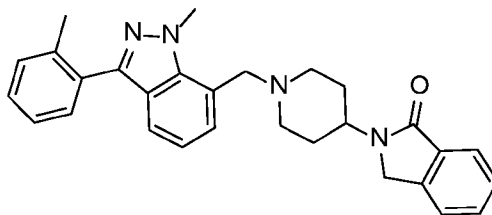
[0359] The material, 1-(3-fluorophenyl)-1H-indazole-4-carboxylic acid, was prepared from methyl 1H-indazole-4-carboxylate and 1-bromo-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-71**. LC-MS (Method 1): *t*_R = 3.16 min, *m/z* (M+H)⁺ = 257.

STEP 2: Synthesis of 2-(1-(1-(3-fluorophenyl)-1H-indazole-4-carbonyl)piperidin-4-yl)isoindolin-1-one (Cpd 107)

[0360] The title compound was prepared from 1-(3-fluorophenyl)-1H-indazole-4-carboxylic acid and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in

Example 1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.43 (d, *J* = 0.9 Hz, 1H), 7.98 (dt, *J* = 8.7, 0.8 Hz, 1H), 7.70 – 7.62 (m, 4H), 7.62 – 7.55 (m, 3H), 7.47 (ddd, *J* = 7.5, 4.6, 3.8 Hz, 1H), 7.34 (dd, *J* = 7.1, 0.7 Hz, 1H), 7.30 – 7.22 (m, 1H), 5.74 (s, 1H), 4.53 – 4.48 (m, 2H), 4.33 (td, *J* = 10.0, 5.0 Hz, 1H), 4.01 (q, *J* = 7.1 Hz, 1H), 1.78 (d, *J* = 69.2 Hz, 4H), 1.20 – 1.11 (m, 2H); LC-MS (Method 2): *t*_R = 5.24 min, *m/z* (M+H)⁺ = 455.

Example 108. 2-(1-((1-methyl-3-(o-tolyl)-1H-indazol-7-yl)methyl)piperidin-4-yl)isoindolin-1-one (Cpd 108)



Cpd 108

STEP 1: Synthesis of methyl 1-methyl-3-(o-tolyl)-1H-indazole-7-carboxylate

[0361] The material, methyl 1-methyl-3-(o-tolyl)-1H-indazole-7-carboxylate, was prepared from methyl 3-bromo-1-methyl-1H-indazole-7-carboxylate and o-tolylboronic acid following a similar procedure as described in the synthesis of **Int-15** (STEP-1). LC-MS (Method 1): $t_R = 3.71$ min, m/z (M+H)⁺ = 281.

STEP 2: Synthesis of 1-methyl-3-(o-tolyl)-1H-indazole-7-carbaldehyde

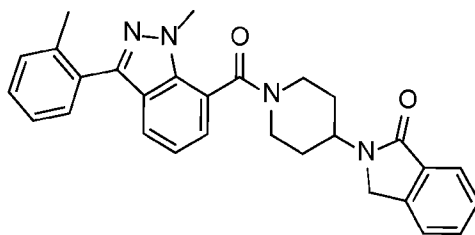
[0362] The material, 1-methyl-3-(o-tolyl)-1H-indazole-7-carbaldehyde, was prepared from methyl 1-methyl-3-(o-tolyl)-1H-indazole-7-carboxylate following a similar procedure as described in the synthesis of **Int-30**. ¹H NMR (400 MHz, DMSO-d₆) δ 10.34 (s, 1H), 8.07 (dd, $J = 7.2, 1.1$ Hz, 1H), 7.90 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.47 – 7.28 (m, 6H), 4.40 (s, 3H), 2.30 (s, 3H); LC-MS (Method 1): $t_R = 3.675$ min, m/z (M+H)⁺ = 251.

STEP 3: Synthesis of 2-(1-((1-methyl-3-(o-tolyl)-1H-indazol-7-yl)methyl)piperidin-4-yl)isoindolin-1-one (Cpd 108)

[0363] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-7-carbaldehyde and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in

Example 53. ¹H NMR (400 MHz, DMSO-d₆) δ 7.66 (dt, $J = 7.6, 1.1$ Hz, 1H), 7.62 – 7.52 (m, 2H), 7.52 – 7.42 (m, 3H), 7.42 – 7.27 (m, 3H), 7.26 – 7.19 (m, 1H), 7.07 (dd, $J = 8.2, 6.9$ Hz, 1H), 4.45 (d, $J = 1.7$ Hz, 5H), 4.08 (dq, $J = 11.2, 5.5$ Hz, 1H), 3.88 (s, 2H), 3.00 (d, $J = 11.4$ Hz, 2H), 2.34 (s, 3H), 2.21 (t, $J = 11.5$ Hz, 2H), 1.76 (dt, $J = 23.7, 7.9$ Hz, 4H); LC-MS (Method 2): $t_R = 4.33$ min, m/z (M+H)⁺ = 451.

Example 109. 2-(1-(1-methyl-3-(o-tolyl)-1H-indazole-7-carbonyl)piperidin-4-yl)isoindolin-1-one (Cpd 109)



Cpd 109

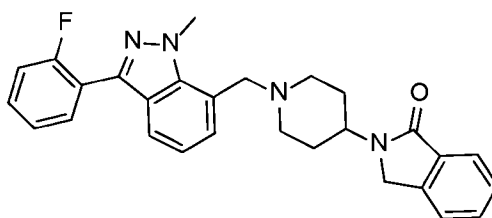
STEP 1: Synthesis of 1-methyl-3-(o-tolyl)-1H-indazole-7-carboxylic acid

[0364] The material, 1-methyl-3-(o-tolyl)-1H-indazole-7-carboxylic acid, was prepared from methyl 3-bromo-1-methyl-1H-indazole-7-carboxylate and o-tolylboronic acid following a similar procedure as described in the synthesis of **Int-15**. LC-MS (Method 1): $t_R = 3.29$ min, m/z (M+H)⁺ = 267.

STEP 2: Synthesis of 2-(1-(1-methyl-3-(o-tolyl)-1H-indazole-7-carbonyl)piperidin-4-yl)isoindolin-1-one (Cpd 109)

[0365] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-7-carboxylic acid and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.64 (dd, $J = 8.2, 1.0$ Hz, 1H), 7.59 (t, $J = 5.4$ Hz, 2H), 7.48 – 7.44 (m, 3H), 7.41 – 7.29 (m, 4H), 7.24 – 7.18 (m, 1H), 4.79 (t, $J = 15.2$ Hz, 1H), 4.50 (d, $J = 17.0$ Hz, 2H), 4.36 (s, 1H), 3.98 (s, 3H), 3.72 (s, 1H), 3.07 (s, 1H), 2.33 (d, $J = 2.7$ Hz, 3H), 2.00 – 1.59 (m, 5H); LC-MS (Method 2): $t_R = 5.52$ min, m/z (M+H)⁺ = 465.

Example 110. 2-(1-((3-(2-fluorophenyl)-1-methyl-1H-indazol-7-yl)methyl)piperidin-4-yl)isoindolin-1-one (Cpd 110)



Cpd 110

STEP 1: Synthesis of methyl 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carboxylate

[0366] The material, methyl 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carboxylate, was prepared from methyl 3-bromo-1-methyl-1H-indazole-7-carboxylate and (2-

fluorophenyl)boronic acid following a similar procedure as described in the synthesis of **Int-15** (STEP-1). LC-MS (Method 1): $t_R = 3.61$ min, m/z (M+H)⁺ = 285.

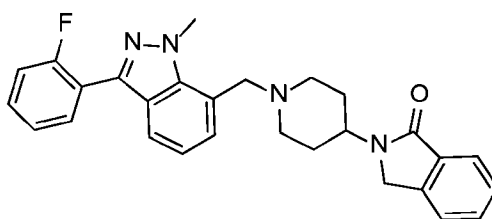
STEP 2: Synthesis of 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde

[0367] The material, 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde, was prepared from methyl 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carboxylate following a similar procedure as described in the synthesis of **Int-30**. ¹H NMR (400 MHz, DMSO-d₆) δ 10.35 (d, $J = 1.7$ Hz, 1H), 8.07 (ddq, $J = 18.2, 8.1, 1.4$ Hz, 2H), 7.73 (tt, $J = 7.6, 1.8$ Hz, 1H), 7.60 – 7.49 (m, 1H), 7.39 (qdd, $J = 9.1, 4.5, 2.5$ Hz, 3H), 4.42 (d, $J = 1.4$ Hz, 3H); LC-MS (Method 1): $t_R = 3.48$ min, m/z (M+H)⁺ = 255.

STEP 3: Synthesis of 2-(1-((3-(2-fluorophenyl)-1-methyl-1H-indazol-7-yl)methyl)piperidin-4-yl)isoindolin-1-one (Cpd 110)

[0368] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.73 (td, $J = 7.6, 1.8$ Hz, 1H), 7.69 – 7.60 (m, 2H), 7.60 – 7.43 (m, 4H), 7.43 – 7.32 (m, 2H), 7.24 (dd, $J = 7.0, 1.1$ Hz, 1H), 7.11 (dd, $J = 8.2, 6.9$ Hz, 1H), 4.46 (d, $J = 13.7$ Hz, 5H), 4.09 (td, $J = 11.3, 5.7$ Hz, 1H), 3.88 (s, 2H), 2.98 (d, $J = 11.4$ Hz, 2H), 2.25 – 2.15 (m, 2H), 1.77 (dd, $J = 11.8, 3.5$ Hz, 2H), 1.72 (s, 2H); LC-MS (Method 2): $t_R = 4.23$ min, m/z (M+H)⁺ = 455.

Example 110. 2-(1-((3-(2-fluorophenyl)-1-methyl-1H-indazol-7-yl)methyl)piperidin-4-yl)isoindolin-1-one (Cpd 110)



Cpd 110

STEP 1: Synthesis of methyl 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carboxylate

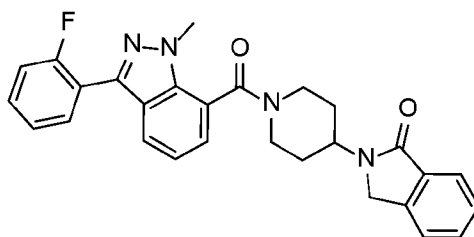
[0369] The material, methyl 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carboxylate, was prepared from methyl 3-bromo-1-methyl-1H-indazole-7-carboxylate and (2-fluorophenyl)boronic acid following a similar procedure as described in the synthesis of **Int-15** (STEP 1). LC-MS (Method 1): $t_R = 3.61$ min, m/z (M+H)⁺ = 285.

STEP 2: Synthesis of 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde

[0370] The material, 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde, was prepared from methyl 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carboxylate following a similar procedure as described in the synthesis of **Int-30**. ¹H NMR (400 MHz, DMSO-d₆) δ 10.35 (d, *J* = 1.7 Hz, 1H), 8.07 (ddq, *J* = 18.2, 8.1, 1.4 Hz, 2H), 7.73 (tt, *J* = 7.6, 1.8 Hz, 1H), 7.60 – 7.49 (m, 1H), 7.39 (qdd, *J* = 9.1, 4.5, 2.5 Hz, 3H), 4.42 (d, *J* = 1.4 Hz, 3H); LC-MS (Method 1): *t*_R = 3.48 min, *m/z* (M+H)⁺ = 255.

STEP 3: Synthesis of 2-(1-((3-(2-fluorophenyl)-1-methyl-1H-indazol-7-yl)methyl)piperidin-4-yl)isoindolin-1-one (Cpd 110)

[0371] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.73 (td, *J* = 7.6, 1.8 Hz, 1H), 7.69 – 7.60 (m, 2H), 7.60 – 7.43 (m, 4H), 7.43 – 7.32 (m, 2H), 7.24 (dd, *J* = 7.0, 1.1 Hz, 1H), 7.11 (dd, *J* = 8.2, 6.9 Hz, 1H), 4.46 (d, *J* = 13.7 Hz, 5H), 4.09 (td, *J* = 11.3, 5.7 Hz, 1H), 3.88 (s, 2H), 2.98 (d, *J* = 11.4 Hz, 2H), 2.25 – 2.15 (m, 2H), 1.77 (dd, *J* = 11.8, 3.5 Hz, 2H), 1.72 (s, 2H); LC-MS (Method 2): *t*_R = 4.23 min, *m/z* (M+H)⁺ = 455.

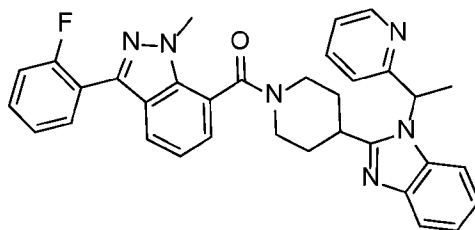
Example 111. 2-(1-(3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carbonyl)piperidin-4-yl)isoindolin-1-one (Cpd 111)**Cpd 111**STEP 1: Synthesis of 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carboxylic acid

[0372] The material, 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carboxylic acid, was prepared from methyl 3-bromo-1-methyl-1H-indazole-7-carboxylate and (2-fluorophenyl)boronic acid following a similar procedure as described in the synthesis of **Int-15**. LC-MS (Method 1): *t*_R = 3.18 min, *m/z* (M+H)⁺ = 271.

STEP 2: Synthesis of 2-(1-(3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carbonyl)piperidin-4-yl)isoindolin-1-one (Cpd 111)

[0373] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carboxylic acid and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.83 – 7.74 (m, 2H), 7.69 (dd, *J* = 7.7, 3.5 Hz, 1H), 7.60 (dd, *J* = 7.9, 4.2 Hz, 2H), 7.57 – 7.34 (m, 5H), 7.27 (q, *J* = 7.5 Hz, 1H), 4.81 (t, *J* = 15.6 Hz, 1H), 4.52 (d, *J* = 17.1 Hz, 2H), 4.38 (s, 1H), 4.09 (d, *J* = 57.7 Hz, 3H), 3.60 (d, *J* = 7.4 Hz, 1H), 3.18 – 3.03 (m, 2H), 1.96 – 1.62 (m, 4H); LC-MS (Method 2): *t*_R = 5.315 min, *m/z* (M+H)⁺ = 469.

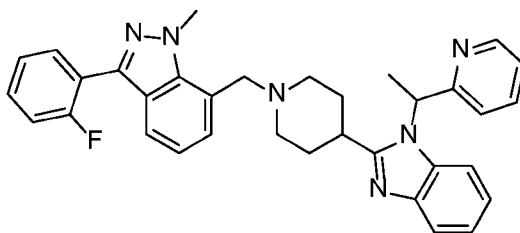
Example 112. (3-(2-fluorophenyl)-1-methyl-1H-indazol-7-yl)(4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd. 112)



Cpd 112

[0374] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carboxylic acid and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 3HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.60 – 8.53 (m, 1H), 7.87 – 7.66 (m, 2H), 7.60 – 7.47 (m, 2H), 7.44 – 7.39 (m, 1H), 7.39 – 7.33 (m, 2H), 7.27 (tt, *J* = 17.3, 7.9 Hz, 3H), 7.06 (dt, *J* = 13.2, 7.0 Hz, 2H), 6.98 (q, *J* = 7.3 Hz, 1H), 6.13 (d, *J* = 7.6 Hz, 1H), 4.86 – 4.62 (m, 1H), 4.07 (d, *J* = 45.7 Hz, 3H), 3.72 (d, *J* = 13.5 Hz, 1H), 3.54 (s, 2H), 3.37 (q, *J* = 12.7 Hz, 1H), 3.12 (t, *J* = 11.9 Hz, 1H), 2.18 (d, *J* = 13.4 Hz, 1H), 2.00 – 1.87 (m, 4H), 1.76 (s, 1H), 1.28 – 1.13 (m, 1H); LC-MS (Method 2): *t*_R = 4.735 min, *m/z* (M+H)⁺ = 559.

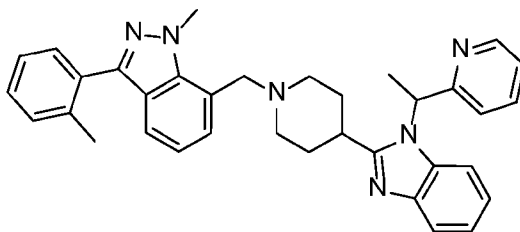
Example 113. 3-(2-fluorophenyl)-1-methyl-7-((4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1H-indazole (Cpd 113)



Cpd 113

[0375] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 3HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.57 (ddd, *J* = 4.8, 1.9, 0.9 Hz, 1H), 7.73 (tdd, *J* = 7.3, 5.3, 1.8 Hz, 2H), 7.62 (ddd, *J* = 8.3, 3.2, 1.1 Hz, 1H), 7.55 – 7.44 (m, 2H), 7.43 – 7.26 (m, 3H), 7.21 (dd, *J* = 17.4, 7.3 Hz, 2H), 7.14 – 7.07 (m, 1H), 7.11 – 7.01 (m, 2H), 6.97 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 6.08 (q, *J* = 7.0 Hz, 1H), 5.74 (s, 1H), 4.47 (s, 3H), 3.91 – 3.79 (m, 2H), 3.11 (s, 1H), 2.95 (t, *J* = 12.7 Hz, 2H), 2.18 (s, 1H), 2.25 – 2.08 (m, 1H), 1.96 – 1.77 (m, 6H); LC-MS (Method 2): *t*_R = 4.24 min, *m/z* (M+H)⁺ = 545.

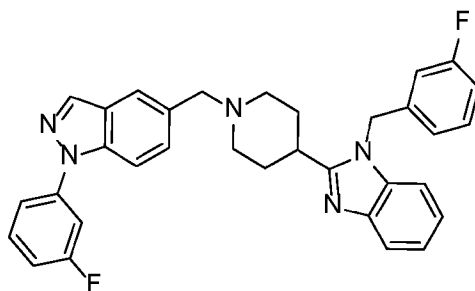
Example 114. 1-methyl-7-((4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(o-tolyl)-1H-indazole (Cpd 114)



Cpd 114

[0376] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-7-carbaldehyde and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 3HCl following a similar procedure as described in **Example 53**. LC-MS (Method 2): *t*_R = 4.35 min, *m/z* (M+H)⁺ = 541.

Example 115. 5-((4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-(3-fluorophenyl)-1H-indazole (Cpd 115)



Cpd 115

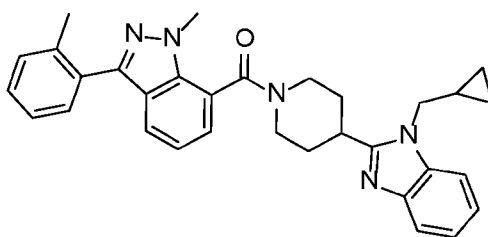
STEP 1: Synthesis of 1-(3-fluorophenyl)-1H-indazole-5-carbaldehyde

[0377] The material, 1-(3-fluorophenyl)-1H-indazole-5-carbaldehyde, was prepared from methyl 1-(3-fluorophenyl)-1H-indazole-5-carboxylate following a similar procedure as described in the synthesis of **Int-30**. LC-MS (Method 1): $t_R = 3.42$ min, m/z ($M+H$)⁺ = 241.

STEP 2: Synthesis of 5-((4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-(3-fluorophenyl)-1H-indazole (Cpd 115)

[0378] The title compound was prepared from 1-(3-fluorophenyl)-1H-indazole-5-carbaldehyde and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.37 (d, $J = 0.9$ Hz, 1H), 7.87 (dt, $J = 8.7, 0.9$ Hz, 1H), 7.78 (dd, $J = 1.6, 0.8$ Hz, 1H), 7.71 – 7.55 (m, 4H), 7.50 (dd, $J = 8.8, 1.6$ Hz, 1H), 7.44 – 7.36 (m, 1H), 7.36 – 7.28 (m, 1H), 7.26 – 7.18 (m, 1H), 7.18 – 7.11 (m, 2H), 7.11 – 7.04 (m, 1H), 6.90 (ddd, $J = 10.0, 2.6, 1.6$ Hz, 1H), 6.82 (ddd, $J = 7.7, 1.6, 0.9$ Hz, 1H), 5.54 (s, 2H), 3.62 (s, 2H), 3.00 – 2.84 (m, 3H), 2.13 – 2.03 (m, 2H), 1.94 – 1.83 (q, 2H), 1.74 – 1.66 (m, 2H); LC-MS (Method 2): $t_R = 4.53$ min, m/z ($M+H$)⁺ = 534.

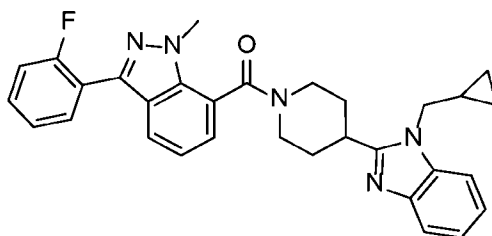
Example 116. (4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-methyl-3-(*o*-tolyl)-1H-indazol-7-yl)methanone (Cpd 116)



Cpd 116

[0379] The title compound was prepared from 1-methyl-3-(*o*-tolyl)-1H-indazole-7-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.69 – 7.43 (m, 4H), 7.36 (dddd, *J* = 14.5, 12.3, 8.3, 6.0 Hz, 4H), 7.19 (dq, *J* = 29.3, 7.3 Hz, 3H), 4.20 – 3.97 (m, 5H), 2.34 (s, 3H), 2.07 (d, *J* = 13.1 Hz, 1H), 1.91 (s, 2H), 1.84 (d, *J* = 13.8 Hz, 1H), 1.29 – 1.21 (m, 6H), 0.53 – 0.40 (m, 4H); LC-MS (Method 2): *t*_R = 4.86 min, *m/z* (M+H)⁺ = 504.

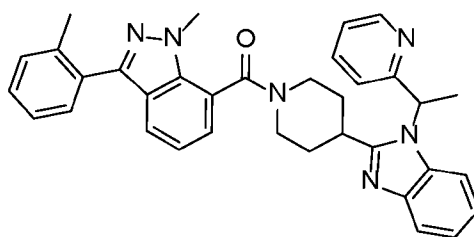
Example 117. (4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(2-fluorophenyl)-1-methyl-1H-indazol-7-yl)methanone (Cpd 117)



Cpd 117

[0380] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.84 – 7.73 (m, 2H), 7.54 (ddd, *J* = 15.4, 6.1, 3.3 Hz, 3H), 7.48 – 7.33 (m, 3H), 7.29 (q, *J* = 7.0 Hz, 1H), 7.17 (q, *J* = 7.5 Hz, 2H), 4.74 (d, *J* = 14.9 Hz, 1H), 4.21 – 4.14 (m, 3H), 4.05 (s, 2H), 3.76 (d, *J* = 13.5 Hz, 1H), 3.58 (d, *J* = 14.9 Hz, 1H), 2.09 (d, *J* = 13.0 Hz, 1H), 1.97 – 1.81 (m, 2H), 1.21 (dq, *J* = 26.4, 6.5 Hz, 4H), 0.55 – 0.45 (m, 2H), 0.44 (d, *J* = 4.7 Hz, 2H); LC-MS (Method 2): *t*_R = 4.69 min, *m/z* (M+H)⁺ = 508.

Example 118. (1-methyl-3-(*o*-tolyl)-1H-indazol-7-yl)(4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 118)

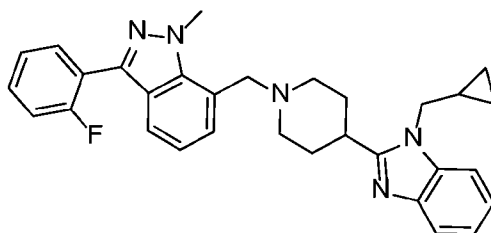


Cpd 118

[0381] The title compound was prepared from 1-methyl-3-(*o*-tolyl)-1H-indazole-7-carboxylic acid and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 3HCl following a

similar procedure as described in **Example 1**. LC-MS (Method 2): $t_R = 4.85$ min, m/z ($M+H$) $^+ = 555$.

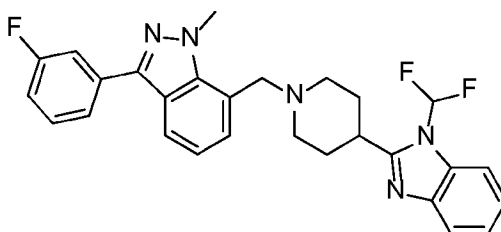
Example 119. 7-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(2-fluorophenyl)-1-methyl-1H-indazole (Cpd 119)



Cpd 119

[0382] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.74 (td, $J = 7.6, 1.8$ Hz, 1H), 7.64 (dd, $J = 7.8, 3.0$ Hz, 1H), 7.57 – 7.46 (m, 3H), 7.45 – 7.32 (m, 2H), 7.26 (d, $J = 6.9$ Hz, 1H), 7.21 – 7.08 (m, 3H), 4.51 (s, 3H), 4.15 (d, $J = 6.8$ Hz, 2H), 3.90 (s, 2H), 3.00 (d, $J = 11.0$ Hz, 3H), 2.31 – 2.17 (m, 2H), 1.89 (d, $J = 9.9$ Hz, 4H), 1.28 – 1.08 (m, 1H), 0.55 – 0.33 (m, 4H); LC-MS (Method 2): $t_R = 4.15$ min, m/z ($M+H$) $^+ = 494$.

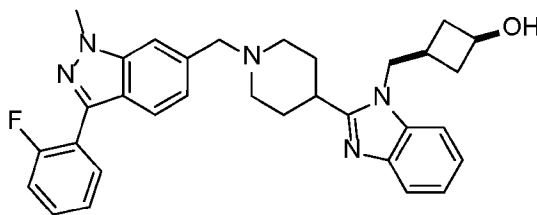
Example 120. 7-((4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 120)



Cpd 120

[0383] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.18 (t, $J = 57.5$ Hz, 1H), 7.99 (d, $J = 8.1$ Hz, 1H), 7.78 (d, $J = 7.7$ Hz, 1H), 7.70 – 7.61 (m, 3H), 7.55 (q, $J = 7.5$ Hz, 1H), 7.38 – 7.11 (m, 5H), 4.46 (s, 3H), 3.87 (s, 2H), 3.22 – 3.10 (m, 1H), 2.97 (d, $J = 11.2$ Hz, 2H), 2.27 – 2.13 (m, 2H), 1.97 – 1.74 (m, 4H); LC-MS (Method 2): $t_R = 4.81$ min, m/z ($M+H$) $^+ = 490$.

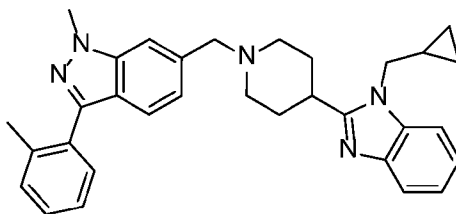
Example 121. (1s,3s)-3-((2-(1-((3-(2-fluorophenyl)-1-methyl-1H-indazol-6-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol (Cpd 121)



Cpd 121

[0384] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and (1s,3s)-3-((2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.76 (t, J = 7.6 Hz, 1H), 7.68 (dd, J = 8.4, 3.2 Hz, 1H), 7.61 (s, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.42 – 7.29 (m, 2H), 7.22 (d, J = 8.4 Hz, 1H), 7.17 – 7.09 (m, 2H), 4.98 (d, J = 6.3 Hz, 1H), 4.21 (d, J = 6.3 Hz, 2H), 4.12 (s, 3H), 3.82 (q, J = 7.1 Hz, 1H), 3.69 (s, 2H), 3.05 – 2.82 (m, 3H), 2.25 – 2.02 (m, 5H), 1.95 (td, J = 12.8, 9.4 Hz, 2H), 1.81 (d, J = 12.7 Hz, 2H), 1.62 – 1.51 (m, 2H); LC-MS (Method 2): t_R = 3.78 min, m/z ($M+H$) $^+$ = 524.

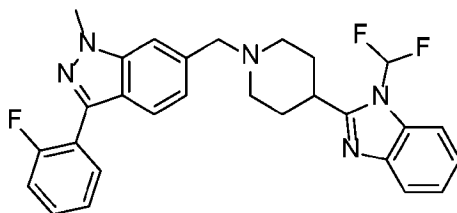
Example 122. 6-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-methyl-3-(o-tolyl)-1H-indazole (Cpd 122)



Cpd 122

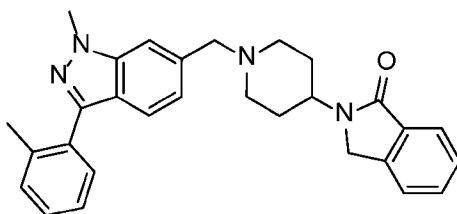
[0385] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-6-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.60 (s, 1H), 7.57 – 7.49 (m, 3H), 7.47 (dd, J = 6.6, 2.3 Hz, 1H), 7.37 – 7.28 (m, 3H), 7.22 – 7.08 (m, 3H), 4.12 (d, J = 6.8 Hz, 2H), 4.09 (s, 3H), 3.69 (s, 2H), 3.10 – 2.88 (m, 3H), 2.35 (s, 3H), 2.19 (t, J = 11.8 Hz, 2H), 1.96 (q, J = 12.0 Hz, 2H), 1.84 (d, J = 12.7 Hz, 2H), 1.15 (h, J = 6.0 Hz, 1H), 0.47 (dd, J = 7.7, 4.8 Hz, 2H), 0.40 (t, J = 4.7 Hz, 2H); LC-MS (Method 2): t_R = 4.25 min, m/z ($M+H$) $^+$ = 490.

Example 123. 6-((4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(2-fluorophenyl)-1-methyl-1H-indazole (Cpd 123)

**Cpd 123**

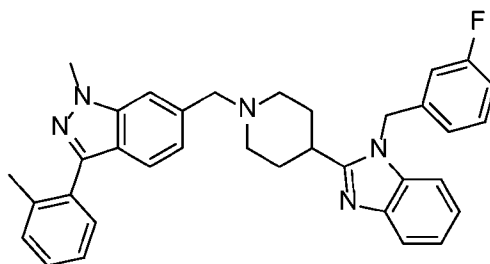
[0386] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.16 (t, J = 57.4 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.71 – 7.62 (m, 3H), 7.61 (s, 1H), 7.48 (q, J = 7.0 Hz, 1H), 7.41 – 7.26 (m, 4H), 7.21 (d, J = 8.4 Hz, 1H), 4.11 (s, 3H), 3.69 (s, 2H), 3.12 (dt, J = 10.0, 4.8 Hz, 1H), 2.97 (d, J = 11.1 Hz, 2H), 2.18 (td, J = 10.9, 3.9 Hz, 2H), 2.00 – 1.82 (m, 4H); LC-MS (Method 2): t_R = 4.66 min, m/z ($M+H$) $^+$ = 490.

Example 124. 2-(1-((1-methyl-3-(o-tolyl)-1H-indazol-6-yl)methyl)piperidin-4-yl)isoindolin-1-one (Cpd 124)

**Cpd 124**

[0387] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-6-carbaldehyde and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.65 (d, J = 7.5 Hz, 1H), 7.60 – 7.50 (m, 4H), 7.47 – 7.44 (m, 2H), 7.39 – 7.27 (m, 3H), 7.17 (d, J = 8.4 Hz, 1H), 4.46 (s, 2H), 4.08 (s, 3H), 4.07 – 4.00 (m, 1H), 3.65 (s, 2H), 2.96 (d, J = 11.1 Hz, 2H), 2.34 (s, 3H), 2.13 (t, J = 11.5 Hz, 2H), 1.82 (q, J = 11.6 Hz, 2H), 1.69 (d, J = 12.0 Hz, 2H); LC-MS (Method 2): t_R = 4.36 min, m/z ($M+H$) $^+$ = 451.

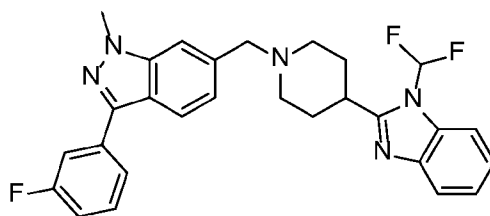
Example 125. 6-((4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-methyl-3-(o-tolyl)-1H-indazole (Cpd 125)



Cpd 125

[0388] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-6-carbaldehyde and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.62 – 7.55 (m, 2H), 7.52 (d, J = 8.3 Hz, 1H), 7.46 (dd, J = 6.6, 2.2 Hz, 1H), 7.42 – 7.26 (m, 5H), 7.18 – 7.11 (m, 3H), 7.07 (td, J = 8.7, 2.6 Hz, 1H), 6.90 (d, J = 10.0 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 5.54 (s, 2H), 4.08 (s, 3H), 3.64 (s, 2H), 2.98 – 2.90 (m, 3H), 2.34 (s, 3H), 2.09 (t, J = 11.6 Hz, 2H), 1.90 (q, J = 11.5 Hz, 2H), 1.69 (d, J = 12.7 Hz, 2H); LC-MS (Method 2): t_R = 4.68 min, m/z ($M+H$) $^+$ = 544.

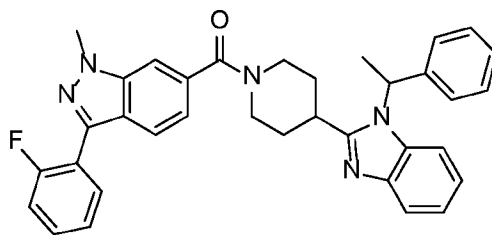
Example 126. 6-((4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 126)



Cpd 126

[0389] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.16 (t, J = 57.4 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.74 – 7.59 (m, 4H), 7.55 (q, J = 7.6 Hz, 1H), 7.34 – 7.24 (m, 3H), 7.21 (td, J = 8.6, 2.6 Hz, 1H), 4.10 (s, 3H), 3.69 (s, 2H), 3.20 – 3.07 (m, 1H), 2.97 (d, J = 11.0 Hz, 2H), 2.18 (dt, J = 11.1, 5.9 Hz, 2H), 1.97 – 1.89 (m, 4H); LC-MS (Method 2): t_R = 4.83 min, m/z ($M+H$) $^+$ = 490.

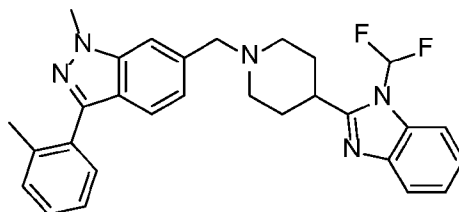
Example 127. (3-(2-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-(1-phenylethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 127)



Cpd 127

[0390] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 1-(1-phenylethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.84 – 7.73 (m, 3H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.50 (q, *J* = 7.0 Hz, 1H), 7.44 – 7.18 (m, 8H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.04 – 6.94 (m, 2H), 6.09 (q, *J* = 7.0 Hz, 1H), 4.60 (br s, 1H), 4.16 (s, 3H), 3.73 (br s, 1H), 3.51 – 3.41 (m, 1H), 3.32 – 2.92 (m, 2H), 2.11 – 1.65 (m, 7H; LC-MS (Method 2): *t*_R = 4.98 min, *m/z* (M+H)⁺ = 558.

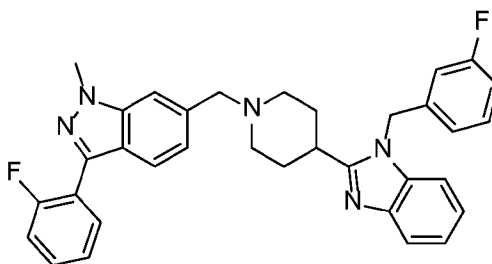
Example 128. 6-((4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-methyl-3-(o-tolyl)-1H-indazole (Cpd 128)



Cpd 128

[0391] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-6-carbaldehyde and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.16 (t, *J* = 57.5 Hz, 1H), 7.71 – 7.61 (m, 2H), 7.59 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 6.6, 2.2 Hz, 1H), 7.40 – 7.26 (m, 5H), 7.17 (d, *J* = 8.4 Hz, 1H), 4.09 (s, 3H), 3.68 (s, 2H), 3.13 (dq, *J* = 10.9, 5.9 Hz, 1H), 2.98 (d, *J* = 11.0 Hz, 2H), 2.34 (s, 3H), 2.18 (td, *J* = 11.1, 4.3 Hz, 2H), 2.00 – 1.83 (m, 4H); LC-MS (Method 2): *t*_R = 4.80 min, *m/z* (M+H)⁺ = 486.

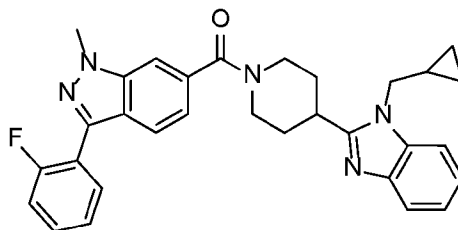
Example 129. 6-((4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(2-fluorophenyl)-1-methyl-1H-indazole (Cpd 129)



Cpd 129

[0392] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.79 – 7.71 (m, 1H), 7.67 (dd, J = 8.5, 3.2 Hz, 1H), 7.60 – 7.58 (m, 2H), 7.52 – 7.44 (m, 1H), 7.44 – 7.28 (m, 4H), 7.19 (d, J = 8.4 Hz, 1H), 7.17 – 7.11 (m, 2H), 7.07 (td, J = 8.6, 2.6 Hz, 1H), 6.90 (d, J = 9.9 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 5.54 (s, 2H), 4.10 (s, 3H), 3.65 (s, 2H), 2.98 – 2.87 (m, 3H), 2.09 (t, J = 11.6 Hz, 2H), 1.91 (qd, J = 11.6, 6.0 Hz, 2H), 1.69 (d, J = 12.7 Hz, 2H); LC-MS (Method 2): t_R = 4.51 min, m/z ($M+H$) $^+$ = 548.

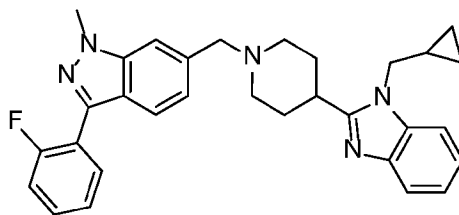
Example 130. (4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(2-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 130)



Cpd 130

[0393] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.83 (s, 1H), 7.82 – 7.74 (m, 2H), 7.56 – 7.48 (m, 3H), 7.43 – 7.31 (m, 2H), 7.23 (d, J = 8.4 Hz, 1H), 7.19 – 7.12 (m, 2H), 4.62 (br s, 1H), 4.17 – 4.15 (m, 5H), 3.76 (br s, 1H), 3.40 – 3.00 (m, 3H), 2.11 – 1.74 (m, 4H), 1.18 (p, J = 6.4 Hz, 1H), 0.54 – 0.36 (m, 4H); LC-MS (Method 2): t_R = 4.62 min, m/z ($M+H$) $^+$ = 508.

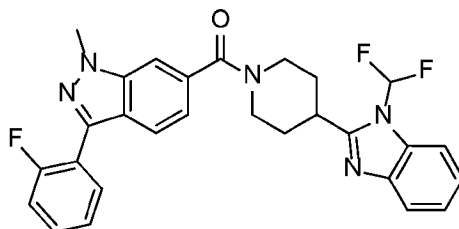
Example 131. 6-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(2-fluorophenyl)-1-methyl-1H-indazole (Cpd 131)



Cpd 131

[0394] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.76 (td, $J = 7.6, 1.8$ Hz, 1H), 7.68 (dd, $J = 8.4, 3.2$ Hz, 1H), 7.61 (s, 1H), 7.54 – 7.45 (m, 3H), 7.42 – 7.29 (m, 2H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.18 – 7.08 (m, 2H), 4.15 – 4.08 (m, 5H), 3.70 (s, 2H), 3.06 – 2.87 (m, 3H), 2.19 (t, $J = 11.5$ Hz, 2H), 1.96 (qd, $J = 12.3, 3.6$ Hz, 2H), 1.84 (d, $J = 12.7$ Hz, 2H), 1.15 (h, $J = 6.1$ Hz, 1H), 0.48 (dd, $J = 7.0, 2.8$ Hz, 2H), 0.40 (t, $J = 4.8$ Hz, 2H); LC-MS (Method 2): $t_R = 4.11$ min, m/z ($M+H$) $^+ = 494$.

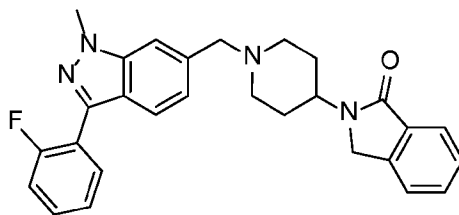
Example 132. (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(2-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 132)



Cpd 132

[0395] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.22 (t, $J = 57.4$ Hz, 1H), 7.83 (s, 1H), 7.80 – 7.75 (m, 2H), 7.67 (dd, $J = 8.9, 5.9$ Hz, 2H), 7.52 – 7.48 (m, 1H), 7.44 – 7.27 (m, 4H), 7.23 (d, $J = 8.4$ Hz, 1H), 4.63 (br s, 1H), 4.16 (s, 3H), 3.77 (br s, 1H), 3.53 – 3.43 (m, 1H), 3.35 – 2.94 (m, 2H), 2.18 – 1.78 (m, 4H); LC-MS (Method 2): $t_R = 5.75$ min, m/z ($M+H$) $^+ = 504$.

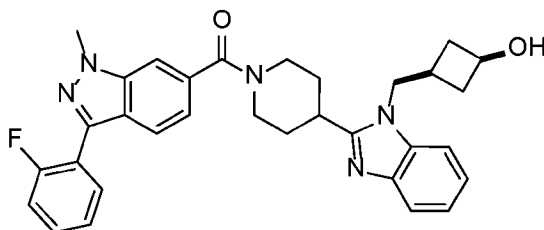
Example 133. 2-(1-((3-(2-fluorophenyl)-1-methyl-1H-indazol-6-yl)methyl)piperidin-4-yl)isoindolin-1-one (Cpd 133)



Cpd 133

[0396] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.76 (td, J = 7.6, 1.7 Hz, 1H), 7.69 – 7.64 (m, 2H), 7.61 – 7.54 (m, 3H), 7.51 – 7.43 (m, 2H), 7.41 – 7.29 (m, 2H), 7.21 (d, J = 8.4 Hz, 1H), 4.46 (s, 2H), 4.11 (s, 3H), 4.08 – 3.96 (m, 1H), 3.65 (s, 2H), 2.96 (d, J = 11.0 Hz, 2H), 2.13 (t, J = 11.6 Hz, 2H), 1.82 (qd, J = 12.2, 3.8 Hz, 2H), 1.69 (dd, J = 12.2, 3.9 Hz, 2H); LC-MS (Method 2): t_R = 4.19 min, m/z ($M+H$) $^+$ = 455.

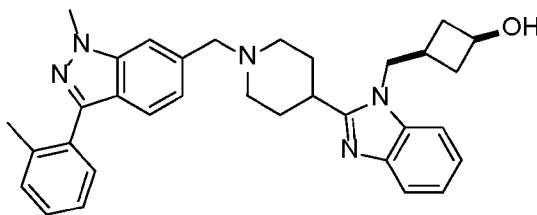
Example 134. (3-(2-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-(((1s,3s)-3-hydroxycyclobutyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 134)



Cpd 134

[0397] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and (1s,3s)-3-((2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.83 (s, 1H), 7.82 – 7.72 (m, 2H), 7.59 – 7.45 (m, 3H), 7.44 – 7.31 (m, 2H), 7.23 (d, J = 8.4 Hz, 1H), 7.20 – 7.08 (m, 2H), 4.99 (d, J = 6.2 Hz, 1H), 4.62 (br s, 1H), 4.26 (d, J = 6.3 Hz, 2H), 4.10 (s, 3H), 3.88 – 3.68 (m, 2H), 3.35 – 2.98 (m, 3H), 2.22 – 1.69 (m, 7H), 1.65 – 1.54 (m, 2H); LC-MS (Method 2): t_R = 4.18 min, m/z ($M+H$) $^+$ = 538.

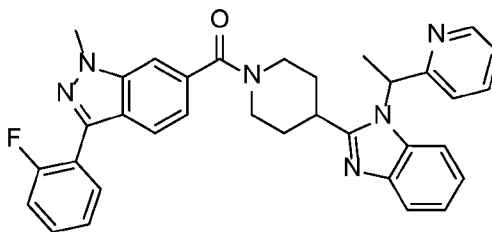
Example 135. (1s,3s)-3-((2-(1-((1-methyl-3-(o-tolyl)-1H-indazol-6-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol (Cpd 135)



Cpd 135

[0398] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-6-carbaldehyde and (1s,3s)-3-((2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.59 (s, 1H), 7.53 (t, *J* = 8.6 Hz, 2H), 7.49 – 7.43 (m, 2H), 7.38 – 7.28 (m, 3H), 7.19 – 7.09 (m, 3H), 4.98 (d, *J* = 6.3 Hz, 1H), 4.21 (d, *J* = 6.3 Hz, 2H), 4.09 (s, 3H), 3.83 (q, *J* = 7.1 Hz, 1H), 3.69 (s, 2H), 3.05 – 2.83 (m, 3H), 2.35 (s, 3H), 2.22 – 2.11 (m, 4H), 2.11 – 2.02 (m, 1H), 1.95 (q, *J* = 11.9 Hz, 2H), 1.81 (d, *J* = 12.9 Hz, 2H), 1.62 – 1.51 (m, 2H); LC-MS (Method 2): *t*_R = 3.89 min, *m/z* (M+H)⁺ = 520.

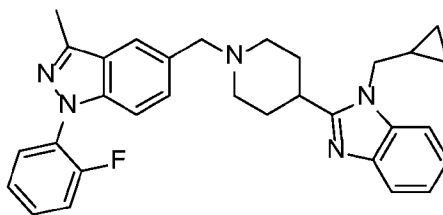
Example 136. (3-(2-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 136)



Cpd 136

[0399] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.57 (d, *J* = 4.8 Hz, 1H), 7.85 – 7.68 (m, 4H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 7.8, 5.4 Hz, 1H), 7.44 – 7.32 (m, 2H), 7.29 (dd, *J* = 7.5, 5.0 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.11 – 7.02 (m, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.13 (q, *J* = 7.0 Hz, 1H), 4.62 (br s, 1H), 4.16 (s, 3H), 3.74 (br s, 1H), 3.57 – 3.44 (m, 1H), 3.33 – 2.93 (m, 2H), 2.18 – 1.64 (m, 7H); LC-MS (Method 2): *t*_R = 4.63 min, *m/z* (M+H)⁺ = 559.

Example 137. 5-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-(2-fluorophenyl)-3-methyl-1H-indazole (Cpd 137)



Cpd 137

STEP 1: Synthesis of methyl 1-(2-fluorophenyl)-3-methyl-1H-indazole-5-carboxylate

[0400] The material, methyl 1-(2-fluorophenyl)-3-methyl-1H-indazole-5-carboxylate, was prepared from methyl 3-methyl-1H-indazole-5-carboxylate and 1-bromo-2-fluorobenzene following a similar procedure as described in the synthesis of **Int-71** (STEP 1). LC-MS (Method 1): $t_R = 3.24$ min, m/z ($M+H$) $^+ = 285$.

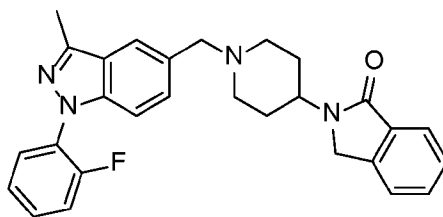
STEP 2: Synthesis of 1-(2-fluorophenyl)-3-methyl-1H-indazole-5-carbaldehyde

[0401] The material, 1-(2-fluorophenyl)-3-methyl-1H-indazole-5-carbaldehyde, was prepared from methyl 1-(2-fluorophenyl)-3-methyl-1H-indazole-5-carboxylate following a similar procedure as described in the synthesis of **Int-30**. LC-MS (Method 1): $t_R = 3.33$ min, m/z ($M+H$) $^+ = 255$.

STEP 3: Synthesis of 5-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-(2-fluorophenyl)-3-methyl-1H-indazole (Cpd 137)

[0402] The title compound was prepared from 1-(2-fluorophenyl)-3-methyl-1H-indazole-5-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.72 (s, 1H), 7.68 – 7.59 (m, 1H), 7.54 – 7.49 (m, 4H), 7.46 (dd, $J = 8.7, 1.5$ Hz, 1H), 7.39 (ddd, $J = 8.5, 5.3, 3.8$ Hz, 1H), 7.30 (dd, $J = 8.6, 3.3$ Hz, 1H), 7.13 (pd, $J = 7.2, 1.4$ Hz, 2H), 4.11 (d, $J = 6.8$ Hz, 2H), 3.65 (s, 2H), 2.96 (d, $J = 11.4$ Hz, 3H), 2.57 (s, 3H), 2.21 – 2.11 (m, 2H), 1.99 – 1.87 (m, 2H), 1.83 (d, $J = 12.7$ Hz, 2H), 1.24 – 1.06 (m, 1H), 0.53 – 0.35 (m, 4H); LC-MS (Method 2): $t_R = 4.06$ min, m/z ($M+H$) $^+ = 494$.

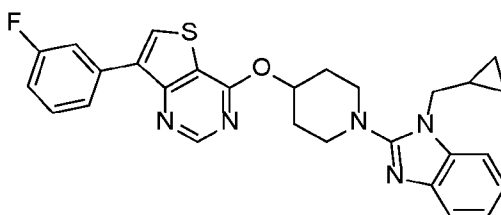
Example 138. 2-(1-((1-(2-fluorophenyl)-3-methyl-1H-indazol-5-yl)methyl)piperidin-4-yl)isoindolin-1-one (Cpd 138)



Cpd 138

[0403] The title compound was prepared from 1-(2-fluorophenyl)-3-methyl-1H-indazole-5-carbaldehyde and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.74 – 7.65 (m, 2H), 7.65 – 7.60 (m, 1H), 7.60 – 7.54 (m, 2H), 7.54 – 7.42 (m, 4H), 7.42 – 7.27 (m, 2H), 4.45 (s, 2H), 4.11 – 3.93 (m, 1H), 3.61 (s, 2H), 2.94 (d, *J* = 11.2 Hz, 2H), 2.57 (s, 3H), 2.20 – 2.00 (m, 2H), 1.89 (s, 1H), 1.86 – 1.73 (m, 1H), 1.69 (d, *J* = 10.5 Hz, 2H); LC-MS (Method 2): *t*_R = 4.12 min, *m/z* (M+H)⁺ = 455.

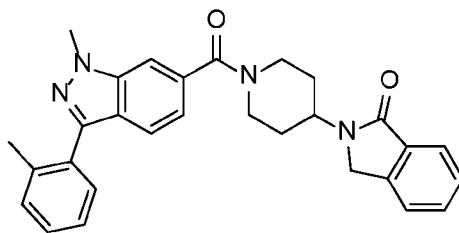
Example 139. 4-((1-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-7-(3-fluorophenyl)thieno[3,2-d]pyrimidine (Cpd 139)



Cpd 139

[0404] The title compound was prepared from 7-(3-fluorophenyl)-4-(piperidin-4-yloxy)thieno[3,2-d]pyrimidine, 2HCl and 2-chloro-1-(cyclopropylmethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.90 (s, 1H), 8.73 (s, 1H), 8.04 (ddd, *J* = 10.9, 2.8, 1.4 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.54 (q, *J* = 7.6 Hz, 1H), 7.49 – 7.38 (m, 2H), 7.23 (td, *J* = 8.6, 2.6 Hz, 1H), 7.13 – 7.05 (m, 2H), 5.64 (tt, *J* = 7.9, 3.9 Hz, 1H), 3.97 (d, *J* = 6.8 Hz, 2H), 3.48 (dt, *J* = 11.4, 4.3 Hz, 2H), 3.23 (ddd, *J* = 12.4, 8.7, 3.2 Hz, 2H), 2.30 – 2.19 (m, 2H), 2.03 (dtd, *J* = 12.3, 8.3, 3.4 Hz, 2H), 1.22 (h, *J* = 5.1 Hz, 1H), 0.47 (dd, *J* = 8.0, 3.8 Hz, 2H), 0.41 (d, *J* = 4.9 Hz, 2H); LC-MS (Method 2): *t*_R = 5.43 min, *m/z* (M+H)⁺ = 500.

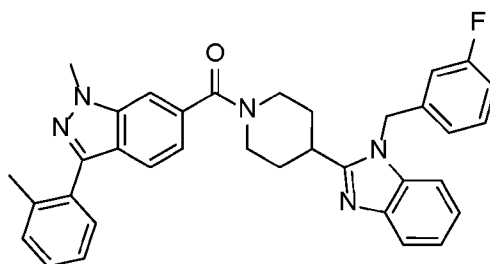
Example 140. 2-(1-(1-methyl-3-(o-tolyl)-1H-indazole-6-carbonyl)piperidin-4-yl)isoindolin-1-one (Cpd 140)



Cpd 140

[0405] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-6-carboxylic acid and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.79 (s, 1H), 7.66 (t, J = 8.7 Hz, 2H), 7.59 (d, J = 4.2 Hz, 2H), 7.50-7.45 (m, 2H), 7.39-7.30 (m, 3H), 7.19 (d, J = 8.3 Hz, 1H), 4.67 (br s, 1H), 4.50 (s, 2H), 4.38-4.27 (m, 1H), 4.13 (s, 3H), 3.72 (br s, 1H), 3.25 (br s, 1H), 2.95 (br s, 1H), 2.35 (s, 3H), 1.92-1.64 (m, 4H); LC-MS (Method 2): t_R = 5.39 min, m/z ($M+H$) $^+$ = 465.

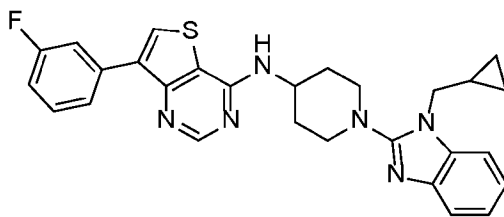
Example 141. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-methyl-3-(o-tolyl)-1H-indazol-6-yl)methanone (Cpd 141)



Cpd 141

[0406] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-6-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.78 (s, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.50 – 7.45 (m, 1H), 7.42 – 7.27 (m, 5H), 7.21 – 7.11 (m, 3H), 7.11 – 7.04 (m, 1H), 6.94 (d, J = 9.9 Hz, 1H), 6.85 (d, J = 7.7 Hz, 1H), 5.58 (s, 2H), 4.57 (br s, 1H), 4.13 (s, 3H), 3.73 (br s, 1H), 3.40 – 3.33 (m, 1H), 3.20 (br s, 1H), 3.00 (br s, 1H), 2.34 (s, 3H), 2.01 – 1.59 (m, 4H); LC-MS (Method 2): t_R = 5.05 min, m/z ($M+H$) $^+$ = 558.

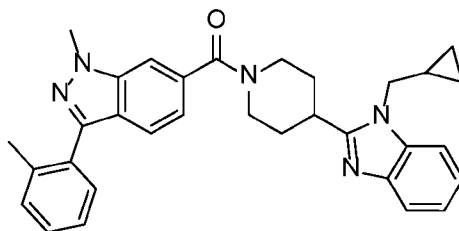
Example 142. N-(1-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-7-(3-fluorophenyl)thieno[3,2-d]pyrimidin-4-amine (Cpd 142)



Cpd 142

[0407] The title compound was prepared from 7-(3-fluorophenyl)-N-(piperidin-4-yl)thieno[3,2-d]pyrimidin-4-amine, 2HCl and 2-chloro-1-(cyclopropylmethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.57 (s, 1H), 8.48 (s, 1H), 8.04 (ddd, *J* = 11.0, 2.8, 1.4 Hz, 1H), 7.92 (dd, *J* = 7.8, 4.5 Hz, 2H), 7.54 – 7.37 (m, 3H), 7.19 (td, *J* = 8.6, 2.6 Hz, 1H), 7.13 – 7.03 (m, 2H), 4.47 – 4.33 (m, 1H), 3.95 (d, *J* = 6.8 Hz, 2H), 3.56 (d, *J* = 12.6 Hz, 2H), 3.06 (t, *J* = 12.2 Hz, 2H), 2.03 (d, *J* = 12.4 Hz, 2H), 1.86 (qd, *J* = 12.3, 3.8 Hz, 2H), 1.26 – 1.12 (m, 1H), 0.52 – 0.42 (m, 2H), 0.41 (d, *J* = 4.7 Hz, 2H); LC-MS (Method 2): *t*_R = 4.20 min, *m/z* (M+H)⁺ = 499.

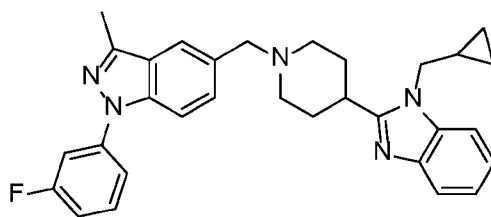
Example 143. (4-(1-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-methyl-3-(o-tolyl)-1H-indazol-6-yl)methanone (Cpd 143)



Cpd 143

[0408] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-6-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.80 (s, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.48 (dd, *J* = 6.8, 2.1 Hz, 1H), 7.40 – 7.28 (m, 3H), 7.19 – 7.12 (m, 3H), 4.62 (br s, 1H), 4.17 – 4.14 (m, 5H), 3.78 (br s, 1H), 3.40 – 3.00 (m, 3H), 2.35 (s, 3H), 2.09 – 1.70 (m, 4H), 1.28 – 1.13 (m, 1H), 0.55 – 0.36 (m, 4H); LC-MS (Method 2): *t*_R = 4.81 min, *m/z* (M+H)⁺ = 504.

Example 144. 5-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-(3-fluorophenyl)-3-methyl-1H-indazole (Cpd 144)



Cpd 144

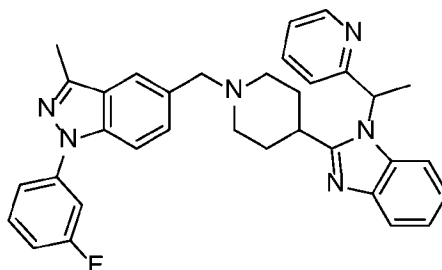
STEP 1: Synthesis of 1-(3-fluorophenyl)-3-methyl-1H-indazole-5-carbaldehyde

[0409] The material, 1-(3-fluorophenyl)-3-methyl-1H-indazole-5-carbaldehyde, was prepared from methyl 1-(3-fluorophenyl)-3-methyl-1H-indazole-5-carboxylate following a similar procedure as described in the synthesis of **Int-30**. LC-MS (Method 1): $t_R = 3.54$ min, m/z $(M+H)^+ = 255$.

STEP 2: Synthesis of 5-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-(3-fluorophenyl)-3-methyl-1H-indazole (Cpd 144)

[0410] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-1H-indazole-5-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.88 (d, $J = 8.6$ Hz, 1H), 7.76 (s, 1H), 7.69 – 7.51 (m, 6H), 7.23 – 7.09 (m, 3H), 4.13 (d, $J = 6.8$ Hz, 2H), 3.68 (s, 2H), 2.98 (d, $J = 11.4$ Hz, 3H), 2.60 (s, 3H), 2.19 (t, $J = 11.5$ Hz, 2H), 1.97 (s, 1H), 1.95 – 1.81 (m, 3H), 1.21 – 1.06 (m, 1H), 0.54 – 0.43 (m, 2H), 0.46 – 0.37 (m, 2H); LC-MS (Method 2): $t_R = 4.22$ min, m/z $(M+H)^+ = 494$.

Example 145. 1-(3-fluorophenyl)-3-methyl-5-((4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1H-indazole (Cpd 145)

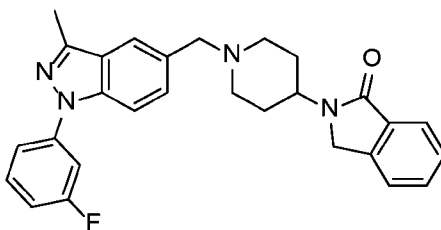


Cpd 145

[0411] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-1H-indazole-5-carbaldehyde and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 3HCl

following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.58 (dt, $J = 4.7, 1.2$ Hz, 1H), 7.87 (d, $J = 8.7$ Hz, 1H), 7.80 – 7.69 (m, 2H), 7.69 – 7.47 (m, 5H), 7.35 – 7.24 (m, 1H), 7.18 (dd, $J = 10.5, 7.1$ Hz, 2H), 7.13 – 7.03 (m, 2H), 7.03 – 6.93 (m, 1H), 6.08 (q, $J = 7.0$ Hz, 1H), 3.66 (s, 2H), 3.17 – 2.86 (m, 4H), 2.59 (s, 3H), 2.11 (dd, $J = 19.6, 10.3$ Hz, 2H), 2.05 – 1.81 (m, 5H), 1.76 (dd, $J = 23.4, 13.7$ Hz, 1H); LC-MS (Method 2): $t_R = 4.30$ min, m/z ($M+H$) $^+ = 545$.

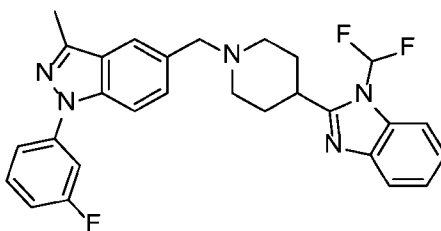
Example 146. 2-((1-((1-(3-fluorophenyl)-3-methyl-1H-indazol-5-yl)methyl)piperidin-4-yl)isoindolin-1-one (Cpd 146)



Cpd 146

[0412] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-1H-indazole-5-carbaldehyde and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.85 (d, $J = 8.7$ Hz, 1H), 7.72 (s, 1H), 7.67 – 7.62 (m, 2H), 7.61 – 7.54 (m, 4H), 7.50 (dd, $J = 8.7, 1.5$ Hz, 1H), 7.48 – 7.43 (m, 1H), 7.21 – 7.11 (m, 1H), 4.46 (s, 2H), 4.02 (tt, $J = 11.6, 4.2$ Hz, 1H), 3.62 (s, 2H), 2.94 (d, $J = 11.1$ Hz, 2H), 2.57 (s, 3H), 2.11 (td, $J = 11.9, 2.4$ Hz, 2H), 1.84 – 1.77 (m, 2H), 1.69 (dd, $J = 12.6, 4.0$ Hz, 2H); LC-MS (Method 2): $t_R = 4.36$ min, m/z ($M+H$) $^+ = 455$.

Example 147. 5-((4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-(3-fluorophenyl)-3-methyl-1H-indazole (Cpd 147)

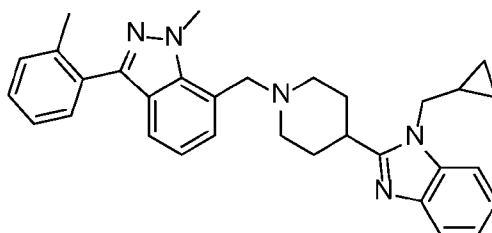


Cpd 147

[0413] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-1H-indazole-5-carbaldehyde and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.33 – 8.01 (m, 3H), 7.75 – 7.59 (m, 6H), 7.38 – 7.30 (m, 2H), 7.27 – 7.20 (m, 1H), 4.53 (d, $J = 4.6$ Hz, 2H),

3.07 (q, $J = 11.3$ Hz, 2H), 2.64 (s, 3H), 2.27 – 2.13 (m, 4H); LC-MS (Method 2): $t_R = 4.83$ min, m/z (M+H) $^+ = 490$.

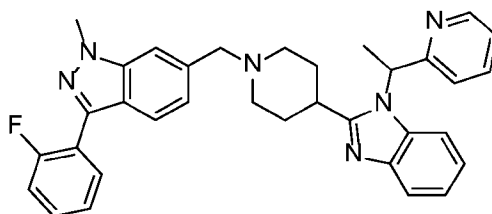
Example 148. 7-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-methyl-3-(o-tolyl)-1H-indazole (Cpd 148)



Cpd 148

[0414] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-7-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.55 – 7.42 (m, 4H), 7.39 – 7.35 (m, 1H), 7.35 – 7.27 (m, 2H), 7.22 (d, $J = 6.9$ Hz, 1H), 7.17 – 7.09 (m, 2H), 7.06 (dd, $J = 8.1, 6.9$ Hz, 1H), 4.46 (s, 3H), 4.14 (d, $J = 6.8$ Hz, 2H), 3.88 (s, 2H), 3.00 (d, $J = 11.3$ Hz, 3H), 2.33 (s, 3H), 2.24 (td, $J = 11.2, 4.5$ Hz, 2H), 1.88 (d, $J = 6.5$ Hz, 5H), 1.23 – 1.11 (m, 1H), 0.50 (dd, $J = 3.4, 2.2$ Hz, 1H), 0.41 (dt, $J = 5.2, 2.8$ Hz, 2H); LC-MS (Method 2): $t_R = 4.31$ min, m/z (M+H) $^+ = 490$.

Example 149. 3-(2-fluorophenyl)-1-methyl-6-((4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1H-indazole (Cpd 149)

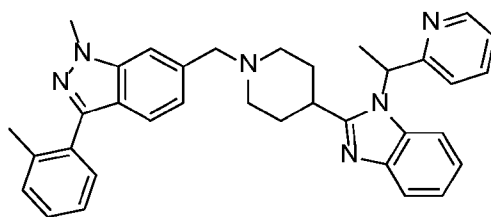


Cpd 149

[0415] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.56 (d, $J = 4.8$ Hz, 1H), 7.79 – 7.74 (m, 1H), 7.72 (d, $J = 8.4$ Hz, 1H), 7.67 (dd, $J = 8.6, 3.2$ Hz, 1H), 7.60 (s, 1H), 7.54 (d, $J = 7.9$ Hz, 1H), 7.48 (q, $J = 7.0$ Hz, 1H), 7.42 – 7.36 (m, 1H), 7.34 (d, $J = 7.7$ Hz, 1H), 7.29 (dt, $J = 7.3, 4.1$ Hz, 1H), 7.22 – 7.17 (m, 2H), 7.11 – 7.02 (m, 2H), 6.97 (t, $J = 7.6$ Hz, 1H), 6.07 (q, $J = 7.1$ Hz, 1H), 4.11 (s, 3H), 3.67 (s, 2H), 3.16 – 2.86 (m, 3H),

2.21 – 1.84 (m, 5H), 1.91 (d, $J = 7.1$ Hz, 3H), 1.72 (d, $J = 12.8$ Hz, 1H); LC-MS (Method 2): $t_R = 4.21$ min, m/z (M+H)⁺ = 545.

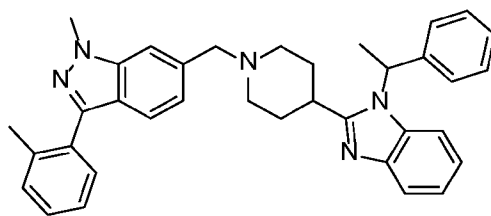
Example 150. 1-methyl-6-((4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(o-tolyl)-1H-indazole (Cpd 150)



Cpd 150

[0416] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-6-carbaldehyde and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.56 (d, $J = 4.8$ Hz, 1H), 7.73 (td, $J = 7.7, 1.7$ Hz, 1H), 7.58 (s, 1H), 7.53 (d, $J = 8.1$ Hz, 2H), 7.46 (dd, $J = 6.6, 2.2$ Hz, 1H), 7.37 – 7.28 (m, 4H), 7.17 (dd, $J = 8.3, 4.3$ Hz, 2H), 7.11 – 7.02 (m, 2H), 6.97 (t, $J = 7.6$ Hz, 1H), 6.07 (q, $J = 7.0$ Hz, 1H), 4.08 (s, 3H), 3.66 (s, 2H), 3.12 – 2.90 (m, 3H), 2.34 (s, 3H), 2.22 – 1.83 (m, 5H), 1.92 (d, $J = 7.0$ Hz, 3H), 1.72 (d, $J = 12.9$ Hz, 1H); LC-MS (Method 2): $t_R = 4.33$ min, m/z (M+H)⁺ = 541.

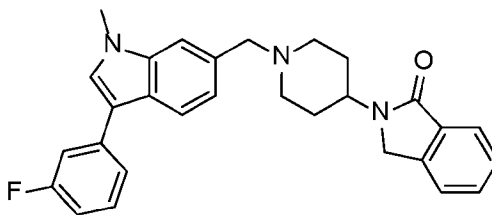
Example 151. 1-methyl-6-((4-(1-(1-phenylethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(o-tolyl)-1H-indazole (Cpd 151)



Cpd 151

[0417] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-6-carbaldehyde and 1-(1-phenylethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.57 – 7.52 (m, 3H), 7.46 (dd, $J = 6.5, 2.2$ Hz, 1H), 7.40 – 7.20 (m, 6H), 7.17 (t, $J = 7.1$ Hz, 3H), 7.10 – 7.02 (m, 2H), 6.97 (t, $J = 7.5$ Hz, 1H), 6.02 (q, $J = 7.0$ Hz, 1H), 4.08 (s, 3H), 3.66 (s, 2H), 3.08 – 2.89 (m, 3H), 2.34 (s, 3H), 2.22 – 1.81 (m, 5H), 1.89 (d, $J = 7.1$ Hz, 3H), 1.72 (d, $J = 12.7$ Hz, 1H); LC-MS (Method 2): $t_R = 4.72$ min, m/z (M+H)⁺ = 540.

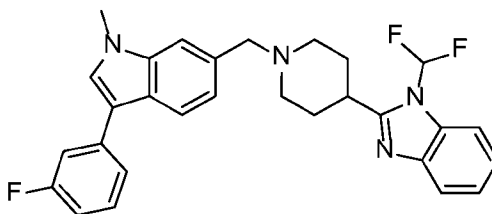
Example 152. 2-(1-((3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)methyl)piperidin-4-yl)isoindolin-1-one (Cpd 152)



Cpd 152

[0418] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.83 (d, J = 8.2 Hz, 1H), 7.76 (s, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.57 – 7.56 (m, 2H), 7.51 (d, J = 7.8 Hz, 1H), 7.49 – 7.39 (m, 4H), 7.14 (d, J = 8.2 Hz, 1H), 7.01 (td, J = 8.6, 2.5 Hz, 1H), 4.46 (s, 2H), 4.02 (ddd, J = 11.9, 7.7, 4.1 Hz, 1H), 3.82 (s, 3H), 3.61 (s, 2H), 2.96 (d, J = 11.1 Hz, 2H), 2.09 (t, J = 11.5 Hz, 2H), 1.81 (qd, J = 12.4, 3.8 Hz, 2H), 1.73 – 1.64 (m, 2H); LC-MS (Method 2): t_R = 4.72 min, m/z ($M+H$) $^+$ = 454.

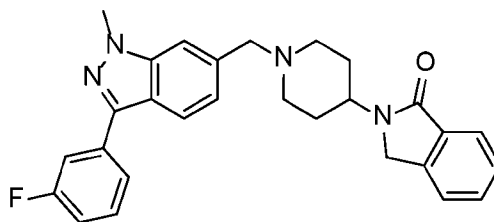
Example 153. 1-(difluoromethyl)-2-(1-((3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazole (Cpd 153)



Cpd 153

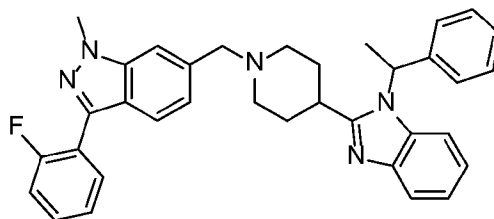
[0419] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.16 (t, J = 57.4 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.76 (s, 1H), 7.71 – 7.59 (m, 2H), 7.51 (d, J = 7.8 Hz, 1H), 7.48 – 7.38 (m, 3H), 7.34 – 7.25 (m, 2H), 7.14 (d, J = 8.2 Hz, 1H), 7.01 (td, J = 8.5, 2.5 Hz, 1H), 3.83 (s, 3H), 3.65 (s, 2H), 3.13 – 3.05 (m, 1H), 2.97 (d, J = 11.1 Hz, 2H), 2.19 – 2.08 (m, 2H), 1.92 – 1.87 (m, 4H); LC-MS (Method 2): t_R = 5.19 min, m/z ($M+H$) $^+$ = 489.

Example 154. 2-(1-((3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methyl)piperidin-4-yl)isoindolin-1-one (Cpd 154)

**Cpd 154**

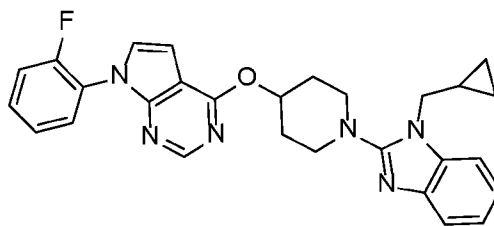
[0420] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 2-(piperidin-4-yl)isoindolin-1-one, HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.62 – 7.51 (m, 4H), 7.46 (dt, *J* = 8.1, 4.2 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.21 (td, *J* = 8.6, 2.6 Hz, 1H), 4.46 (s, 2H), 4.10 (s, 3H), 4.08 – 3.95 (m, 1H), 3.66 (s, 2H), 2.96 (d, *J* = 11.2 Hz, 2H), 2.13 (t, *J* = 11.5 Hz, 2H), 1.89 – 1.76 (m, 2H), 1.70 (d, *J* = 10.7 Hz, 2H); LC-MS (Method 2): *t*_R = 4.44 min, *m/z* (M+H)⁺ = 455.

Example 155. 3-(2-fluorophenyl)-1-methyl-6-((4-(1-(1-phenylethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1H-indazole (Cpd 155)

**Cpd 155**

[0421] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 1-(1-phenylethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.75 (t, *J* = 7.5 Hz, 1H), 7.67 (dd, *J* = 8.5, 3.2 Hz, 1H), 7.59 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.48 (q, *J* = 7.0 Hz, 1H), 7.42 – 7.14 (m, 8H), 7.11 – 7.00 (m, 2H), 7.00 – 6.93 (m, 1H), 6.02 (q, *J* = 7.0 Hz, 1H), 4.11 (s, 3H), 3.66 (s, 2H), 3.08 – 2.89 (m, 3H), 2.23 – 1.79 (m, 5H), 1.89 (d, *J* = 7.1 Hz, 3H), 1.72 (d, *J* = 12.7 Hz, 1H); LC-MS (Method 2): *t*_R = 4.56 min, *m/z* (M+H)⁺ = 544.

Example 156. 4-((1-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-7-(2-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine (Cpd 156)



Cpd 156

STEP 1: Synthesis of 4-chloro-7-(2-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine

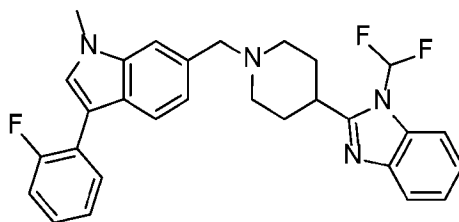
[0422] The material, 4-chloro-7-(2-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine, was prepared from 4-chloro-7H-pyrrolo[2,3-d]pyrimidine and 1-bromo-2-fluorobenzene following a similar procedure as described in **Int-71** (STEP 1). LC-MS (Method 1): $t_R = 3.515$ min, m/z ($M+H$) $^+ = 248$.

STEP 2: Synthesis of 4-((1-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-7-(2-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine (Cpd 156)

[0423] The material, 1-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-ol, was prepared from 2-chloro-1-(cyclopropylmethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 49** (STEP 1).

[0424] The title compound was prepared from 4-chloro-7-(2-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine and 1-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-ol following a similar procedure as described in **Example 49** (STEP 2). ^1H NMR (400 MHz, DMSO- d_6) δ 8.56 (s, 1H), 7.96 (d, $J = 3.7$ Hz, 1H), 7.89 (dq, $J = 10.7, 2.4$ Hz, 1H), 7.81 (ddd, $J = 8.2, 2.1, 0.9$ Hz, 1H), 7.70 (s, 1H), 7.63 (td, $J = 8.2, 6.6$ Hz, 1H), 7.57 – 7.49 (m, 1H), 7.33 (s, 2H), 7.27 (tdd, $J = 8.6, 2.6, 0.9$ Hz, 1H), 6.81 (dd, $J = 5.1, 3.7$ Hz, 1H), 5.69 – 5.63 (m, 1H), 4.14 (d, $J = 6.7$ Hz, 2H), 3.78 (s, 4H), 2.29 (s, 2H), 2.11 – 2.01 (m, 2H), 1.34 – 1.24 (m, 1H), 0.59 – 0.53 (m, 2H), 0.50 – 0.45 (m, 2H); LC-MS (Method 2): $t_R = 5.20$ min, m/z ($M+H$) $^+ = 483$.

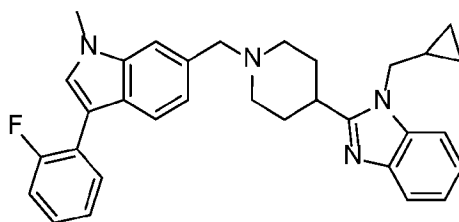
Example 157. 1-(difluoromethyl)-2-(1-((3-(2-fluorophenyl)-1-methyl-1H-indol-6-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazole (Cpd 157)



Cpd 157

[0425] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.16 (t, J = 57.4 Hz, 1H), 7.73 – 7.58 (m, 5H), 7.44 (s, 1H), 7.28 (dt, J = 7.2, 3.7 Hz, 5H), 7.11 (d, J = 8.2 Hz, 1H), 3.85 (s, 3H), 3.66 (s, 2H), 3.11 (p, J = 8.0 Hz, 1H), 2.97 (d, J = 11.1 Hz, 2H), 2.18 – 2.12 (m, 2H), 2.01 – 1.82 (m, 4H); LC-MS (Method 2): t_R = 5.16 min, m/z ($M+H$) $^+$ = 489.

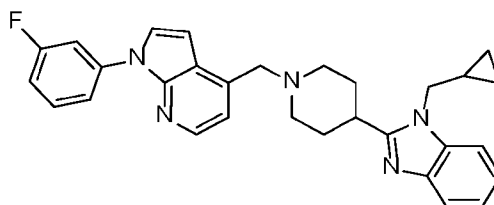
Example 158. 1-(cyclopropylmethyl)-2-(1-((3-(2-fluorophenyl)-1-methyl-1H-indol-6-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazole (Cpd 158)



Cpd 158

[0426] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.69 (dt, J = 8.1, 4.9 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.52 (t, J = 6.7 Hz, 2H), 7.44 (s, 1H), 7.33 – 7.22 (m, 3H), 7.17 – 7.09 (m, 3H), 4.11 (d, J = 6.8 Hz, 2H), 3.85 (s, 3H), 3.66 (s, 2H), 3.00 – 2.90 (m, 3H), 2.16 (t, J = 11.4 Hz, 2H), 1.94 (qd, J = 12.5, 3.8 Hz, 2H), 1.83 (d, J = 12.6 Hz, 2H), 1.14 (p, J = 7.0 Hz, 1H), 0.48 (q, J = 5.4 Hz, 2H), 0.39 (t, J = 4.8 Hz, 2H); LC-MS (Method 2): t_R = 4.50 min, m/z ($M+H$) $^+$ = 493.

Example 159. 1-(cyclopropylmethyl)-2-(1-((1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazole, 2TFA (Cpd 159)



Cpd 159

STEP 1: Synthesis of methyl 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carboxylate

[0427] The material, methyl 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carboxylate, was prepared from methyl 1H-pyrrolo[2,3-b]pyridine-4-carboxylate and 1-bromo-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-71** (STEP 1). LC-MS (Method 1): $t_R = 3.60$ min, m/z (M+H)⁺ = 271.

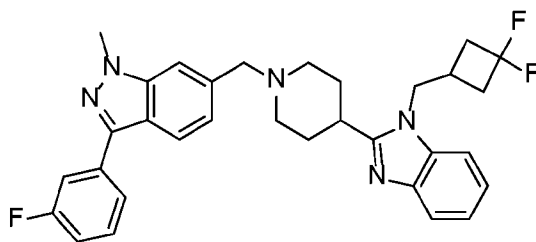
STEP 2: Synthesis of 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carbaldehyde

[0428] The material, 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carbaldehyde, was prepared from methyl 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carboxylate following a similar procedure in as described in the synthesis of **Int-30**. LC-MS (Method 1): $t_R = 3.43$ min, m/z (M+H)⁺ = 241.

STEP 3: Synthesis of 1-(cyclopropylmethyl)-2-(1-((1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazole, 2TFA (Cpd 159)

[0429] The title compound was prepared from 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.49 (d, $J = 4.8$ Hz, 1H), 8.22 (d, $J = 3.8$ Hz, 1H), 7.93 (dt, $J = 10.9, 2.3$ Hz, 1H), 7.84 (dd, $J = 7.9, 2.1$ Hz, 1H), 7.66 – 7.55 (m, 3H), 7.45 (d, $J = 4.9$ Hz, 1H), 7.21 (td, $J = 8.5, 3.7$ Hz, 3H), 7.14 (d, $J = 3.8$ Hz, 1H), 4.78 – 4.59 (m, 2H), 4.16 (d, $J = 7.0$ Hz, 2H), 3.62 (s, 2H), 3.27 (d, $J = 37.4$ Hz, 3H), 2.16 (d, $J = 17.3$ Hz, 4H), 1.19 (dd, $J = 14.2, 7.9$ Hz, 1H), 0.53 – 0.37 (m, 4H); LC-MS (Method 2): $t_R = 4.09$ min, m/z (M+H)⁺ = 480.

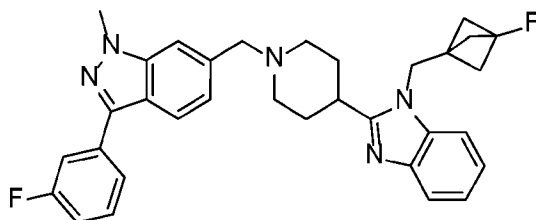
Example 160. 6-((4-(1-((3,3-difluorocyclobutyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 160)



Cpd 160

[0430] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 1-((3,3-difluorocyclobutyl)methyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.70 (dd, *J* = 10.5, 2.5 Hz, 1H), 7.62 (s, 1H), 7.59 – 7.51 (m, 3H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.25 – 7.09 (m, 3H), 4.38 (d, *J* = 5.5 Hz, 2H), 4.11 (s, 3H), 3.70 (s, 2H), 3.04 – 2.91 (m, 3H), 2.66 – 2.35 (m, 5H), 2.20 (t, *J* = 11.5 Hz, 2H), 1.95 (td, *J* = 12.8, 9.2 Hz, 2H), 1.82 (d, *J* = 12.7 Hz, 2H); LC-MS (Method 2): *t*_R = 4.60 min, *m/z* (M+H)⁺ = 544.

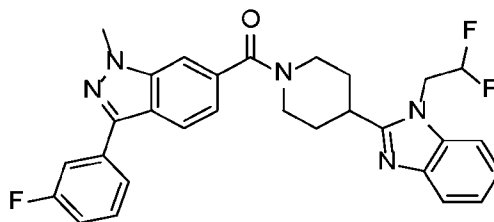
Example 161. 6-((4-(1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 161)



Cpd 161

[0431] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.70 (dd, *J* = 10.5, 2.6 Hz, 1H), 7.62 (s, 1H), 7.58 – 7.51 (m, 2H), 7.47 – 7.43 (m, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.21 (td, *J* = 8.6, 2.6 Hz, 1H), 7.17 – 7.10 (m, 2H), 4.57 (s, 2H), 4.11 (s, 3H), 3.70 (s, 2H), 2.97 (d, *J* = 11.0 Hz, 2H), 2.85 – 2.78 (m, 1H), 2.18 (t, *J* = 11.5 Hz, 2H), 2.02 – 1.86 (m, 8H), 1.80 (d, *J* = 12.6 Hz, 2H); LC-MS (Method 2): *t*_R = 4.56 min, *m/z* (M+H)⁺ = 538.

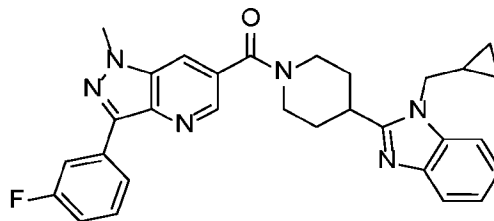
Example 162. (4-(1-(2,2-difluoroethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 162)



Cpd 162

[0432] The title compound was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone and 1,1-difluoro-2-iodoethane following a similar procedure as described in **Example 22** (STEP 2). ^1H NMR (400 MHz, DMSO- d_6) δ 8.16 (d, J = 8.4 Hz, 1H), 7.85 – 7.83 (m, 2H), 7.72 (dd, J = 10.4, 2.5 Hz, 1H), 7.59 – 7.53 (m, 3H), 7.31 – 7.14 (m, 4H), 6.43 (tt, J = 56.4, 4.0 Hz, 1H), 4.90 – 4.76 (m, 2H), 4.63 (br s, 1H), 4.16 (s, 3H), 3.76 (br s, 1H), 3.46 – 3.14 (m, 2H), 3.04 (br s, 1H), 2.11 – 1.69 (m, 4H); LC-MS (Method 2): t_R = 4.74 min, m/z ($M+H$) $^+$ = 518.

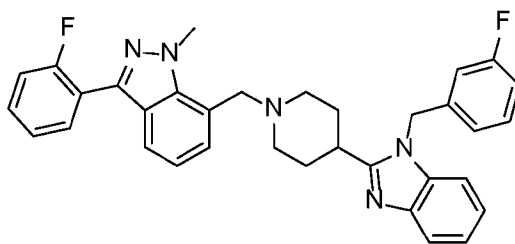
Example 163. (4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)methanone (Cpd 163)



Cpd 163

[0433] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-b]pyridine-6-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.69 (d, J = 1.9 Hz, 1H), 8.40 (d, J = 1.8 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H), 8.25 (dd, J = 10.7, 2.6 Hz, 1H), 7.59 – 7.54 (m, 3H), 7.27 – 7.10 (m, 3H), 4.63 (br s, 1H), 4.19 – 4.16 (m, 5H), 3.76 (br s, 1H), 3.42 – 3.24 (m, 2H), 3.13 (br s, 1H), 2.12 – 1.75 (m, 4H), 1.19 (p, J = 6.2 Hz, 1H), 0.50 (d, J = 8.0 Hz, 2H), 0.43 (d, J = 4.9 Hz, 2H); LC-MS (Method 2): t_R = 4.84 min, m/z ($M+H$) $^+$ = 509.

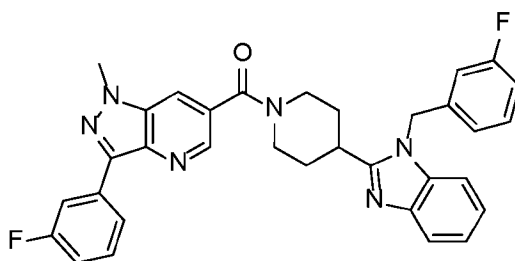
Example 164. 7-((4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(2-fluorophenyl)-1-methyl-1H-indazole (Cpd 164)



Cpd 164

[0434] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.85 (s, 2H), 7.72 (td, J = 7.6, 1.9 Hz, 1H), 7.63 – 7.58 (m, 1H), 7.58 – 7.54 (m, 1H), 7.52 – 7.45 (m, 1H), 7.43 – 7.31 (m, 3H), 7.22 (d, J = 6.9 Hz, 1H), 7.17 – 7.12 (m, 1H), 7.09 (dd, J = 8.3, 6.7 Hz, 1H), 6.92 (d, J = 9.8 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 5.74 (s, 1H), 5.55 (s, 2H), 4.46 (s, 3H), 2.93 (d, J = 11.6 Hz, 3H), 2.14 (t, J = 11.1 Hz, 3H), 1.71 (d, J = 12.4 Hz, 5H); LC-MS (Method 2): t_R = 4.67 min, m/z ($M+H$) $^+$ = 548.

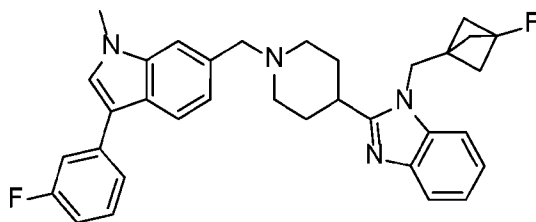
Example 165. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)methanone (Cpd 165)



Cpd 165

[0435] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-b]pyridine-6-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.67 (d, J = 1.9 Hz, 1H), 8.37 (d, J = 1.9 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H), 8.24 (d, J = 10.6 Hz, 1H), 7.64 – 7.51 (m, 2H), 7.42 – 7.29 (m, 2H), 7.23 (td, J = 8.5, 2.6 Hz, 1H), 7.20 – 7.12 (m, 2H), 7.08 (td, J = 8.6, 2.6 Hz, 1H), 6.94 (d, J = 9.9 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 5.59 (s, 2H), 4.59 (br s, 1H), 4.17 (s, 3H), 3.72 (br s, 1H), 3.42–3.21 (br s, 2H), 3.05 (br s, 1H), 1.99 – 1.62 (m, 4H); LC-MS (Method 2): t_R = 5.10 min, m/z ($M+H$) $^+$ = 563.

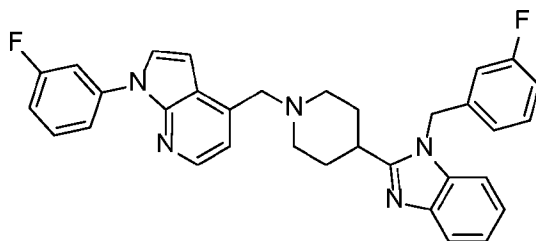
Example 166. 1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-2-(1-((3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazole (Cpd 166)



Cpd 166

[0436] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde and 1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.84 (d, *J* = 8.2 Hz, 1H), 7.76 (s, 1H), 7.52 (t, *J* = 7.0 Hz, 2H), 7.47 – 7.41 (m, 4H), 7.19 – 7.07 (m, 3H), 7.02 (td, *J* = 8.4, 2.5 Hz, 1H), 4.57 (s, 2H), 3.83 (s, 3H), 3.66 (s, 2H), 2.98 (d, *J* = 10.9 Hz, 2H), 2.79 (d, *J* = 11.8 Hz, 1H), 2.14 (t, *J* = 11.4 Hz, 2H), 1.97 – 1.87 (m, 8H), 1.79 (d, *J* = 12.6 Hz, 2H); LC-MS (Method 2): *t*_R = 4.80 min, *m/z* (M+H)⁺ = 537.

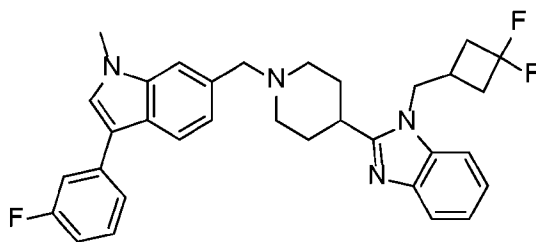
Example 167. 1-(3-fluorobenzyl)-2-(1-((1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazole (Cpd 167)



Cpd 167

[0437] The title compound was prepared from 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carbaldehyde and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.59 – 7.53 (m, 1H), 7.47 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.38 – 7.28 (m, 4H), 7.19 (d, *J* = 6.6 Hz, 1H), 7.15 – 7.12 (m, 2H), 7.10 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.04 (dd, *J* = 8.2, 6.9 Hz, 1H), 6.95 – 6.89 (m, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 5.56 (s, 2H), 4.43 (s, 3H), 3.84 (s, 2H), 2.94 (d, *J* = 11.7 Hz, 3H), 2.32 (s, 3H), 2.14 (t, *J* = 11.3 Hz, 2H), 1.89 – 1.77 (m, 2H), 1.71 (d, *J* = 12.5 Hz, 2H); LC-MS (Method 2): *t*_R = 4.61 min, *m/z* (M+H)⁺ = 534.

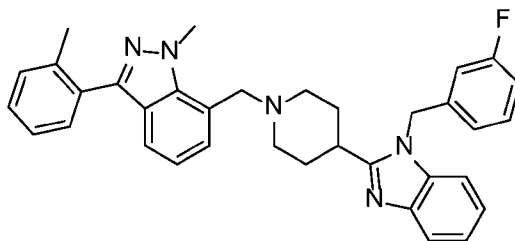
Example 168. 1-((3,3-difluorocyclobutyl)methyl)-2-(1-((3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazole (Cpd 168)



Cpd 168

[0438] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde and 1-((3,3-difluorocyclobutyl)methyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.83 (d, $J = 8.2$ Hz, 1H), 7.76 (s, 1H), 7.60 – 7.38 (m, 6H), 7.21 – 7.06 (m, 3H), 7.05 – 6.97 (m, 1H), 4.37 (d, $J = 5.6$ Hz, 2H), 3.83 (s, 3H), 3.66 (s, 2H), 2.99 – 2.92 (m, 3H), 2.66 – 2.32 (m, 5H), 2.16 (t, $J = 11.5$ Hz, 2H), 2.00 – 1.85 (m, 2H), 1.81 (d, $J = 12.7$ Hz, 2H); LC-MS (Method 2): $t_R = 4.79$ min, m/z (M+H) $^+ = 544$.

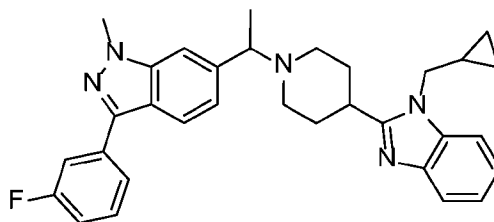
Example 169. 7-((4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-methyl-3-(o-tolyl)-1H-indazole (Cpd 169)



Cpd 169

[0439] The title compound was prepared from 1-methyl-3-(o-tolyl)-1H-indazole-7-carbaldehyde and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.59 – 7.53 (m, 1H), 7.47 (dd, $J = 8.2, 1.1$ Hz, 1H), 7.45 – 7.39 (m, 2H), 7.38 – 7.28 (m, 4H), 7.19 (d, $J = 6.6$ Hz, 1H), 7.15 – 7.12 (m, 2H), 7.10 (dd, $J = 8.9, 3.0$ Hz, 1H), 7.04 (dd, $J = 8.2, 6.9$ Hz, 1H), 6.95 – 6.89 (m, 1H), 6.83 (d, $J = 7.6$ Hz, 1H), 5.56 (s, 2H), 4.43 (s, 3H), 3.84 (s, 2H), 2.94 (d, $J = 11.7$ Hz, 3H), 2.32 (s, 3H), 2.14 (t, $J = 11.3$ Hz, 2H), 1.89 – 1.77 (m, 2H), 1.71 (d, $J = 12.5$ Hz, 2H); LC-MS (Method 2): $t_R = 4.83$ min, m/z (M+H) $^+ = 544$.

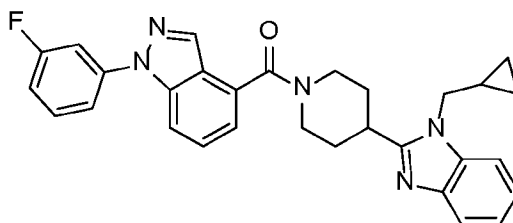
Example 170. 6-(1-(4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)ethyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 170)



Cpd 170

[0440] To a mixture of 1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethan-1-one (53.7 mg, 0.2 mmol) and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (65.7 mg, 0.200 mmol) in CH₂Cl₂ (1.5 ml) was added Et₃N (0.056 ml, 0.40 mmol) and stirred for 5 min. Then, titanium(IV) isopropoxide (0.176 ml, 0.60 mmol) was added. After 5 min, sodium triacetoxyborohydride (212 mg, 1.0 mmol) was added and stirred at rt for overnight. The mixture was poured into EtOAc/2N Na₂CO₃ (aq) (10 mL/10 mL). The aqueous layer was extracted with EtOAc (5 mL x 2). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent to give 6-(1-(4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)ethyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (56.4 mg, 0.111 mmol, 55.5 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.04 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.70 (dd, *J* = 10.5, 2.5 Hz, 1H), 7.60 (s, 1H), 7.58 – 7.47 (m, 3H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.25 – 7.17 (m, 1H), 7.17 – 7.08 (m, 2H), 4.11 (s, 3H), 4.08 (d, *J* = 6.8 Hz, 2H), 3.71 (q, *J* = 6.7 Hz, 1H), 3.12 (d, *J* = 11.1 Hz, 1H), 2.97 – 2.80 (m, 2H), 2.16 (t, *J* = 11.3 Hz, 1H), 2.08 (t, *J* = 11.3 Hz, 1H), 2.02 – 1.81 (m, 3H), 1.77 (d, *J* = 12.7 Hz, 1H), 1.43 (d, *J* = 6.6 Hz, 3H), 1.11 (h, *J* = 5.9 Hz, 1H), 0.45 (d, *J* = 7.8 Hz, 2H), 0.36 (d, *J* = 4.9 Hz, 2H); LC-MS (Method 2): *t*_R = 4.79 min, *m/z* (M+H)⁺ = 543.

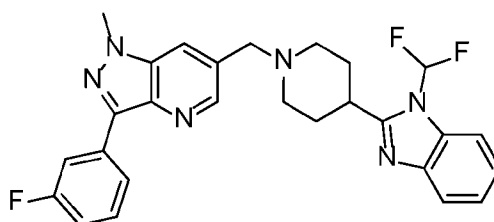
Example 171. (4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-4-yl)methanone (Cpd 171)



Cpd 171

[0441] The title compound was prepared from 1-(3-fluorophenyl)-1H-indazole-4-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.41 (d, *J* = 0.9 Hz, 1H), 8.01 (dt, *J* = 8.7, 0.9 Hz, 1H), 7.73 – 7.65 (m, 3H), 7.64 – 7.56 (m, 3H), 7.37 (dd, *J* = 7.1, 0.7 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.23 – 7.13 (m, 2H), 4.19 (d, *J* = 6.8 Hz, 2H), 3.64 (qd, *J* = 6.6, 3.9 Hz, 1H), 3.15 (qd, *J* = 7.4, 4.2 Hz, 1H), 1.28 (s, 8H), 0.50 (d, *J* = 35.5 Hz, 4H); LC-MS (Method 2): *t*_R = 4.76 min, *m/z* (M+H)⁺ = 494.

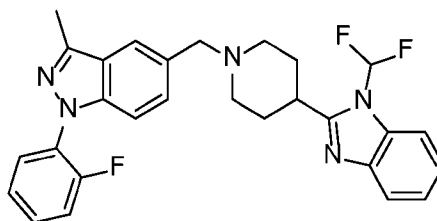
Example 172. 6-((4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-b]pyridine (Cpd 172)



Cpd 172

[0442] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-b]pyridine-6-carbaldehyde and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.63 (s, 1H), 8.30 (d, *J* = 7.4 Hz, 1H), 8.28 – 8.22 (m, 1H), 8.12 (s, 1H), 8.16 (t, *J* = 57.4 Hz, 1H), 7.70 – 7.61 (m, 2H), 7.55 (q, *J* = 7.5 Hz, 1H), 7.35 – 7.25 (m, 2H), 7.20 (ddd, *J* = 10.1, 8.3, 2.6 Hz, 1H), 4.14 (s, 3H), 3.76 (s, 2H), 3.14 (q, *J* = 5.8 Hz, 1H), 2.98 (d, *J* = 11.1 Hz, 2H), 2.21 (t, *J* = 10.9 Hz, 2H), 1.96 – 1.90 (m, 4H); LC-MS (Method 2): *t*_R = 4.79 min, *m/z* (M+H)⁺ = 491.

Example 173. 5-((4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-(2-fluorophenyl)-3-methyl-1H-indazole (Cpd 173)

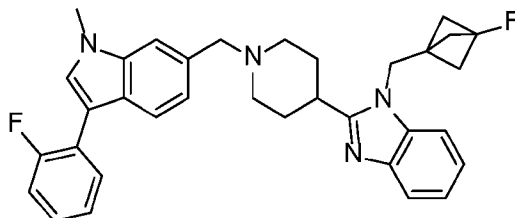


Cpd 173

[0443] The title compound was prepared from 1-(2-fluorophenyl)-3-methyl-1H-indazole-5-carbaldehyde and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.17 (t, *J* =

57.4 Hz, 1H), 7.74 (s, 1H), 7.69 – 7.63 (m, 3H), 7.56 – 7.50 (m, 2H), 7.46 (dd, $J = 8.7, 1.5$ Hz, 1H), 7.41 (ddd, $J = 8.5, 5.3, 3.9$ Hz, 1H), 7.35 – 7.28 (m, 3H), 3.67 (s, 2H), 3.13 (p, $J = 7.8$ Hz, 1H), 2.97 (d, $J = 11.3$ Hz, 2H), 2.59 (s, 3H), 2.22 – 2.11 (m, 2H), 1.90 (d, $J = 3.3$ Hz, 4H); LC-MS (Method 2): $t_R = 4.65$ min, m/z (M+H)⁺ = 490.

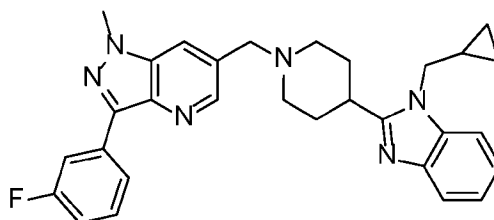
Example 174. 1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-2-(1-((3-(2-fluorophenyl)-1-methyl-1H-indol-6-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazole (Cpd 174)



Cpd 174

[0444] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde and 1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.73 – 7.59 (m, 3H), 7.53 (d, $J = 7.4$ Hz, 1H), 7.48 – 7.44 (m, 2H), 7.28 (dq, $J = 8.9, 4.8$ Hz, 3H), 7.16 – 7.10 (m, 3H), 4.57 (s, 2H), 3.85 (s, 3H), 3.66 (s, 2H), 2.98 (d, $J = 11.0$ Hz, 2H), 2.80 (dq, $J = 11.9, 6.1$ Hz, 1H), 2.14 (t, $J = 11.4$ Hz, 2H), 1.96 – 1.85 (m, 8H), 1.79 (d, $J = 12.5$ Hz, 2H); LC-MS (Method 2): $t_R = 4.81$ min, m/z (M+H)⁺ = 537.

Example 175. 6-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-b]pyridine (Cpd 175)

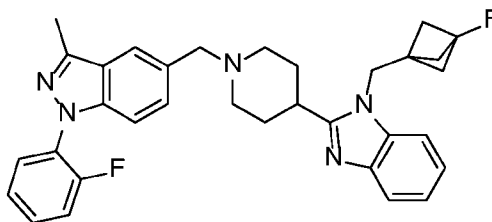


Cpd 175

[0445] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-b]pyridine-6-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.64 (d, $J = 1.8$ Hz, 1H), 8.30 (d, $J = 7.8$ Hz, 1H), 8.28 – 8.22 (m, 1H), 8.12 (s, 1H), 7.60 – 7.49 (m, 3H), 7.20 (td, $J = 8.6, 2.5$ Hz, 1H), 7.17 – 7.09 (m, 2H), 4.15 (s, 3H), 4.12 (d, $J = 6.8$ Hz, 2H), 3.77 (s, 2H), 3.00 – 2.93 (m, 3H), 2.23 (t, $J = 11.4$ Hz, 2H), 1.97 (qd, $J = 11.6, 6.2$ Hz,

2H), 1.84 (d, $J = 12.8$ Hz, 2H), 1.14 (p, $J = 6.8$ Hz, 1H), 0.53 – 0.45 (m, 2H), 0.40 (t, $J = 4.8$ Hz, 2H); LC-MS (Method 2): $t_R = 4.20$ min, m/z (M+H) $^+ = 495$.

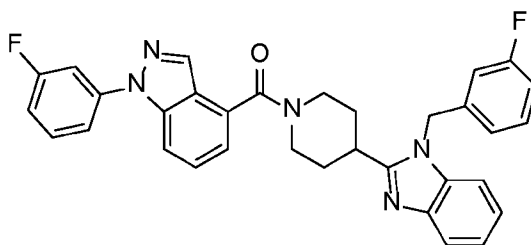
Example 176. 5-((4-(1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-(2-fluorophenyl)-3-methyl-1H-indazole (Cpd 176)



Cpd 176

[0446] The title compound was prepared from 1-(2-fluorophenyl)-3-methyl-1H-indazole-5-carbaldehyde and 1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.74 (dd, $J = 1.5, 0.8$ Hz, 1H), 7.69 – 7.63 (m, 1H), 7.57 – 7.45 (m, 5H), 7.44 – 7.38 (m, 1H), 7.35 – 7.29 (m, 1H), 7.19 – 7.10 (m, 2H), 4.59 (s, 2H), 3.67 (s, 2H), 2.97 (d, $J = 11.2$ Hz, 2H), 2.87 – 2.79 (m, 1H), 2.59 (s, 3H), 2.16 (dd, $J = 12.3, 9.6$ Hz, 2H), 1.93 (d, $J = 2.6$ Hz, 7H), 1.90 (s, 3H); LC-MS (Method 2): $t_R = 4.41$ min, m/z (M+H) $^+ = 538$.

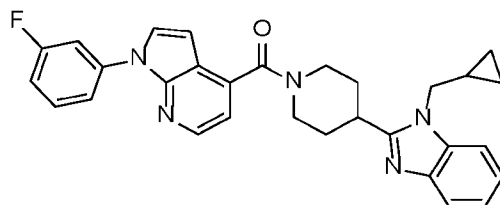
Example 177. (4-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-indazol-4-yl)methanone (Cpd 177)



Cpd 177

[0447] The title compound was prepared from 1-(3-fluorophenyl)-1H-indazole-4-carboxylic acid and 1-(3-fluorobenzyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.36 (d, $J = 0.9$ Hz, 1H), 7.97 (dt, $J = 8.6, 0.8$ Hz, 1H), 7.71 – 7.53 (m, 5H), 7.41 – 7.24 (m, 4H), 7.19 – 7.12 (m, 2H), 7.08 (td, $J = 8.6, 2.6$ Hz, 1H), 6.96 – 6.91 (m, 1H), 6.84 (d, $J = 7.6$ Hz, 1H), 5.58 (s, 2H), 3.66 – 3.54 (m, 1H), 2.67 (s, 2H), 1.27 – 1.21 (m, 6H); LC-MS (Method 2): $t_R = 5.05$ min, m/z (M+H) $^+ = 548$.

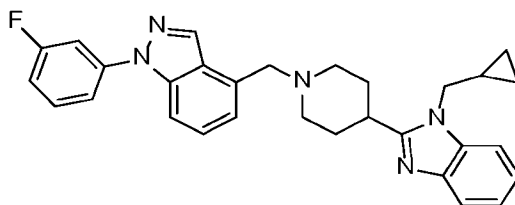
Example 178. 4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)methanone (Cpd 178)



Cpd 178

[0448] The title compound was prepared from 1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-4-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.43 (d, J = 4.8 Hz, 1H), 8.15 (d, J = 3.8 Hz, 1H), 7.93 (dt, J = 10.9, 2.3 Hz, 1H), 7.83 (ddd, J = 8.2, 2.1, 0.9 Hz, 1H), 7.63 – 7.53 (m, 3H), 7.26 (d, J = 4.8 Hz, 1H), 7.24 – 7.10 (m, 3H), 6.71 (d, J = 3.8 Hz, 1H), 5.74 (s, 1H), 4.68 (d, J = 13.0 Hz, 1H), 4.15 (d, J = 6.9 Hz, 2H), 3.55 (d, J = 14.0 Hz, 1H), 3.20 – 3.08 (m, 1H), 2.05 (d, J = 13.2 Hz, 1H), 1.92 (t, J = 12.0 Hz, 1H), 1.80 (s, 2H), 1.24 (dd, J = 6.6, 5.4 Hz, 1H), 1.21 – 1.14 (m, 1H), 0.55 – 0.34 (m, 4H); LC-MS (Method 2): t_R = 4.61 min, m/z ($M+H$) $^+$ = 494.

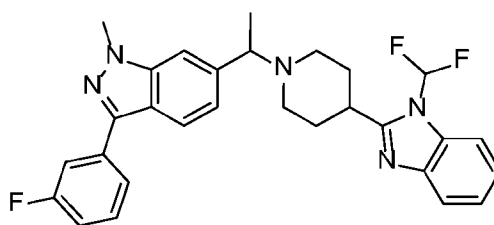
Example 179. 4-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-(3-fluorophenyl)-1H-indazole (Cpd 179)



Cpd 179

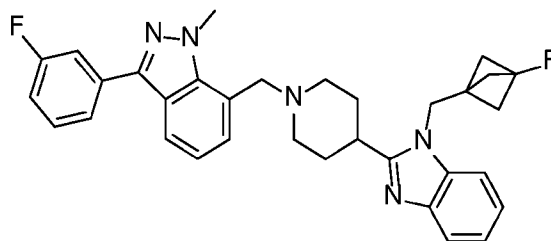
[0449] The title compound was prepared from 1-(3-fluorophenyl)-1H-indazole-4-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.64 (d, J = 0.9 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.69 – 7.60 (m, 3H), 7.55 – 7.50 (m, 2H), 7.47 (dd, J = 8.6, 7.0 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.17 – 7.09 (m, 2H), 4.12 (d, J = 6.8 Hz, 2H), 3.91 (s, 2H), 3.04 – 2.92 (m, 3H), 2.22 (t, J = 11.4 Hz, 2H), 2.03 – 1.90 (m, 2H), 1.87 – 1.80 (m, 2H), 1.22 – 1.09 (m, 1H), 0.51 – 0.36 (m, 4H); LC-MS (Method 2): t_R = 4.105 min, m/z ($M+H$) $^+$ = 480.

Example 180. 6-(1-(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)ethyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 180)

**Cpd 180**

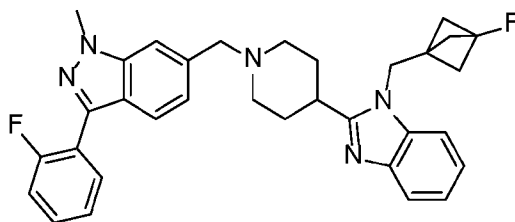
[0450] The title compound was prepared from 1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethan-1-one and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 170**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.11 (t, J = 57.4 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.73 – 7.58 (m, 4H), 7.55 (td, J = 8.0, 6.2 Hz, 1H), 7.31 – 7.26 (m, 3H), 7.21 (td, J = 8.6, 2.6 Hz, 1H), 4.11 (s, 3H), 3.72 (q, J = 6.7 Hz, 1H), 3.15 – 2.97 (m, 2H), 2.94 (d, J = 11.2 Hz, 1H), 2.21 – 1.99 (m, 2H), 1.94 – 1.80 (m, 4H), 1.42 (d, J = 6.7 Hz, 3H); LC-MS (Method 2): t_R = 5.05 min, m/z ($M+H$) $^+$ = 504.

Example 181. 7-((4-(1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 181)

**Cpd 181**

[0451] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-7-carbaldehyde and 1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.99 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.67 (dt, J = 10.5, 2.1 Hz, 1H), 7.55 (td, J = 8.0, 6.1 Hz, 1H), 7.52 – 7.48 (m, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.29 – 7.19 (m, 2H), 7.19 – 7.07 (m, 3H), 4.58 (s, 2H), 4.48 (s, 3H), 3.87 (s, 2H), 2.97 (d, J = 11.2 Hz, 2H), 2.89 – 2.80 (m, 1H), 2.26 – 2.15 (m, 2H), 1.93 (d, J = 2.5 Hz, 6H), 1.88 – 1.75 (m, 4H); LC-MS (Method 2): t_R = 4.66 min, m/z ($M+H$) $^+$ = 538.

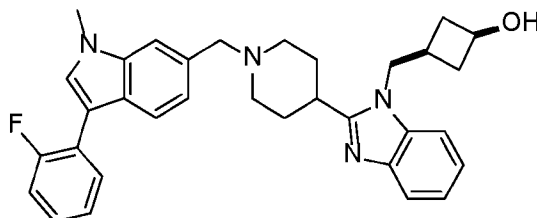
Example 182. 6-((4-(1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-(2-fluorophenyl)-1-methyl-1H-indazole (Cpd 182)



Cpd 182

[0452] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.76 (td, J = 7.6, 1.8 Hz, 1H), 7.69 (dd, J = 8.5, 3.2 Hz, 1H), 7.61 (s, 1H), 7.55 – 7.42 (m, 3H), 7.41 – 7.30 (m, 2H), 7.22 (d, J = 8.5 Hz, 1H), 7.17 – 7.10 (m, 2H), 4.57 (s, 2H), 4.12 (s, 3H), 3.70 (s, 2H), 3.08 – 2.76 (m, 3H), 2.18 (br s, 2H), 2.04 – 1.85 (m, 8H), 1.80 (d, J = 12.5 Hz, 2H); LC-MS (Method 2): t_R = 4.46 min, m/z ($M+H$) $^+$ = 538.

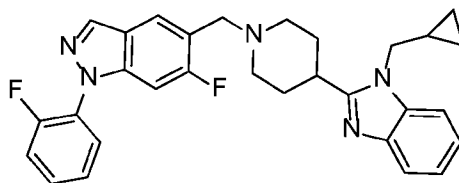
Example 183. (1s,3s)-3-((2-(1-((3-(2-fluorophenyl)-1-methyl-1H-indol-6-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol (Cpd 183)



Cpd 183

[0453] The title compound was prepared from 3-(2-fluorophenyl)-1-methyl-1H-indole-6-carbaldehyde and (1s,3s)-3-((2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol, 2HCl following a similar procedure as described in **Example 53**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.73 – 7.59 (m, 3H), 7.55 – 7.49 (m, 1H), 7.46 (d, J = 7.3 Hz, 2H), 7.33 – 7.23 (m, 3H), 7.16 – 7.09 (m, 3H), 4.97 (d, J = 6.4 Hz, 1H), 4.21 (d, J = 6.4 Hz, 2H), 3.86 (s, 3H), 3.83 – 3.76 (m, 1H), 3.68 (br s, 2H), 3.07 – 2.83 (m, 3H), 2.25 – 1.70 (m, 9H), 1.56 (td, J = 10.3, 5.2 Hz, 2H); LC-MS (Method 2): t_R = 4.16 min, m/z ($M+H$) $^+$ = 523.

Example 184. 5-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-6-fluoro-1-(2-fluorophenyl)-1H-indazole (Cpd 184)



Cpd 184

STEP 1: Synthesis of methyl 6-fluoro-1-(2-fluorophenyl)-1H-indazole-5-carboxylate

[0454] The material, methyl 6-fluoro-1-(2-fluorophenyl)-1H-indazole-5-carboxylate, was prepared from methyl 6-fluoro-1H-indazole-5-carboxylate and 1-bromo-2-fluorobenzene following a similar procedure as described in the synthesis of **Int-71** (STEP 1). LC-MS (Method 1): $t_R = 3.43$ min, m/z (M+H)⁺ = 289.

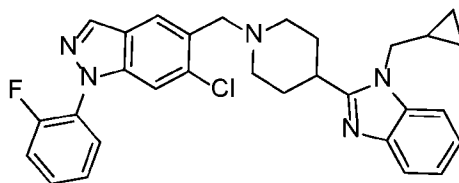
STEP 2: Synthesis of 6-fluoro-1-(2-fluorophenyl)-1H-indazole-5-carbaldehyde

[0455] The material, 6-fluoro-1-(2-fluorophenyl)-1H-indazole-5-carbaldehyde, was prepared from methyl 6-fluoro-1-(2-fluorophenyl)-1H-indazole-5-carboxylate following a similar procedure in the synthesis of **Int-30**. LC-MS (Method 1): $t_R = 3.38$ min, m/z (M+H)⁺ = 259.

STEP 3: Synthesis of 5-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-6-fluoro-1-(2-fluorophenyl)-1H-indazole (Cpd 184)

[0456] The title compound was prepared from 6-fluoro-1-(2-fluorophenyl)-1H-indazole-5-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.44 (d, $J = 1.0$ Hz, 1H), 7.96 (d, $J = 6.9$ Hz, 1H), 7.71 (td, $J = 7.9, 1.6$ Hz, 1H), 7.64 – 7.50 (m, 4H), 7.48 – 7.40 (m, 1H), 7.24 (dd, $J = 10.4, 2.9$ Hz, 1H), 7.15 (pd, $J = 7.2, 1.5$ Hz, 2H), 4.13 (d, $J = 6.8$ Hz, 2H), 3.71 (s, 2H), 3.04 – 2.87 (m, 3H), 2.24 (t, $J = 11.2$ Hz, 2H), 1.95 (q, $J = 12.2$ Hz, 2H), 1.85 (d, $J = 12.4$ Hz, 2H), 1.29 – 1.07 (m, 1H), 0.54 – 0.46 (m, 2H), 0.46 – 0.36 (m, 2H); LC-MS (Method 2): $t_R = 3.96$ min, m/z (M+H)⁺ = 498.

Example 185. 6-chloro-5-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-(2-fluorophenyl)-1H-indazole (Cpd 185)



Cpd 185

STEP 1: Synthesis of methyl 6-chloro-1-(2-fluorophenyl)-1H-indazole-5-carboxylate

[0457] The material, methyl 6-chloro-1-(2-fluorophenyl)-1H-indazole-5-carboxylate, was prepared from methyl 6-chloro-1H-indazole-5-carboxylate and 1-bromo-2-fluorobenzene following a similar procedure as described in the synthesis of **Int-71** (STEP 1).

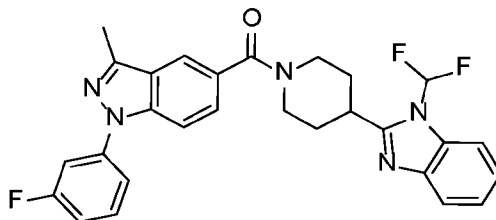
STEP 2: Synthesis of 6-chloro-1-(2-fluorophenyl)-1H-indazole-5-carbaldehyde

[0458] The material, 6-chloro-1-(2-fluorophenyl)-1H-indazole-5-carbaldehyde, was prepared from methyl 6-chloro-1-(2-fluorophenyl)-1H-indazole-5-carboxylate following a similar procedure in the synthesis of **Int-30**. LC-MS (Method 1): $t_R = 3.56$ min, m/z ($M+H$)⁺ = 275, 277.

STEP 3: Synthesis of 6-chloro-5-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-1-(2-fluorophenyl)-1H-indazole (Cpd 185)

[0459] The title compound was prepared from 6-chloro-1-(2-fluorophenyl)-1H-indazole-5-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.46 (d, $J = 1.0$ Hz, 1H), 8.04 (s, 1H), 7.70 (td, $J = 7.9, 1.6$ Hz, 1H), 7.63 – 7.48 (m, 5H), 7.47 – 7.39 (m, 1H), 7.14 (pd, $J = 7.2, 1.5$ Hz, 2H), 6.50 (s, 1H), 4.13 (d, $J = 6.8$ Hz, 2H), 3.71 (s, 2H), 3.01 (d, $J = 11.4$ Hz, 3H), 2.29 (t, $J = 10.8$ Hz, 2H), 1.98 (q, $J = 11.0$ Hz, 2H), 1.85 (d, $J = 12.4$ Hz, 2H), 0.54 – 0.43 (m, 2H), 0.46 – 0.36 (m, 2H); LC-MS (Method 2): $t_R = 4.04$ min, m/z ($M+H$)⁺ = 514, 516.

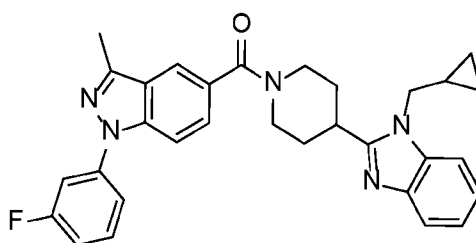
Example 186. (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-3-methyl-1H-indazol-5-yl)methanone (Cpd 186)



Cpd 186

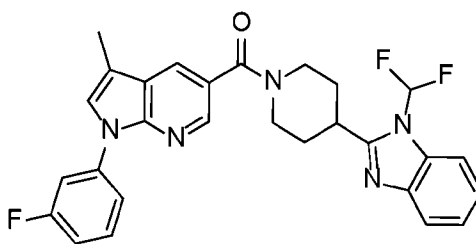
[0460] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-1H-indazole-5-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.22 (t, $J = 57.4$ Hz, 1H), 7.97 (dd, $J = 1.6, 0.8$ Hz, 1H), 7.92 (dd, $J = 8.7, 0.8$ Hz, 1H), 7.71 – 7.54 (m, 6H), 7.35 – 7.28 (m, 2H), 7.24 – 7.15 (m, 1H), 4.22 (d, $J = 277.2$ Hz, 2H), 3.48 (s, 1H), 3.12 (qd, $J = 7.4, 4.2$ Hz, 2H), 2.67 (s, 3H), 1.87 (qd, $J = 12.2, 4.0$ Hz, 4H); LC-MS (Method 2): $t_R = 5.90$ min, m/z (M+H) $^+ = 504$.

Example 187. (4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-3-methyl-1H-indazol-5-yl)methanone (Cpd 187)

**Cpd 187**

[0461] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-1H-indazole-5-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.00 – 7.88 (m, 2H), 7.69 – 7.53 (m, 6H), 7.25 – 7.10 (m, 3H), 4.17 (d, $J = 6.8$ Hz, 2H), 3.08 (qd, $J = 7.3, 4.9$ Hz, 2H), 2.62 (s, 3H), 1.88 (d, $J = 12.1$ Hz, 2H), 1.28 – 1.12 (m, 6H), 0.54 – 0.39 (m, 4H); LC-MS (Method 2): $t_R = 4.81$ min, m/z (M+H) $^+ = 508$.

Example 188. (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methanone (Cpd 188)

**Cpd. 188**

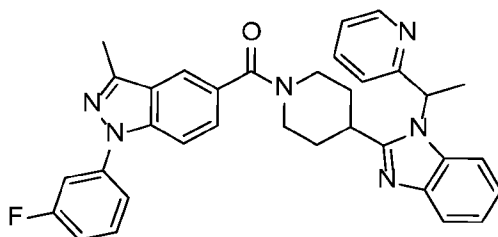
STEP 1: Synthesis of 1-(3-fluorophenyl)-3-methyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid

[0462] The material, 1-(3-fluorophenyl)-3-methyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid, was prepared from methyl 3-methyl-1H-pyrrolo[2,3-b]pyridine-4-carboxylate and 1-bromo-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-71**. LC-MS (Method 1): $t_R = 3.22$ min, m/z ($M+H$)⁺ = 271.

STEP 2: Synthesis of (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methanone (**Cpd 188**)

[0463] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, CDCl₃) δ 8.40 (t, $J = 4.5$ Hz, 1H), 7.81 – 7.41 (m, 5H), 7.41 – 7.30 (m, 4H), 7.14 – 6.95 (m, 2H), 5.00 (d, $J = 12.9$ Hz, 1H), 3.76 – 3.68 (m, 1H), 2.18 (dd, $J = 18.7, 11.4$ Hz, 3H), 2.00 (t, $J = 13.4$ Hz, 2H), 1.25 (s, 3H), 0.86 (d, $J = 17.7$ Hz, 2H); LC-MS (Method 2): $t_R = 6.53$ min, m/z ($M+H$)⁺ = 504.

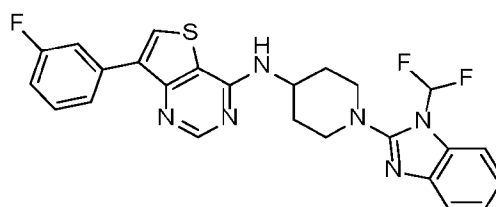
Example 189. (1-(3-fluorophenyl)-3-methyl-1H-indazol-5-yl)(4-(1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 189**)**



Cpd 189

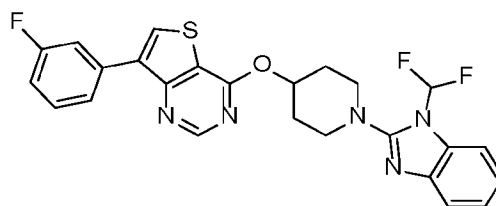
[0464] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-1H-indazole-5-carboxylic acid and 2-(piperidin-4-yl)-1-(1-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazole, 3HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.60 – 8.54 (m, 1H), 8.00 – 7.85 (m, 2H), 7.79 – 7.70 (m, 1H), 7.69 – 7.50 (m, 5H), 7.34 – 7.26 (m, 1H), 7.26 – 7.16 (m, 2H), 7.07 (ddd, $J = 10.7, 7.3, 2.0$ Hz, 2H), 6.98 (ddd, $J = 8.3, 6.9, 1.2$ Hz, 1H), 6.13 (q, $J = 6.9$ Hz, 1H), 4.57 (s, 1H), 3.84 (s, 1H), 3.51 (s, 1H), 2.61 (s, 3H), 1.95 (d, $J = 6.9$ Hz, 3H), 1.86 (s, 3H), 1.24 (dd, $J = 6.6, 5.5$ Hz, 3H); LC-MS (Method 2): $t_R = 4.80$ min, m/z ($M+H$)⁺ = 559.

Example 190. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-7-(3-fluorophenyl)thieno[3,2-d]pyrimidin-4-amine (Cpd 190**)**

**Cpd 190**

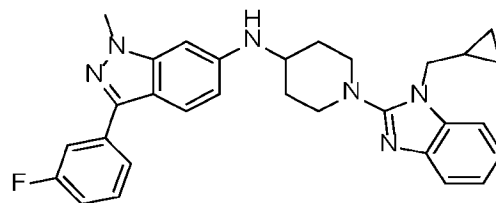
[0465] The title compound was prepared from 7-(3-fluorophenyl)-N-(piperidin-4-yl)thieno[3,2-d]pyrimidin-4-amine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.57 (s, 1H), 8.47 (s, 1H), 8.03 (dt, J = 11.1, 2.2 Hz, 1H), 7.96 – 7.84 (m, 2H), 7.70 (t, J = 57.9 Hz, 1H), 7.53 – 7.44 (m, 3H), 7.28 – 7.14 (m, 3H), 4.50 – 4.33 (m, 1H), 3.64 (d, J = 12.9 Hz, 2H), 3.26 – 3.13 (m, 2H), 2.03 (dd, J = 13.3, 3.8 Hz, 2H), 1.91 (qd, J = 12.1, 3.9 Hz, 2H); LC-MS (Method 2): t_R = 5.41 min, m/z ($M+H$) $^+$ = 495.

Example 191. 4-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-7-(3-fluorophenyl)thieno[3,2-d]pyrimidine (Cpd 191)

**Cpd 191**

[0466] The title compound was prepared from 7-(3-fluorophenyl)-4-(piperidin-4-yloxy)thieno[3,2-d]pyrimidine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.89 (s, 1H), 8.72 (s, 1H), 8.03 (dt, J = 10.8, 2.2 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.75 (t, J = 57.8 Hz, 1H), 7.57 – 7.47 (m, 3H), 7.28 – 7.15 (m, 3H), 5.65 (tt, J = 7.9, 3.8 Hz, 1H), 3.53 (ddd, J = 11.0, 6.7, 3.9 Hz, 2H), 3.38 – 3.30 (m, 2H), 2.27 (ddt, J = 13.9, 7.3, 3.7 Hz, 2H), 2.07 (dtd, J = 12.1, 8.1, 3.5 Hz, 2H); LC-MS (Method 2): t_R = 7.39 min, m/z ($M+H$) $^+$ = 496.

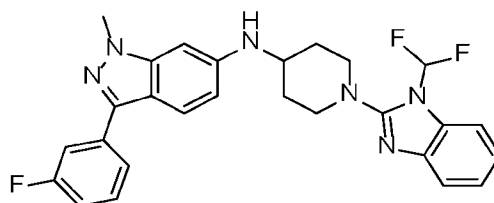
Example 192. N-(1-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 192)



Cpd 192

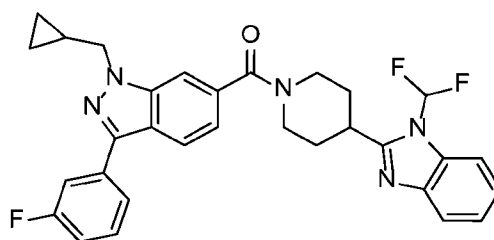
[0467] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl and 2-chloro-1-(cyclopropylmethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.73 (t, *J* = 8.3 Hz, 2H), 7.61 (dt, *J* = 10.4, 2.2 Hz, 1H), 7.54 – 7.37 (m, 3H), 7.16 (td, *J* = 8.7, 2.6 Hz, 1H), 7.10 – 7.05 (m, 2H), 6.69 (dd, *J* = 8.9, 1.8 Hz, 1H), 6.56 (d, *J* = 1.9 Hz, 1H), 6.02 (d, *J* = 8.1 Hz, 1H), 3.97 – 3.89 (m, 5H), 3.67 – 3.57 (m, 1H), 3.52 (d, *J* = 12.6 Hz, 2H), 3.12 (t, *J* = 11.8 Hz, 2H), 2.11 (d, *J* = 12.3 Hz, 2H), 1.64 (q, *J* = 10.5 Hz, 2H), 1.26 – 1.14 (m, 1H), 0.53 – 0.42 (m, 2H), 0.42 – 0.35 (m, 2H); LC-MS (Method 2): *t*_R = 4.69 min, *m/z* (M+H)⁺ = 495.

Example 193. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 193)

**Cpd 193**

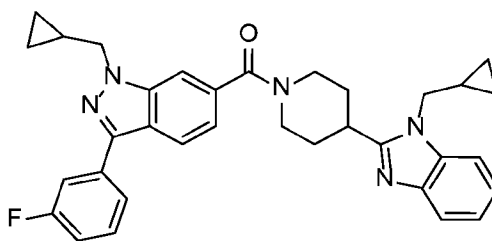
[0468] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.89 – 7.57 (m, 3H), 7.62 (ddd, *J* = 10.6, 2.6, 1.5 Hz, 1H), 7.54 – 7.45 (m, 3H), 7.28 – 7.12 (m, 3H), 6.70 (dd, *J* = 8.9, 1.8 Hz, 1H), 6.57 (d, *J* = 1.9 Hz, 1H), 6.05 (d, *J* = 7.8 Hz, 1H), 3.95 (s, 3H), 3.73 – 3.54 (m, 3H), 3.29 – 3.19 (m, 2H), 2.11 (dd, *J* = 13.4, 3.9 Hz, 2H), 1.78 – 1.64 (m, 2H); LC-MS (Method 2): *t*_R = 5.34 min, *m/z* (M+H)⁺ = 491.

Example 194. (1-(cyclopropylmethyl)-3-(3-fluorophenyl)-1H-indazol-6-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 194)

**Cpd 194**

[0469] The title compound was prepared from 1-(cyclopropylmethyl)-3-(3-fluorophenyl)-1H-indazole-6-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.21 (t, $J = 57.4$ Hz, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 7.91 (s, 1H), 7.84 (d, $J = 7.8$ Hz, 1H), 7.75 – 7.62 (m, 3H), 7.57 (td, $J = 8.1, 6.2$ Hz, 1H), 7.37 – 7.19 (m, 4H), 4.62 (br s, 1H), 4.42 (d, $J = 7.1$ Hz, 2H), 3.75 br (s, 1H), 3.48 (s, 1H), 3.30 – 2.94 (m, 2H), 2.17 – 1.75 (m, 4H), 1.34 (ddt, $J = 12.4, 8.0, 3.9$ Hz, 1H), 0.54 – 0.39 (m, 4H); LC-MS (Method 2): $t_R = 6.00$ min, m/z (M+H) $^+ = 544$.

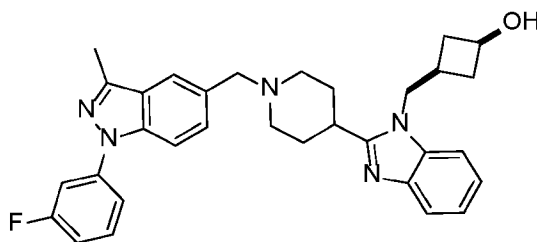
Example 195. (4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(cyclopropylmethyl)-3-(3-fluorophenyl)-1H-indazol-6-yl)methanone (Cpd 195)



Cpd 195

[0470] The title compound was prepared from 1-(cyclopropylmethyl)-3-(3-fluorophenyl)-1H-indazole-6-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.16 (d, $J = 8.4$ Hz, 1H), 7.91 (s, 1H), 7.84 (d, $J = 7.8$ Hz, 1H), 7.72 (dt, $J = 10.0, 2.1$ Hz, 1H), 7.62 – 7.50 (m, 3H), 7.29 – 7.21 (m, 2H), 7.20 – 7.09 (m, 2H), 4.62 (s, 1H), 4.43 (d, $J = 7.0$ Hz, 2H), 4.16 (d, $J = 6.8$ Hz, 2H), 3.75 (br s, 1H), 3.40 – 3.20 (m, 2H), 3.09 (br s, 1H), 2.11 – 1.72 (m, 4H), 1.37 – 1.27 (m, 1H), 1.23 – 1.13 (m, 1H), 0.54 – 0.38 (m, 8H); LC-MS (Method 2): $t_R = 4.71$ min, m/z (M+H) $^+ = 548$.

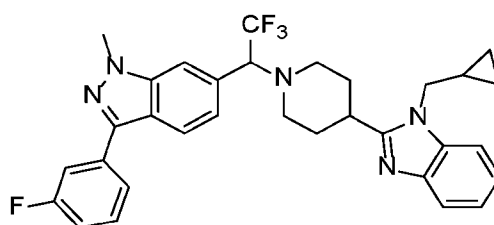
Example 196. (1s,3s)-3-((2-(1-((1-(3-fluorophenyl)-3-methyl-1H-indazol-5-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol (Cpd 196)



Cpd 196

[0471] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-1H-indazole-5-carbaldehyde and (1*s*,3*s*)-3-((2-(piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)cyclobutan-1-ol, 2HCl following a similar procedure as in **Example 53**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.86 (dd, *J* = 8.7, 0.7 Hz, 1H), 7.74 (d, *J* = 1.5 Hz, 1H), 7.68 – 7.43 (m, 6H), 7.21 – 7.06 (m, 3H), 4.98 (d, *J* = 6.3 Hz, 1H), 4.21 (d, *J* = 6.3 Hz, 2H), 3.91 – 3.76 (m, 1H), 3.66 (s, 2H), 2.96 (d, *J* = 11.2 Hz, 2H), 2.88 (d, *J* = 8.6 Hz, 1H), 2.58 (s, 3H), 2.22 – 2.15 (m, 3H), 2.15 – 1.99 (m, 2H), 1.92 (qd, *J* = 11.0, 4.6 Hz, 2H), 1.84 – 1.76 (m, 2H), 1.62 – 1.50 (m, 2H); LC-MS (Method 2): *t*_R = 4.63 min, *m/z* (M+H)⁺ = 524.

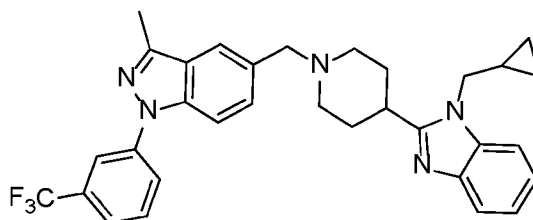
Example 197. 6-(1-(4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)-2,2,2-trifluoroethyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 197)



Cpd 197

[0472] In a microwave tube was placed 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole (0.077 g, 0.3 mmol) and sodium iodide (4.50 mg, 0.03 mmol). Then, 2,2,2-trifluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethyl methanesulfonate (0.157 g, 0.39 mmol) in DMSO (1 ml) and Hunig's base (0.183 ml, 1.05 mmol) were added subsequently. The tube was sealed and heated at 125 °C for overnight. The mixture was diluted with EtOAc (10 mL) and washed with H₂O (10 mL x 3). The organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 5-90% EtOAc/hexane as the eluent to give 6-(1-(4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)-2,2,2-trifluoroethyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole. LC-MS (Method 2): *t*_R = 5.77 min, *m/z* (M+H)⁺ = 562.

Example 198. 5-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazole, 2TFA (Cpd 198)



Cpd 198**STEP 1: Synthesis of methyl 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carboxylate**

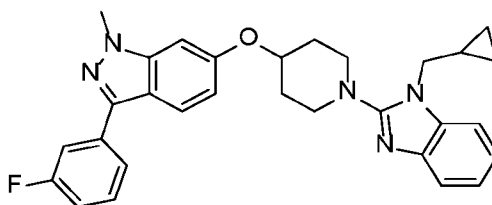
[0473] The material, methyl 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carboxylate, was prepared from methyl 3-methyl-1H-indazole-5-carboxylate and 1-bromo-3-trifluoromethylbenzene following a similar procedure as described in the synthesis of **Int-71** (STEP 1). LC-MS (Method 1): $t_R = 3.85$ min, m/z (M+H)⁺ = 335.

STEP 2: Synthesis of 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carbaldehyde

[0474] The material, 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carbaldehyde, was prepared from methyl 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carboxylate following a similar procedure as described in the synthesis of **Int-30**. LC-MS (Method 1): $t_R = 3.70$ min, m/z (M+H)⁺ = 305.

STEP 3: Synthesis of 5-((4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methyl)-3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazole, 2TFA (Cpd 198)

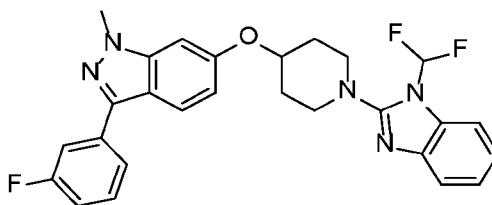
[0475] The title compound was prepared from 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carbaldehyde and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.14 (dd, $J = 7.9, 2.1$ Hz, 1H), 8.08 (s, 1H), 8.07 – 7.99 (m, 2H), 7.85 (t, $J = 8.0$ Hz, 1H), 7.76 (d, $J = 7.9$ Hz, 1H), 7.73 – 7.64 (m, 2H), 7.61 (d, $J = 7.6$ Hz, 1H), 7.27 (p, $J = 7.5$ Hz, 2H), 4.53 (s, 2H), 4.21 (t, $J = 7.7$ Hz, 2H), 3.59 (d, $J = 12.1$ Hz, 2H), 3.48 – 3.33 (m, 2H), 2.66 (s, 3H), 2.33 (p, $J = 1.9$ Hz, 1H), 2.17 (q, $J = 7.8$ Hz, 5H), 1.34 – 1.12 (m, 1H), 0.55 – 0.41 (m, 4H); LC-MS (Method 2): $t_R = 4.61$ min, m/z (M+H)⁺ = 544.

Example 199. 6-((1-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 199)**Cpd 199**

[0476] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-6-(piperidin-4-yloxy)-1H-indazole, HCl and 2-chloro-1-(cyclopropylmethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.00 (s, 1H),

7.75 (d, $J = 8.8$ Hz, 1H), 7.55 – 7.45 (m, 1H), 7.44 – 7.34 (m, 2H), 7.30 – 7.19 (m, 3H), 7.14 (d, $J = 8.9$ Hz, 1H), 7.07 – 7.03 (m, 2H), 4.57 (dt, $J = 7.7, 3.9$ Hz, 1H), 3.86 (d, $J = 6.7$ Hz, 2H), 3.37 (s, 3H), 3.18 – 2.97 (m, 4H), 2.01 – 1.85 (m, 2H), 1.70 – 1.53 (m, 2H), 1.13 (dd, $J = 9.0, 4.0$ Hz, 1H), 0.43 (dt, $J = 8.4, 2.9$ Hz, 2H), 0.35 – 0.30 (m, 2H); LC-MS (Method 2): $t_R = 5.12$ min, m/z (M+H)⁺ = 496.

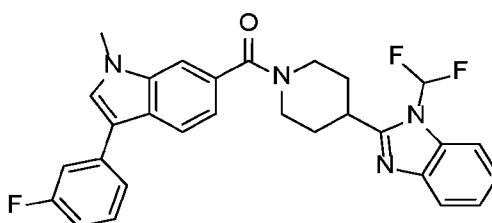
Example 200. 6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 200)



Cpd 200

[0477] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-6-(piperidin-4-yloxy)-1H-indazole, HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.00 (s, 1H), 7.75 (d, $J = 8.8$ Hz, 1H), 7.63 (t, $J = 57.4$ Hz, 1H), 7.51 – 7.42 (m, 3H), 7.30 – 7.11 (m, 6H), 4.62 (dt, $J = 7.3, 3.7$ Hz, 1H), 3.36 (s, 3H), 3.19 – 3.07 (m, 4H), 2.04 – 1.91 (m, 2H), 1.70 (dtd, $J = 12.3, 7.7, 4.1$ Hz, 2H); LC-MS (Method 2): $t_R = 5.76$ min, m/z (M+H)⁺ = 492.

Example 201. (4-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indol-6-yl)methanone (Cpd 201)

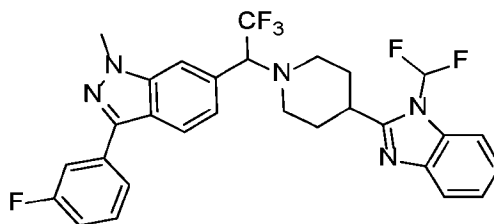


Cpd 201

[0478] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indole-6-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.22 (t, $J = 57.4$ Hz, 1H), 7.93 (d, $J = 8.2$ Hz, 1H), 7.90 (s, 1H), 7.68 (dt, $J = 9.2, 3.9$ Hz, 2H), 7.63 (s, 1H), 7.53 (d, $J = 7.7$ Hz, 1H), 7.50 – 7.41 (m, 2H), 7.35 – 7.28 (m, 2H), 7.21 (dd, $J = 8.3, 1.5$ Hz, 1H), 7.04 (td, J

= 8.5, 2.5 Hz, 1H), 4.70 – 4.00 (m, 2H), 3.87 (s, 3H), 3.48 (tt, J = 11.3, 4.2 Hz, 1H), 3.30 – 3.00 (m, 2H), 2.13 – 1.78 (m, 4H); LC-MS (Method 2): t_R = 6.00 min, m/z ($M+H$)⁺ = 503.

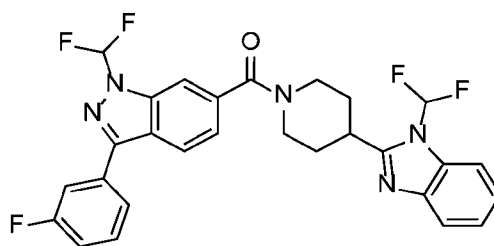
Example 202. 6-(1-(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)-2,2,2-trifluoroethyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 202)



Cpd 202

[0479] In a microwave tube was placed 2,2,2-trifluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethyl 4-nitrobenzenesulfonate (102 mg, 0.2 mmol) and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole (101 mg, 0.40 mmol) and then added MeCN (0.4 ml). The tube was sealed and heated at 130 °C for 4 hr under microwave irradiation. After cooling to rt, to the mixture was added EtOAc/H₂O/saturated Na₂CO₃ (aq) (3 mL/3 mL/0.5 mL). The aqueous layer was extracted with EtOAc (3 mL). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 5-35-40% EtOAc/hexane as the eluent to give product 6-(1-(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)-2,2,2-trifluoroethyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (60 mg, 0.108 mmol, 53.8 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.17 (d, J = 8.5 Hz, 1H), 8.06 (t, J = 57.4 Hz, 1H), 7.84 (dt, J = 7.9, 1.2 Hz, 1H), 7.75 – 7.52 (m, 5H), 7.37 – 7.21 (m, 4H), 4.83 (q, J = 9.5 Hz, 1H), 4.15 (s, 3H), 3.17 – 3.15 (m, 2H), 3.05 – 2.92 (m, 1H), 2.54 (dd, J = 10.8, 4.1 Hz, 1H), 2.20 – 2.09 (m, 1H), 1.95 – 1.81 (m, 4H); LC-MS (Method 2): t_R = 6.65 min, m/z ($M+H$)⁺ = 558.

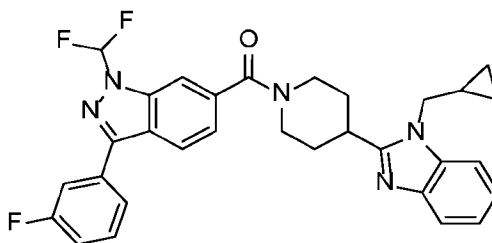
Example 203. (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(difluoromethyl)-3-(3-fluorophenyl)-1H-indazol-6-yl)methanone (Cpd 203)



Cpd 203

[0480] The title compound was prepared from 1-(difluoromethyl)-3-(3-fluorophenyl)-1H-indazole-6-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.35 (t, *J* = 57.5 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.22 (t, *J* = 57.5 Hz, 1H), 8.01 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.78 (dt, *J* = 10.1, 2.2 Hz, 1H), 7.73 – 7.57 (m, 3H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.42 – 7.26 (m, 3H), 4.62 (br s, 1H), 3.70 (br s, 1H), 3.49 (dt, *J* = 14.6, 8.4 Hz, 1H), 3.40 – 3.00 (m, 2H), 2.17 – 1.78 (m, 4H); LC-MS (Method 2): *t*_R = 6.17 min, *m/z* (M+H)⁺ = 540.

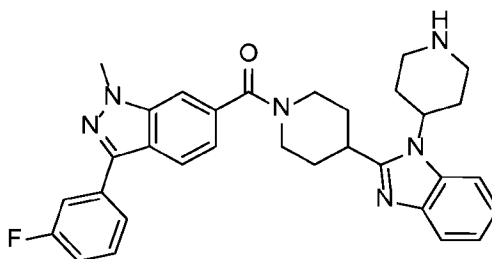
Example 204. (4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(difluoromethyl)-3-(3-fluorophenyl)-1H-indazol-6-yl)methanone (Cpd 204)



Cpd 204

[0481] The title compound was prepared from 1-(difluoromethyl)-3-(3-fluorophenyl)-1H-indazole-6-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.36 (t, *J* = 57.7 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.01 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.78 (dt, *J* = 10.0, 2.2 Hz, 1H), 7.64 (td, *J* = 8.0, 6.0 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 2H), 7.48 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.38 (td, *J* = 8.6, 2.5 Hz, 1H), 7.22 – 7.09 (m, 2H), 4.61 (br s, 1H), 4.16 (d, *J* = 6.8 Hz, 2H), 3.70 (br s, 1H), 3.40 – 3.00 (m, 3H), 2.11 – 1.75 (m, 4H), 1.26 – 1.12 (m, 1H), 0.49 (dd, *J* = 8.0, 3.8 Hz, 2H), 0.45 – 0.37 (m, 2H); LC-MS (Method 2): *t*_R = 5.17 min, *m/z* (M+H)⁺ = 544.

Example 205. (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-(piperidin-4-yl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, 2HCl (Cpd 205)



Cpd 205

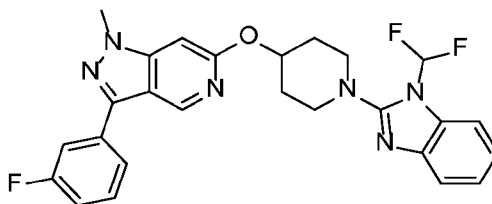
STEP 1: Synthesis of tert-butyl 4-(2-(1-(3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbonyl)piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)piperidine-1-carboxylate

[0482] The starting material, tert-butyl 4-(2-(1-(3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbonyl)piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)piperidine-1-carboxylate, was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone and tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate following a similar procedure as described in **Example 22** (STEP 2). LC-MS (Method 2): $t_R = 3.31$ min, m/z $(M+H)^+ = 637$.

STEP 2: Synthesis of (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-(piperidin-4-yl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, 2HCl (Cpd 205)

[0483] To a solution of tert-butyl 4-(2-(1-(3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbonyl)piperidin-4-yl)-1H-benzo[d]imidazol-1-yl)piperidine-1-carboxylate (37 mg, 0.058 mmol) in CH_2Cl_2 (0.5 ml) was added HCl (4M in dioxane, 0.465 mmol, 0.12 mL, 8 equiv). The mixture was stirred at rt for 1 hr. Then, hexane (3 mL) was added slowly and was stirred for 10 min. Carefully removed the solvent and repeated adding/removal of hexane for 3 times. The residue was dried in vacuo to give (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-(piperidin-4-yl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, 2HCl (32.8 mg, 0.054 mmol, 93 % yield). ^1H NMR (400 MHz, $DMSO-d_6$) δ 9.59 (br s, 1H), 8.96 (d, $J = 10.3$ Hz, 1H), 8.31 (br s, 1H), 8.18 (d, $J = 8.4$ Hz, 1H), 7.88 (s, 1H), 7.84 (d, $J = 7.8$ Hz, 1H), 7.79 (s, 1H), 7.72 (dt, $J = 10.4, 2.1$ Hz, 1H), 7.57 (q, $J = 7.7$ Hz, 1H), 7.49 (s, 2H), 7.30 (d, $J = 8.4$ Hz, 1H), 7.25 (td, $J = 8.7, 2.6$ Hz, 1H), 5.14 (br s, 1H), 4.70 (br s, 1H), 4.17 (s, 3H), 3.82 (br s, 2H), 3.58 – 2.95 (m, 4H), 2.90 – 2.75 (m, 2H), 2.23 – 1.82 (m, 8H). (including one salt NH); LC-MS (Method 2): $t_R = 3.99$ min, m/z $(M+H)^+ = 537$.

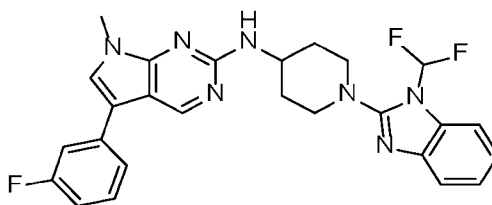
Example 206. 6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-c]pyridine (Cpd 206)



Cpd 206

[0484] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-6-(piperidin-4-yloxy)-1H-pyrazolo[4,3-c]pyridine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.11 (s, 1H), 7.87 (d, *J* = 7.1 Hz, 1H), 7.78 – 7.74 (m, 1H), 7.73 (d, *J* = 58.6 Hz, 1H), 7.57 – 7.46 (m, 3H), 7.32 – 7.15 (m, 3H), 7.04 (s, 1H), 5.32 (dt, *J* = 8.2, 4.2 Hz, 1H), 4.01 (s, 3H), 3.53 (dt, *J* = 11.5, 4.7 Hz, 2H), 3.30 – 3.24 (m, 2H), 2.24 – 2.13 (m, 2H), 1.96 (dtd, *J* = 12.2, 8.2, 3.4 Hz, 2H); LC-MS (Method 2): *t*_R = 5.70 min, *m/z* (M+H)⁺ = 493.

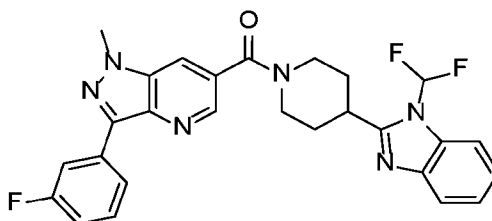
Example 207. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-5-(3-fluorophenyl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-2-amine (Cpd 207)



Cpd 207

[0485] The title compound was prepared from 5-(3-fluorophenyl)-7-methyl-N-(piperidin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.90 (s, 1H), 7.68 (t, *J* = 57.8 Hz, 1H), 7.60 (s, 1H), 7.53 – 7.38 (m, 5H), 7.26 – 7.14 (m, 2H), 7.03 (tq, *J* = 6.0, 2.7 Hz, 2H), 4.02 (dd, *J* = 13.3, 7.2 Hz, 1H), 3.65 (s, 3H), 3.58 (dd, *J* = 10.2, 6.3 Hz, 2H), 3.24 – 3.11 (m, 2H), 2.05 (dd, *J* = 13.2, 3.8 Hz, 2H), 1.86 – 1.72 (m, 2H); LC-MS (Method 2): *t*_R = 4.76 min, *m/z* (M+H)⁺ = 492.

Example 208. (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)methanone (Cpd 208)

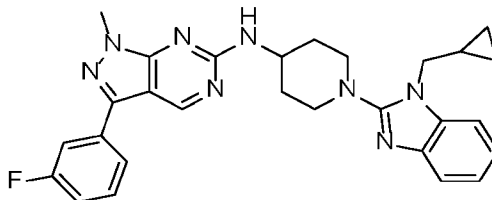


Cpd 208

[0486] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[4,3-b]pyridine-6-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆)

δ 8.69 (d, J = 1.7 Hz, 1H), 8.39 (d, J = 1.7 Hz, 1H), 8.37 – 8.05 (m, 3H), 7.71 – 7.63 (m, 2H), 7.56 (td, J = 8.1, 6.2 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.23 (td, J = 8.6, 2.7 Hz, 1H), 4.64 (br s, 1H), 4.18 (s, 3H), 3.77 (br s, 1H), 3.55 – 3.45 (m, 1H), 3.30 (br s, 1H), 3.06 (br s, 1H), 2.17 – 1.81 (m, 4H); LC-MS (Method 2): t_R = 5.71 min, m/z (M+H)⁺ = 505.

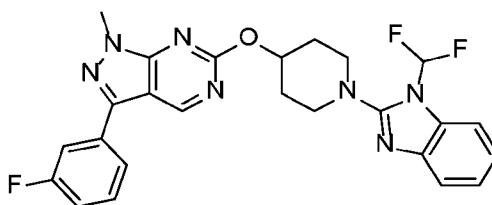
Example 209. N-(1-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine (Cpd 209)



Cpd 209

[0487] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine, 2HCl and 2-chloro-1-(cyclopropylmethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.19 (br s, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.77 – 7.60 (m, 2H), 7.58 (td, J = 8.1, 6.1 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.25 (td, J = 8.6, 2.6 Hz, 1H), 7.11 – 7.05 (m, 2H), 4.06 (s, 1H), 3.94 (d, J = 6.7 Hz, 2H), 3.86 (s, 3H), 3.53 (d, J = 12.3 Hz, 2H), 3.05 (t, J = 12.1 Hz, 2H), 2.06 (d, J = 12.7 Hz, 2H), 1.77 (q, J = 11.3 Hz, 2H), 1.20 (dq, J = 12.8, 6.3 Hz, 1H), 0.47 (dd, J = 7.9, 4.3 Hz, 2H), 0.42 – 0.33 (m, 2H); LC-MS (Method 2): t_R = 4.90 min, m/z (M+H)⁺ = 497.

Example 210. 6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidine (Cpd 210)

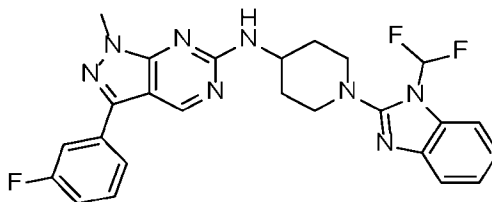


Cpd 210

[0488] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-6-(piperidin-4-yloxy)-1H-pyrazolo[3,4-d]pyrimidine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.19 (br s, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.77 – 7.60 (m, 2H), 7.58 (td, J = 8.1, 6.1 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.25 (td, J = 8.6, 2.6 Hz, 1H), 7.11 – 7.05 (m, 2H), 4.06 (s, 1H), 3.94 (d, J = 6.7 Hz, 2H), 3.86 (s, 3H), 3.53 (d, J = 12.3 Hz, 2H), 3.05 (t, J = 12.1 Hz, 2H),

2.06 (d, $J = 12.7$ Hz, 2H), 1.77 (q, $J = 11.3$ Hz, 2H), 1.20 (dq, $J = 12.8, 6.3$ Hz, 1H), 0.47 (dd, $J = 7.9, 4.3$ Hz, 2H), 0.42 – 0.33 (m, 2H); LC-MS (Method 2): $t_R = 5.62$ min, m/z (M+H)⁺ = 494.

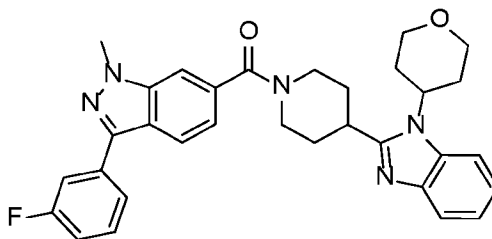
Example 211. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine (Cpd 211)



Cpd 211

[0489] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.19 (s, 1H), 7.83 (d, $J = 7.8$ Hz, 1H), 7.80 – 7.63 (m, 3H), 7.57 – 7.51 (m, 1H), 7.51 – 7.46 (m, 2H), 7.29 – 7.14 (m, 3H), 4.08 (s, 1H), 3.86 (s, 3H), 3.60 (d, $J = 12.7$ Hz, 2H), 3.18 (t, $J = 11.9$ Hz, 2H), 2.04 (br s, 2H), 1.83 (t, $J = 11.3$ Hz, 2H); LC-MS (Method 2): $t_R = 5.49$ min, m/z (M+H)⁺ = 493.

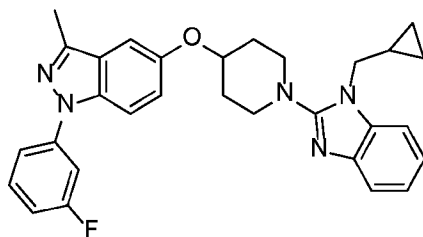
Example 212. (3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)(4-(1-(tetrahydro-2H-pyran-4-yl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, TFA (Cpd 212)



Cpd 212

[0490] The title compound was prepared from (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone and tetrahydro-2H-pyran-4-yl methanesulfonate following a similar procedure as described in **Example 22** (STEP 2). ¹H NMR (400 MHz, DMSO-d₆) δ 8.18 (d, $J = 8.4$ Hz, 1H), 7.91 (s, 1H), 7.85 – 7.83 (m, 2H), 7.72 (dt, $J = 10.0, 2.2$ Hz, 2H), 7.57 (td, $J = 8.0, 6.1$ Hz, 1H), 7.39 (s, 2H), 7.32 – 7.20 (m, 2H), 4.90 (br s, 1H), 4.68 (br s, 1H), 4.15 (s, 3H), 4.04 (dd, $J = 11.6, 4.4$ Hz, 2H), 3.94 – 2.89 (m, 6H), 2.20 – 1.76 (m, 8H); LC-MS (Method 2): $t_R = 4.66$ min, m/z (M+H)⁺ = 538.

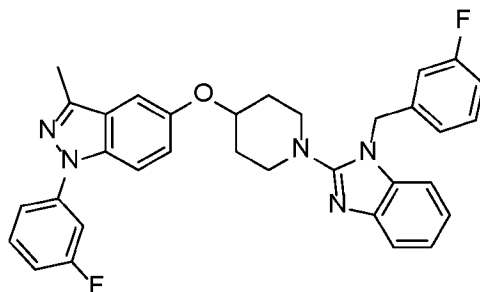
Example 213. 5-((1-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-1-(3-fluorophenyl)-3-methyl-1H-indazole (Cpd 213)



Cpd 213

[0491] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-5-(piperidin-4-yloxy)-1H-indazole, 2HCl and 2-chloro-1-(cyclopropylmethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.84 (d, *J* = 9.1 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.48 – 7.42 (m, 3H), 7.22 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.17 (dt, *J* = 8.1, 1.8 Hz, 1H), 7.12 – 7.08 (m, 2H), 6.99 – 6.96 (m, 1H), 4.72 (dt, *J* = 7.9, 4.0 Hz, 1H), 3.97 (d, *J* = 6.7 Hz, 2H), 3.94 – 3.87 (m, 1H), 3.66 (d, *J* = 6.9 Hz, 1H), 3.54 – 3.44 (m, 2H), 3.18 (ddd, *J* = 12.6, 8.9, 3.3 Hz, 2H), 2.57 (s, 3H), 2.20 – 2.11 (m, 2H), 2.04 (s, 1H), 1.95 – 1.82 (m, 2H), 1.27 – 1.12 (m, 2H); LC-MS (Method 2): *t*_R = 5.48 min, *m/z* (M+H)⁺ = 496.

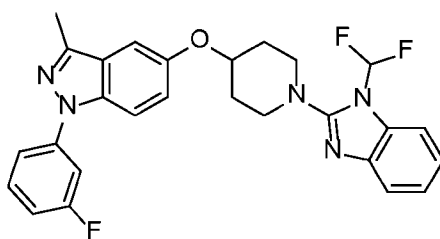
Example 214. 5-((1-(1-(3-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-1-(3-fluorophenyl)-3-methyl-1H-indazole (Cpd 214)



Cpd 214

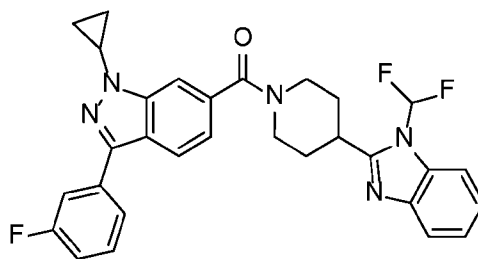
[0492] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-5-(piperidin-4-yloxy)-1H-indazole, 2HCl and 2-chloro-1-(3-fluorobenzyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. LC-MS (Method 2): *t*_R = 5.68 min, *m/z* (M+H)⁺ = 550.

Example 215. 5-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-1-(3-fluorophenyl)-3-methyl-1H-indazole (Cpd 215)

**Cpd 215**

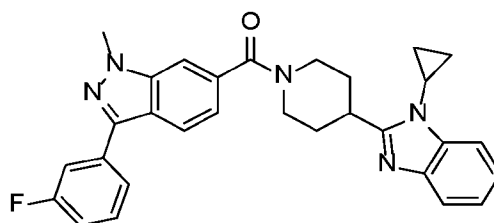
[0493] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-5-(piperidin-4-yloxy)-1H-indazole, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.90 – 7.69 (m, 2H), 7.64 – 7.52 (m, 3H), 7.50 (dt, J = 7.6, 1.7 Hz, 2H), 7.43 (d, J = 2.3 Hz, 1H), 7.29 – 7.09 (m, 4H), 4.73 (dt, J = 7.7, 3.9 Hz, 1H), 3.59 – 3.46 (m, 2H), 3.30 – 3.18 (m, 2H), 2.55 (s, 3H), 2.23 – 1.82 (m, 4H); LC-MS (Method 2): t_R = 6.11 min, m/z ($M+H$) $^+$ = 492.

Example 216. (1-cyclopropyl-3-(3-fluorophenyl)-1H-indazol-6-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 216)

**Cpd 216**

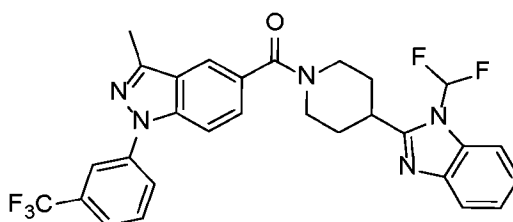
[0494] The title compound was prepared from 1-cyclopropyl-3-(3-fluorophenyl)-1H-indazole-6-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.22 (t, J = 57.3 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.83 – 7.80 (m, 2H), 7.74 – 7.60 (m, 3H), 7.56 (td, J = 8.1, 6.2 Hz, 1H), 7.34 – 7.29 (m, 3H), 7.24 (td, J = 8.6, 2.6 Hz, 1H), 4.62 (br s, 1H), 3.91 (tt, J = 7.1, 4.1 Hz, 1H), 3.79 (br s, 1H), 3.53 – 3.44 (m, 1H), 3.38 – 3.00 (m, 2H), 2.19 – 1.75 (m, 4H), 1.20 – 1.12 (m, 4H); LC-MS (Method 2): t_R = 6.15 min, m/z ($M+H$) $^+$ = 530.

Example 217. (4-(1-cyclopropyl-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 217)

**Cpd 217**

[0495] To a mixture of (4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (91 mg, 0.2 mmol), cyclopropylboronic acid (51.5 mg, 0.60 mmol), copper (II) acetate (36.3 mg, 0.20 mmol), 2,2'-bipyridine (31.2 mg, 0.20 mmol), and Na₂CO₃ (63.6 mg, 0.60 mmol) was added 1,2-dichloroethane (5 ml). The mixture was opened to air and stirred at 65 °C for 8 hr. After cooling to rt, the mixture was filtered through celite and eluted with CH₂Cl₂. The filtrate was concentrated and then purified by silica gel chromatography using 0-5% MeOH/EtOAc as the eluent to give (4-(1-cyclopropyl-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (54.2 mg, 0.110 mmol, 54.9 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 6.7 Hz, 2H), 7.72 (dt, *J* = 10.1, 2.2 Hz, 1H), 7.61 – 7.50 (m, 3H), 7.30 – 7.10 (m, 4H), 4.62 (br s, 1H), 4.15 (s, 3H), 3.77 (br s, 1H), 3.51 (dq, *J* = 11.0, 5.9 Hz, 1H), 3.48 – 3.00 (m, 3H), 2.22 – 1.71 (m, 4H), 1.22 (h, *J* = 4.9 Hz, 2H), 1.07 – 0.99 (m, 2H); LC-MS (Method 2): *t*_R = 4.62 min, *m/z* (M+H)⁺ = 494.

Example 218. (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-yl)methanone (Cpd 218)

**Cpd 218**

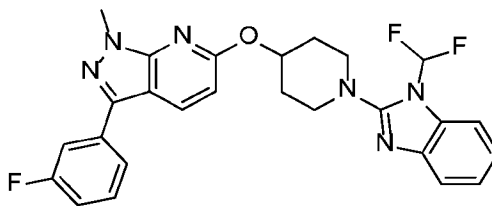
STEP 1: Synthesis of 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carboxylic acid

[0496] The material, 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carboxylic acid, was prepared from methyl 3-methyl-1H-indazole-5-carboxylate and 1-bromo-3-trifluoromethylbenzene following a similar procedure as described in the synthesis of **Int-71**. LC-MS (Method 1): *t*_R = 3.48 min, *m/z* (M+H)⁺ = 321.

STEP 2: Synthesis of (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-yl)methanone (Cpd 218)

[0497] The title compound was prepared from 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.26 – 8.08 (m, 2H), 8.06 (d, J = 2.1 Hz, 1H), 8.01 (dd, J = 1.6, 0.8 Hz, 1H), 7.96 – 7.90 (m, 1H), 7.83 (t, J = 8.0 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.72 – 7.65 (m, 2H), 7.61 (dd, J = 8.7, 1.5 Hz, 1H), 7.38 – 7.28 (m, 2H), 3.62 (pd, J = 6.6, 3.9 Hz, 1H), 3.49 (d, J = 10.7 Hz, 1H), 3.14 (qd, J = 7.4, 4.2 Hz, 2H), 1.89 (qd, J = 12.0, 3.9 Hz, 2H), 1.28 – 1.25 (m, 4H), 1.23 (d, J = 7.2 Hz, 2H); LC-MS (Method 2): t_R = 6.25 min, m/z ($M+H$) $^+$ = 554.

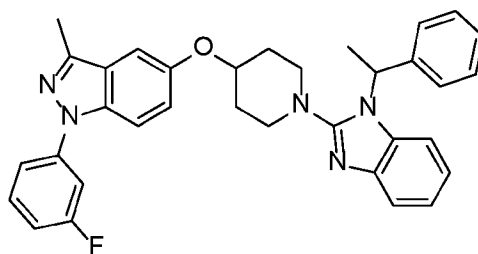
Example 219. 6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-3-(3-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine (Cpd 219)



Cpd 219

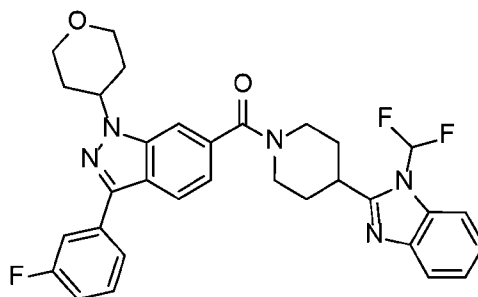
[0498] The title compound was prepared from 3-bromo-6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-1-methyl-1H-pyrazolo[3,4-b]pyridine and (3-fluorophenyl)boronic acid following a similar procedure as described in **Example 15**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.46 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.74 (t, J = 57.8 Hz, 1H), 7.70 (dt, J = 10.3, 2.2 Hz, 1H), 7.56 – 7.47 (m, 3H), 7.28 – 7.15 (m, 3H), 6.75 (d, J = 8.7 Hz, 1H), 5.43 (dq, J = 7.9, 4.0 Hz, 1H), 4.02 (s, 3H), 3.53 (ddd, J = 11.4, 6.2, 3.6 Hz, 2H), 3.35 – 3.30 (m, 2H), 2.25 (ddt, J = 11.4, 7.0, 3.7 Hz, 2H), 2.01 (dtd, J = 12.0, 8.0, 3.4 Hz, 2H); LC-MS (Method 2): t_R = 6.33 min, m/z ($M+H$) $^+$ = 493.

Example 220. 1-(3-fluorophenyl)-3-methyl-5-((1-(1-(1-phenylethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-1H-indazole, 2TFA (Cpd 220)

**Cpd 220**

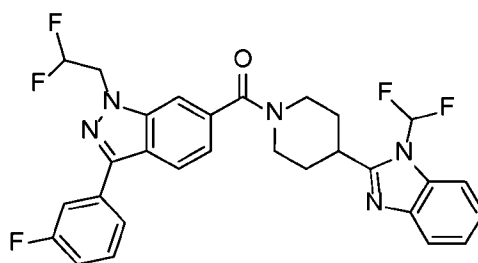
[0499] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-5-(piperidin-4-yloxy)-1H-indazole, 2HCl and 2-chloro-1-(1-phenylethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ^1H NMR (400 MHz, CDCl_3) δ 7.81 (s, 1H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.52 – 7.33 (m, 9H), 7.20 (t, $J = 7.5$ Hz, 1H), 7.14 (s, 2H), 7.04 – 6.96 (m, 2H), 5.69 (s, 1H), 4.67 (s, 1H), 3.86 (s, 2H), 3.68 (s, 2H), 2.61 (s, 4H), 2.00 (s, 6H); LC-MS (Method 2): $t_R = 5.82$ min, m/z ($\text{M} + \text{H}$) $^+ = 546$.

Example 221. (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)-1H-indazol-6-yl)methanone (Cpd 221)

**Cpd 221**

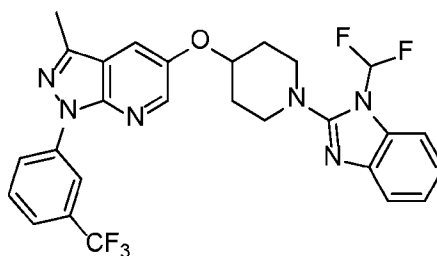
[0500] The title compound was prepared from 3-(3-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)-1H-indazole-6-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.21 (t, $J = 57.4$ Hz, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 7.97 (s, 1H), 7.84 (d, $J = 7.7$ Hz, 1H), 7.73 (dt, $J = 10.5, 2.1$ Hz, 1H), 7.67 (td, $J = 6.3, 2.8$ Hz, 2H), 7.57 (td, $J = 8.1, 6.2$ Hz, 1H), 7.37 – 7.19 (m, 4H), 5.08 (td, $J = 11.2, 5.3$ Hz, 1H), 4.63 (br s, 1H), 4.07 – 3.96 (m, 2H), 3.76 (br s, 1H), 3.65 – 3.54 (m, 2H), 3.49 (br s, 1H), 3.28 (br s, 1H), 3.04 (br s, 1H), 2.27 – 2.11 (m, 2H), 2.11 – 1.74 (m, 6H); LC-MS (Method 2): $t_R = 6.07$ min, m/z ($\text{M} + \text{H}$) $^+ = 574$.

Example 222. (1-(2,2-difluoroethyl)-3-(3-fluorophenyl)-1H-indazol-6-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (Cpd 222)

**Cpd 222**

[0501] The title compound was prepared from 1-(2,2-difluoroethyl)-3-(3-fluorophenyl)-1H-indazole-6-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.22 (t, $J = 57.4$ Hz, 1H), 8.18 (d, $J = 8.4$ Hz, 1H), 7.94 (s, 1H), 7.84 (d, $J = 7.7$ Hz, 1H), 7.77 – 7.63 (m, 3H), 7.59 (td, $J = 8.1, 6.2$ Hz, 1H), 7.37 – 7.23 (m, 4H), 6.49 (tt, $J = 57.4, 4.0$ Hz, 1H), 5.08 (td, $J = 15.5, 3.5$ Hz, 2H), 4.63 (br s, 1H), 3.74 (br s, 1H), 3.53 – 3.44 (m, 1H), 3.23 (br s, 1H), 3.03 (br s, 1H), 2.19 – 1.78 (m, 4H); LC-MS (Method 2): $t_R = 5.93$ min, m/z ($M+H$) $^+ = 554$.

Example 223. 5-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridine (Cpd 223)

**Cpd 223**

STEP 1: Synthesis of 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridin-5-ol

[0502] In a microwave tube was placed 3-methyl-1H-pyrazolo[3,4-b]pyridin-5-ol (300 mg, 2.011 mmol), 1-bromo-3-(trifluoromethyl)benzene (0.293 ml, 2.212 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (172 mg, 1.207 mmol), copper(I) iodide (19.15 mg, 0.101 mmol), cesium carbonate (1638 mg, 5.03 mmol) and then N,N-Dimethylformamide (4 ml) was added. The mixture was sealed and then stirred at 120 °C for 48 hr. The mixture was poured into EtOAc (10 mL). The organic layer was washed with H₂O (10 mL x 3), dried (Na₂SO₄), and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-50% EtOAc/hexane to give 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridin-5-ol (400 mg, 1.364 mmol, 67.8 % yield); LC-MS (Method 1): $t_R = 3.47$ min, m/z ($M+H$) $^+ = 294$.

STEP 2: Synthesis of tert-butyl 4-((3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridin-5-yl)oxy)piperidine-1-carboxylate

[0503] In a microwave vial was placed 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridin-5-ol (400 mg, 1.364 mmol), di-tert-butyl (E)-diazene-1,2-dicarboxylate (628 mg, 2.73 mmol), triphenylphosphine (716 mg, 2.73 mmol) and tert-butyl 4-hydroxypiperidine-1-carboxylate (549 mg, 2.73 mmol). The vial was sealed and the air was removed and refilled with N₂ (repeat for 2 times). Then, THF (3 ml) was added and the mixture was stirred at 45 °C for overnight. The mixture was concentrated and was purified by silica gel chromatography using 5-45% EtOAc/hexane as the eluent to give tert-butyl 4-((3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridin-5-yl)oxy)piperidine-1-carboxylate (291.3 mg, 0.611 mmol, 44.8 % yield); LC-MS (Method 1): t_R = 4.01 min, m/z (M+H)⁺ = 477.

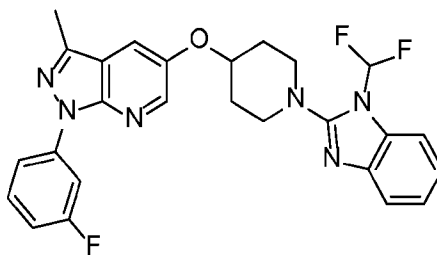
STEP 3: Synthesis of 3-methyl-5-(piperidin-4-yloxy)-1-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridine, 2HCl

[0504] To a solution of tert-butyl 4-((3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridin-5-yl)oxy)piperidine-1-carboxylate (291.3 mg, 0.611 mmol) in CH₂Cl₂ (2 ml) was added HCl (4M in dioxane, 764 µl, 3.06 mmol). The mixture was stirred at rt for 24 hr. Then, hexane (30 mL) was added slowly and was stirred for 10 min. The solvent was carefully removed, and addition/removal of hexane was repeated 3 times. The residue was dried *in vacuo* to give 3-methyl-5-(piperidin-4-yloxy)-1-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridine, 2HCl (79.3 mg, 0.163 mmol, 26.7 % yield). LC-MS (Method 1): t_R = 3.15 min, m/z (M+H)⁺ = 377.

STEP 4: Synthesis of 5-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridine (Cpd 223)

[0505] The title compound was prepared from 3-methyl-5-(piperidin-4-yloxy)-1-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.68 (t, *J* = 2.0 Hz, 1H), 8.63 (d, *J* = 8.3 Hz, 1H), 8.53 (d, *J* = 2.7 Hz, 1H), 8.10 (d, *J* = 2.7 Hz, 1H), 7.93 – 7.72 (m, 2H), 7.66 – 7.59 (m, 1H), 7.52 (ddd, *J* = 6.8, 3.3, 1.8 Hz, 2H), 7.30 – 7.17 (m, 2H), 4.81 (dt, *J* = 8.0, 4.1 Hz, 1H), 3.55 (q, *J* = 6.3 Hz, 2H), 3.30 – 3.23 (m, 2H), 2.62 (s, 3H), 2.20 (dd, *J* = 14.6, 5.6 Hz, 2H), 1.96 (dtd, *J* = 12.3, 8.3, 3.5 Hz, 2H); LC-MS (Method 2): t_R = 6.55 min, m/z (M+H)⁺ = 543.

Example 224. 5-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-1-(3-fluorophenyl)-3-methyl-1H-pyrazolo[3,4-b]pyridine (Cpd 224)



Cpd 224

STEP 1: Synthesis of 1-(3-fluorophenyl)-3-methyl-5-(piperidin-4-yloxy)-1H-pyrazolo[3,4-b]pyridine, 2HCl

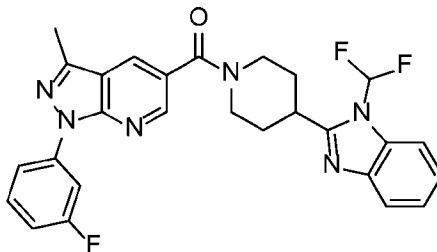
[0506] The material, 1-(3-fluorophenyl)-3-methyl-5-(piperidin-4-yloxy)-1H-pyrazolo[3,4-b]pyridine, 2HCl, was prepared from 3-methyl-1H-pyrazolo[3,4-b]pyridin-5-ol and 1-bromo-3-fluorobenzene following a similar procedure as described in **Example 223** (STEP 1 to STEP 3) LC-MS (Method 1): t_R = 2.84 min, m/z ($M+H$)⁺ = 327.

STEP 2: Synthesis of 5-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-1-(3-fluorophenyl)-3-methyl-1H-pyrazolo[3,4-b]pyridine (Cpd 224)

[0507] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-5-(piperidin-4-yloxy)-1H-pyrazolo[3,4-b]pyridine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 223** (STEP 4).

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.49 (d, J = 2.7 Hz, 1H), 8.21 – 8.13 (m, 2H), 8.08 (d, J = 2.7 Hz, 1H), 7.76 (s, 1H), 7.63 – 7.54 (m, 1H), 7.52 (dt, J = 7.9, 2.0 Hz, 2H), 7.23 (tt, J = 8.9, 6.8 Hz, 2H), 7.14 – 7.07 (m, 1H), 4.80 (dt, J = 8.0, 4.2 Hz, 1H), 3.56 (t, J = 8.2 Hz, 2H), 3.27 (d, J = 9.6 Hz, 2H), 2.60 (s, 3H), 2.25 – 2.15 (m, 2H), 1.97 (ddt, J = 13.1, 8.7, 4.1 Hz, 2H); LC-MS (Method 2): t_R = 6.22 min, m/z ($M+H$)⁺ = 493.

Example 225. (4-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)methanone (Cpd 225)

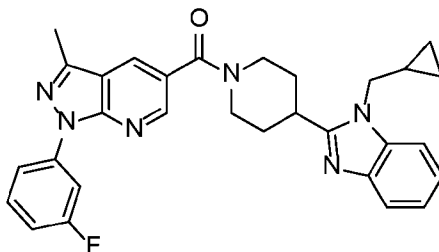


Cpd 225**STEP 1: Synthesis of 1-(3-fluorophenyl)-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid**

[0508] The material, 1-(3-fluorophenyl)-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, was prepared from methyl 3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate and 1-bromo-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-71**. LC-MS (Method 1): $t_R = 3.27$ min, m/z (M+H)⁺ = 272.

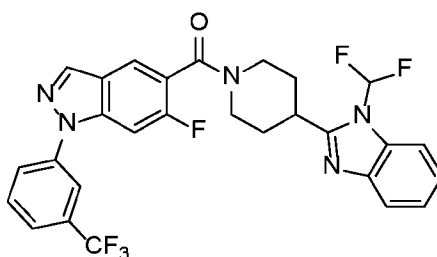
STEP 2: Synthesis of (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)methanone (Cpd 225)

[0509] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.77 (d, $J = 2.0$ Hz, 1H), 8.55 (d, $J = 2.0$ Hz, 1H), 8.24 – 8.16 (m, 3H), 7.75 – 7.65 (m, 2H), 7.61 (td, $J = 8.0, 6.4$ Hz, 1H), 7.39 – 7.29 (m, 2H), 7.22 – 7.11 (m, 1H), 4.63 (s, 1H), 3.84 (s, 1H), 3.62 (pd, $J = 6.6, 3.9$ Hz, 5H), 3.14 (tt, $J = 7.3, 3.6$ Hz, 5H); LC-MS (Method 2): $t_R = 5.94$ min, m/z (M+H)⁺ = 505.

Example 226. (4-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(1-(3-fluorophenyl)-3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)methanone (Cpd 226)**Cpd 226**

[0510] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid and 1-(cyclopropylmethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.76 (d, $J = 2.0$ Hz, 1H), 8.53 (d, $J = 2.0$ Hz, 1H), 8.26 – 8.03 (m, 3H), 7.60 (td, $J = 8.0, 6.3$ Hz, 2H), 7.24 (s, 2H), 7.19 – 7.11 (m, 1H), 4.22 (s, 2H), 3.60 (heptd, $J = 6.5, 3.9$ Hz, 8H), 3.12 (qd, $J = 7.4, 4.2$ Hz, 9H); LC-MS (Method 2): $t_R = 4.87$ min, m/z (M+H)⁺ = 509.

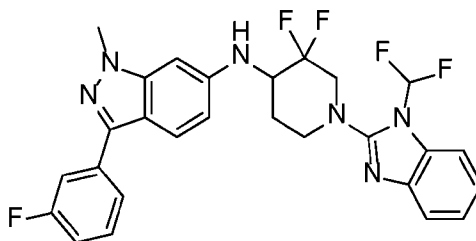
Example 227. (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-yl)methanone (Cpd 227)

**Cpd 227**STEP 1: Synthesis of 6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carboxylic acid

[0511] The material, 6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carboxylic acid, was prepared from methyl 6-fluoro-1H-indazole-5-carboxylate and 1-bromo-3-trifluoromethylbenzene following a similar procedure as described in the synthesis of **Int-71**. LC-MS (Method 1): $t_R = 3.32$ min, m/z (M+H)⁺ = 325.

STEP 2: Synthesis of (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-yl)methanone (**Cpd 227**)

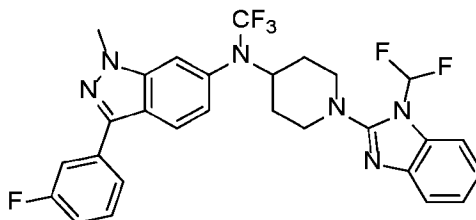
[0512] The title compound was prepared from 6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.53 (d, $J = 0.9$ Hz, 1H), 8.26 – 8.13 (m, 2H), 8.09 (t, $J = 2.6$ Hz, 1H), 8.05 (s, 1H), 7.90 – 7.78 (m, 3H), 7.73 – 7.64 (m, 2H), 7.38 – 7.29 (m, 2H), 4.67 (d, $J = 13.1$ Hz, 1H), 3.62 (dd, $J = 12.0$, 4.8 Hz, 1H), 3.49 (d, $J = 10.7$ Hz, 1H), 2.69 (s, 2H), 2.09 (d, $J = 13.1$ Hz, 1H), 1.98 – 1.77 (m, 3H); LC-MS (Method 2): $t_R = 6.05$ min, m/z (M+H)⁺ = 558.

Example 228. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)-3,3-difluoropiperidin-4-yl)-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 228)**Cpd 228**

[0513] The title compound was prepared from N-(3,3-difluoropiperidin-4-yl)-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400

MHz, DMSO- d_6) δ 7.92 – 7.67 (m, 3H), 7.66 – 7.58 (m, 1H), 7.55 – 7.45 (m, 3H), 7.24 (pd, J = 7.4, 1.5 Hz, 2H), 7.16 (td, J = 8.6, 2.6 Hz, 1H), 6.83 (dd, J = 8.8, 1.9 Hz, 1H), 6.74 (d, J = 1.9 Hz, 1H), 6.24 (d, J = 9.1 Hz, 1H), 4.43 – 4.26 (m, 1H), 3.94 (s, 3H), 3.87 – 3.62 (m, 3H), 3.34 (d, J = 11.2 Hz, 1H), 2.21 – 2.05 (m, 2H); LC-MS (Method 2): t_R = 6.94 min, m/z ($M+H$) $^+$ = 527.

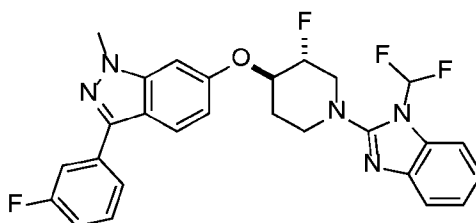
Example 229. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-1-methyl-N-(trifluoromethyl)-1H-indazol-6-amine (Cpd 229)



Cpd 229

[0514] The title compound was prepared from 3-(3-fluorophenyl)-6-(((3R,4R)-3-fluoropiperidin-4-yl)oxy)-1-methyl-1H-indazole, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.02 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.76 (t, J = 57.4 Hz, 1H), 7.55d, J = 8.8 Hz, 7.47 (m, 3H), 7.32 – 7.15 (m, 6H), 4.85 – 4.60 (m, 2H), 3.48 (tt, J = 12.3, 7.6 Hz, 1H), 3.36 (s, 3H), 3.29 – 3.10 (m, 3H), 2.23 – 2.09 (m, 1H), 1.66 (td, J = 13.9, 5.4 Hz, 1H); LC-MS (Method 2): t_R = 6.58 min, m/z ($M+H$) $^+$ = 559.

Example 230. 6-(((3R,4R)-1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)-3-fluoropiperidin-4-yl)oxy)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 230)

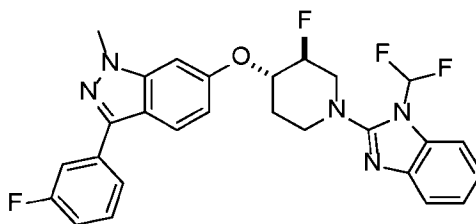


Cpd 230

[0515] The title compound was prepared from 3-(3-fluorophenyl)-6-(((3R,4R)-3-fluoropiperidin-4-yl)oxy)-1-methyl-1H-indazole, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.02 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.76 (t, J = 57.4 Hz, 1H), 7.55d, J = 8.8 Hz, 7.47 (m, 3H), 7.32 – 7.15 (m, 6H), 4.85 – 4.60 (m, 2H), 3.48 (tt, J = 12.3, 7.6

Hz, 1H), 3.36 (s, 3H), 3.29 – 3.10 (m, 3H), 2.23 – 2.09 (m, 1H), 1.66 (td, $J = 13.9, 5.4$ Hz, 1H); LC-MS (Method 2): $t_R = 6.06$ min, m/z (M+H)⁺ = 510.

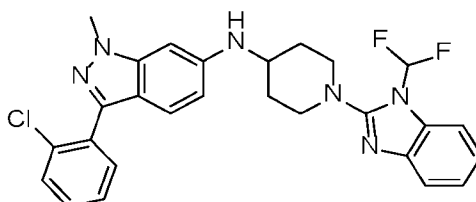
Example 231. 6-(((3S,4S)-1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)-3-fluoropiperidin-4-yl)oxy)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 231)



Cpd 231

[0516] The title compound was prepared from 3-(3-fluorophenyl)-6-(((3S,4S)-3-fluoropiperidin-4-yl)oxy)-1-methyl-1H-indazole, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.02 (s, 1H), 7.77 (d, $J = 8.8$ Hz, 1H), 7.68 (t, $J = 57.4$ Hz, 1H), 7.55d, $J = 8.8$ Hz, 7.47 (m, 3H), 7.31 – 7.16 (m, 6H), 4.85 – 4.60 (m, 2H), 3.53 – 3.43 (m, 1H), 3.36 (s, 3H), 3.29 – 3.09 (m, 3H), 2.14 (d, $J = 12.7$ Hz, 1H), 1.66 (q, $J = 8.3$ Hz, 1H); LC-MS (Method 2): $t_R = 6.16$ min, m/z (M+H)⁺ = 510.

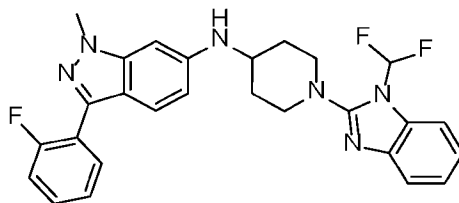
Example 232. 3-(2-chlorophenyl)-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine (Cpd 232)



Cpd 232

[0517] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (2-chlorophenyl)boronic acid following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.71 (t, $J = 57.4$ Hz, 1H), 7.59 – 7.39 (m, 6H), 7.26 – 7.15 (m, 3H), 6.62 (dd, $J = 8.8, 1.8$ Hz, 1H), 6.55 (d, $J = 1.8$ Hz, 1H), 5.99 (d, $J = 7.9$ Hz, 1H), 3.94 (s, 3H), 3.65 – 3.57 (m, 3H), 3.30 – 3.18 (m, 2H), 2.14 – 2.06 (m, 2H), 1.70 (q, $J = 10.1$ Hz, 2H); LC-MS (Method 2): $t_R = 5.37$ min, m/z (M+H)⁺ = 507.

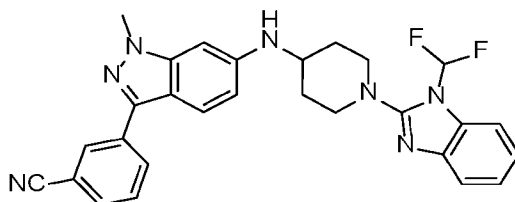
Example 233. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(2-fluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 233)



Cpd 233

[0518] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (2-fluorophenyl)boronic acid following a similar procedure as described in **Example 15**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.89 – 7.55 (m, 2H), 7.52 – 7.47 (m, 2H), 7.46 – 7.12 (m, 6H), 6.65 (dd, J = 8.9, 1.8 Hz, 1H), 6.55 (d, J = 1.9 Hz, 1H), 6.00 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.72 – 3.55 (m, 3H), 3.30 – 3.18 (m, 2H), 2.15 – 2.06 (m, 2H), 1.70 (q, J = 9.9 Hz, 2H); LC-MS (Method 2): t_R = 5.25 min, m/z ($M+H$) $^+$ = 491.

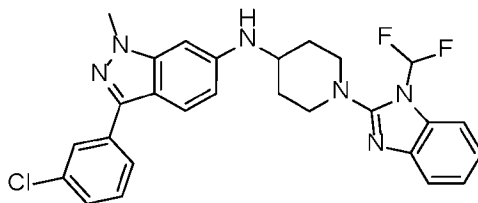
Example 234. 3-(6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)amino)-1-methyl-1H-indazol-3-yl)benzonitrile (Cpd 234)



Cpd 234

[0519] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (3-cyanophenyl)boronic acid following a similar procedure as described in **Example 15**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.24 – 8.21 (m, 2H), 7.82 – 7.75 (m, 2H), 7.88 – 7.54 (m, 2H), 7.53 – 7.46 (m, 2H), 7.25 – 7.16 (m, 2H), 6.72 (dd, J = 9.0, 1.8 Hz, 1H), 6.57 (d, J = 1.9 Hz, 1H), 6.08 (d, J = 7.9 Hz, 1H), 3.96 (s, 3H), 3.73 – 3.54 (m, 3H), 3.30 – 3.18 (m, 2H), 2.15 – 2.07 (m, 2H), 1.70 (d, J = 11.3 Hz, 2H); LC-MS (Method 2): t_R = 5.30 min, m/z ($M+H$) $^+$ = 498.

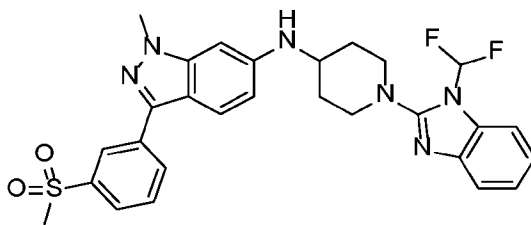
Example 235. 3-(3-chlorophenyl)-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine (Cpd 235)



Cpd 235

[0520] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (3-chlorophenyl)boronic acid following a similar procedure as described in **Example 15**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.87–7.85 (m, 2H), 7.71 (d, J = 2.2 Hz, 1H), 7.69 (t, J = 57.4 Hz, 1H), 7.52–7.45 (m, 3H), 7.39 (ddd, J = 8.0, 2.2, 1.1 Hz, 1H), 7.24–7.17 (m, 2H), 6.70 (dd, J = 8.8, 1.8 Hz, 1H), 6.56 (d, J = 1.9 Hz, 1H), 6.05 (d, J = 7.9 Hz, 1H), 3.95 (s, 3H), 3.66–3.58 (m, 2H), 3.28–3.17 (m, 3H), 2.15–2.06 (m, 2H), 1.70 (q, J = 10.2 Hz, 2H); LC-MS (Method 2): t_R = 5.79 min, m/z ($M+H$) $^+$ = 507.

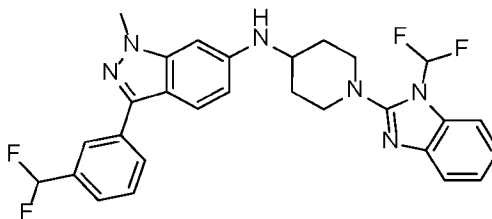
Example 236. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-3-(3-(methylsulfonyl)phenyl)-1H-indazol-6-amine (Cpd 236)



Cpd 236

[0521] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (3-(methylsulfonyl)phenyl)boronic acid following a similar procedure as described in **Example 15**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.37 (t, J = 1.8 Hz, 1H), 8.24 (dt, J = 7.9, 1.4 Hz, 1H), 7.92–7.55 (m, 4H), 7.53–7.46 (m, 2H), 7.25–7.16 (m, 2H), 6.74 (dd, J = 8.9, 1.8 Hz, 1H), 6.59 (d, J = 1.9 Hz, 1H), 6.09 (d, J = 7.9 Hz, 1H), 3.98 (s, 3H), 3.72–3.52 (m, 3H), 3.27 (s, 3H), 3.23 (d, J = 11.7 Hz, 2H), 2.15–2.07 (m, 2H), 1.72 (t, J = 10.6 Hz, 2H); LC-MS (Method 2): t_R = 4.85 min, m/z ($M+H$) $^+$ = 551.

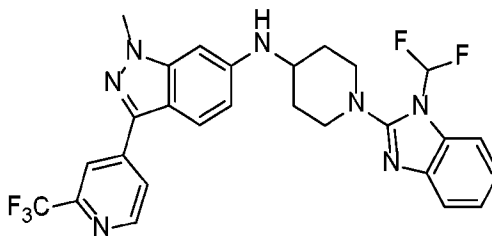
Example 237. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-(difluoromethyl)phenyl)-1-methyl-1H-indazol-6-amine (Cpd 237)



Cpd 237

[0522] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (3-(difluoromethyl)phenyl)boronic acid following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.10 – 8.03 (m, 2H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.71 (t, *J* = 57.9 Hz, 1H), 7.64 – 7.45 (m, 4H), 7.25 – 7.17 (m, 2H), 7.13 (t, *J* = 55.9 Hz, 1H), 6.71 (dd, *J* = 8.9, 1.8 Hz, 1H), 6.57 (d, *J* = 1.8 Hz, 1H), 6.05 (d, *J* = 7.9 Hz, 1H), 3.95 (s, 3H), 3.72 – 3.53 (m, 3H), 3.30 – 3.19 (m, 2H), 2.11 (d, *J* = 12.5 Hz, 2H), 1.70 (q, *J* = 9.7 Hz, 2H); LC-MS (Method 2): *t*_R = 5.49 min, *m/z* (M+H)⁺ = 523.

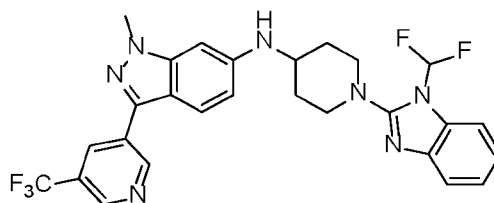
Example 238. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-3-(2-(trifluoromethyl)pyridin-4-yl)-1H-indazol-6-amine (Cpd 238)



Cpd 238

[0523] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (2-(trifluoromethyl)pyridin-4-yl)boronic acid following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.80 (d, *J* = 5.1 Hz, 1H), 8.23 (s, 1H), 8.20 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.89 – 7.83 (m, 1H), 7.72 (t, *J* = 57.9 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.25 – 7.16 (m, 2H), 6.79 (dd, *J* = 8.9, 1.8 Hz, 1H), 6.63 (d, *J* = 1.9 Hz, 1H), 6.17 (d, *J* = 7.9 Hz, 1H), 4.01 (s, 3H), 3.75 – 3.50 (m, 3H), 3.30 – 3.18 (m, 2H), 2.15 – 2.07 (m, 2H), 1.71 (q, *J* = 10.2 Hz, 2H); LC-MS (Method 2): *t*_R = 5.56 min, *m/z* (M+H)⁺ = 542.

Example 239. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-3-(5-(trifluoromethyl)pyridin-3-yl)-1H-indazol-6-amine (Cpd 239)

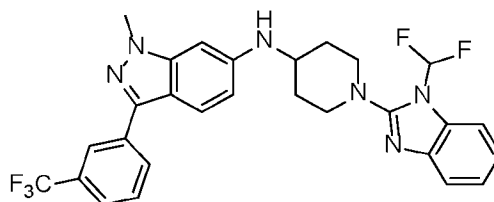


Cpd 239

[0524] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (5-(trifluoromethyl)pyridin-3-yl)boronic acid following a similar procedure as described in

Example 15. ^1H NMR (400 MHz, DMSO- d_6) δ 8.80 (d, J = 5.1 Hz, 1H), 8.23 (s, 1H), 8.20 (dd, J = 5.1, 1.6 Hz, 1H), 7.89 – 7.83 (m, 1H), 7.72 (t, J = 57.9 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.25 – 7.16 (m, 2H), 6.79 (dd, J = 8.9, 1.8 Hz, 1H), 6.63 (d, J = 1.8 Hz, 1H), 6.17 (d, J = 7.9 Hz, 1H), 4.01 (s, 3H), 3.73 – 3.54 (m, 3H), 3.30 – 3.19 (m, 2H), 2.14 – 2.07 (m, 2H), 1.71 (q, J = 10.1 Hz, 2H); LC-MS (Method 2): t_R = 5.56 min, m/z ($M+H$) $^+$ = 542.

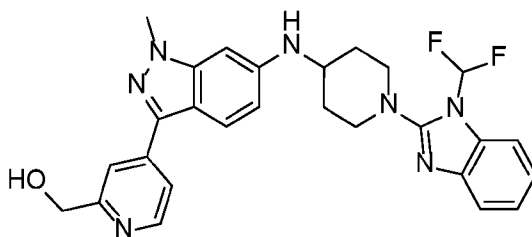
Example 240. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-3-(3-(trifluoromethyl)phenyl)-1H-indazol-6-amine (Cpd 240)



Cpd 240

[0525] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (3-(trifluoromethyl)phenyl)boronic acid following a similar procedure as described in **Example 15.** ^1H NMR (400 MHz, DMSO- d_6) δ 8.24 – 8.17 (m, 1H), 8.14 (s, 1H), 7.88 – 7.54 (m, 4H), 7.53 – 7.46 (m, 2H), 7.25 – 7.16 (m, 2H), 6.73 (dd, J = 8.9, 1.8 Hz, 1H), 6.58 (d, J = 1.9 Hz, 1H), 6.08 (d, J = 7.9 Hz, 1H), 3.97 (s, 3H), 3.60 (dd, J = 13.1, 3.9 Hz, 3H), 3.28 – 3.17 (m, 2H), 2.15 – 2.07 (m, 2H), 1.78 – 1.63 (m, 2H); LC-MS (Method 2): t_R = 5.93 min, m/z ($M+H$) $^+$ = 541.

Example 241. (4-(6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)amino)-1-methyl-1H-indazol-3-yl)pyridin-2-yl)methanol (Cpd 241)

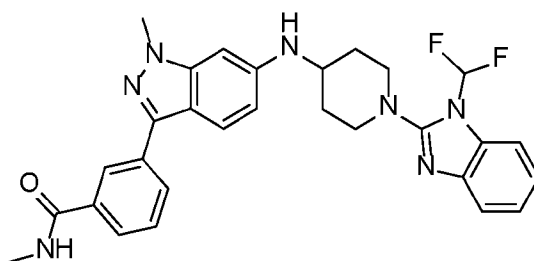


Cpd 241

[0526] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (2-(hydroxymethyl)pyridin-4-yl)boronic acid following a similar procedure as described in

Example 15. ^1H NMR (400 MHz, DMSO- d_6) δ 8.50 (d, J = 5.1 Hz, 1H), 7.98 (s, 1H), 7.80 (d, J = 8.9 Hz, 1H), 7.76 – 7.69 (m, 1H), 7.71 (t, J = 57.4 Hz, 1H), 7.49 (dd, J = 7.4, 1.5 Hz, 2H), 7.25 – 7.16 (m, 2H), 6.75 (dd, J = 9.0, 1.8 Hz, 1H), 6.60 (d, J = 1.8 Hz, 1H), 6.10 (d, J = 7.9 Hz, 1H), 5.48 (t, J = 6.0 Hz, 1H), 4.61 (d, J = 6.0 Hz, 2H), 3.98 (s, 3H), 3.73 – 3.52 (m, 3H), 3.30 – 3.19 (m, 2H), 2.11 (d, J = 12.7 Hz, 2H), 1.71 (d, J = 11.4 Hz, 2H); LC-MS (Method 2): t_R = 3.94 min, m/z ($M+H$) $^+$ = 504.

Example 242. 3-(6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)amino)-1-methyl-1H-indazol-3-yl)-N-methylbenzamide (Cpd 242)

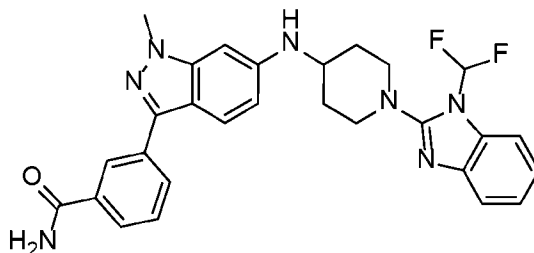


Cpd 242

[0527] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (3-(methylcarbamoyl)phenyl)boronic acid following a similar procedure as described in **Example 15.** ^1H NMR (400 MHz, DMSO- d_6) δ 8.56 – 8.51 (m, 1H), 8.31 (t, J = 1.8 Hz, 1H), 8.18 – 7.68 (m, 4H), 7.61 – 7.46 (m, 3H), 7.25 – 7.16 (m, 2H), 6.71 (dd, J = 8.9, 1.8 Hz, 1H), 6.57 (d, J = 1.9 Hz, 1H), 6.04 (d, J = 7.9 Hz, 1H), 3.95 (s, 3H), 3.73 – 3.54 (m, 3H), 3.30 – 3.18 (m, 2H), 2.80 (d,

$J = 4.5$ Hz, 3H), 2.11 (d, $J = 12.6$ Hz, 2H), 1.78 – 1.64 (m, 2H); LC-MS (Method 2): $t_R = 4.55$ min, m/z (M+H)⁺ = 530.

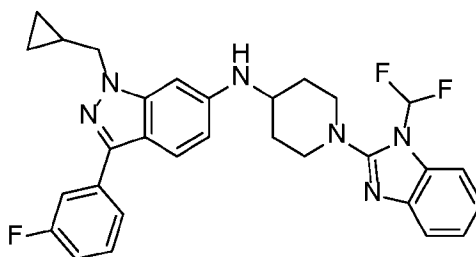
Example 243. 3-(6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)amino)-1-methyl-1H-indazol-3-yl)benzamide (Cpd 243)



Cpd 243

[0528] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (3-carbamoylphenyl)boronic acid following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.35 (t, $J = 1.8$ Hz, 1H), 8.23 – 7.66 (m, 5H), 7.61 – 7.32 (m, 4H), 7.25 – 7.16 (m, 2H), 6.71 (dd, $J = 8.9, 1.8$ Hz, 1H), 6.57 (d, $J = 1.8$ Hz, 1H), 6.03 (d, $J = 7.9$ Hz, 1H), 3.95 (s, 3H), 3.72 – 3.55 (m, 3H), 3.30 – 3.18 (m, 2H), 2.11 (dd, $J = 13.6, 3.8$ Hz, 2H), 1.78 – 1.64 (m, 2H); LC-MS (Method 2): $t_R = 4.40$ min, m/z (M+H)⁺ = 516.

Example 244. 1-(cyclopropylmethyl)-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-1H-indazol-6-amine (Cpd 244)

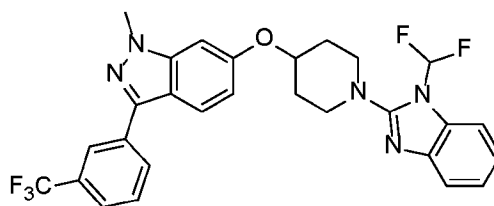


Cpd 244

[0529] The title compound was prepared from 1-(cyclopropylmethyl)-3-(3-fluorophenyl)-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.77 – 7.71 (m, 2H), 7.70 (t, $J = 57.4$ Hz, 1H), 7.62 (ddd, $J = 10.5, 2.6, 1.5$ Hz, 1H), 7.54 – 7.45 (m, 3H), 7.27 – 7.11 (m, 3H), 6.69 (dd, $J = 8.9, 1.8$ Hz, 1H), 6.63 (d, $J = 1.9$ Hz, 1H), 6.00 (d, $J = 8.0$ Hz, 1H), 4.20 (d, $J = 6.8$ Hz, 2H), 3.74 – 3.51 (m, 3H), 3.30 – 3.19 (m,

2H), 2.09 (dd, $J = 13.3, 3.8$ Hz, 2H), 1.77 – 1.63 (m, 2H), 1.34 – 1.19 (m, 1H), 0.49 (dq, $J = 8.0, 2.5$ Hz, 2H), 0.45 – 0.35 (m, 2H); LC-MS (Method 2): $t_R = 5.98$ min, m/z (M+H)⁺ = 531.

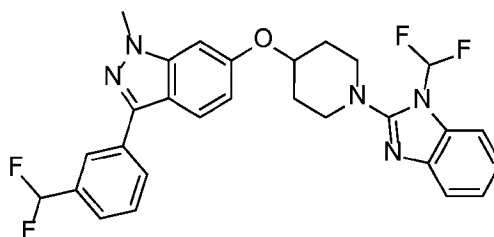
Example 245. 6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-1-methyl-3-(3-(trifluoromethyl)phenyl)-1H-indazole (Cpd 245)



Cpd 245

[0530] The title compound was prepared from 3-bromo-6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-1-methyl-1H-indazole and (3-(trifluoromethyl)phenyl)boronic acid following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.02 (s, 1H), 7.81 – 7.58 (m, 6H), 7.47 – 7.44 (m, 2H), 7.24 – 7.13 (m, 3H), 4.64 (dt, $J = 7.1, 3.5$ Hz, 1H), 3.34 (s, 3H), 3.09 (t, $J = 5.6$ Hz, 4H), 2.02 – 1.92 (m, 2H), 1.67 (dt, $J = 13.1, 6.5$ Hz, 2H); LC-MS (Method 2): $t_R = 5.96$ min, m/z (M+H)⁺ = 542.

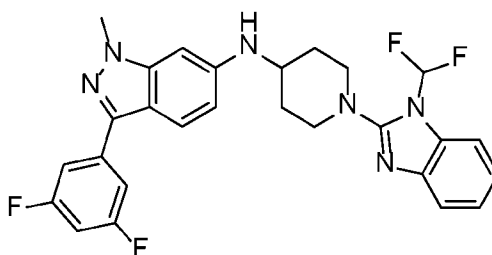
Example 246. 6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-3-(3-(difluoromethyl)phenyl)-1-methyl-1H-indazole (Cpd 246)



Cpd 246

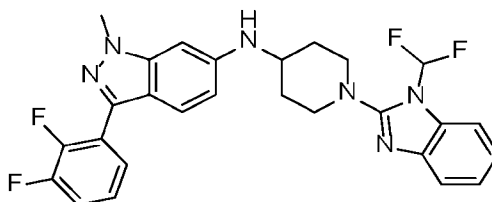
[0531] The title compound was prepared from 3-bromo-6-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-1-methyl-1H-indazole and (3-(difluoromethyl)phenyl)boronic acid following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.01 (s, 1H), 7.80 – 7.40 (m, 8H), 7.25 – 7.13 (m, 3H), 7.07 (t, $J = 55.9$ Hz, 1H), 4.62 (dt, $J = 7.1, 3.6$ Hz, 1H), 3.32 (s, 3H), 3.10 (q, $J = 6.4$ Hz, 4H), 2.01 – 1.91 (m, 2H), 1.67 (dd, $J = 13.0, 6.5$ Hz, 2H); LC-MS (Method 2): $t_R = 5.63$ min, m/z (M+H)⁺ = 524.

Example 247. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3,5-difluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 247)

**Cpd 247**

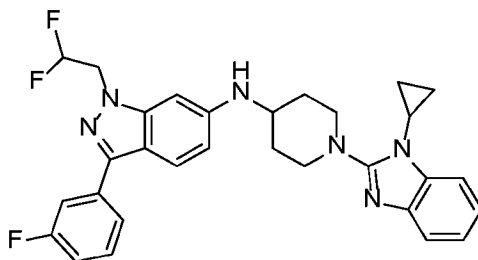
[0532] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (3,5-difluorophenyl)boronic acid following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.76 (d, *J* = 8.9 Hz, 1H), 7.71 (t, *J* = 57.9 Hz, 1H), 7.56 – 7.45 (m, 4H), 7.27 – 7.14 (m, 3H), 6.72 (dd, *J* = 8.9, 1.8 Hz, 1H), 6.57 (d, *J* = 1.8 Hz, 1H), 6.08 (d, *J* = 7.9 Hz, 1H), 3.95 (s, 3H), 3.72 – 3.53 (m, 3H), 3.30 – 3.18 (m, 2H), 2.14 – 2.06 (m, 2H), 1.77 – 1.63 (m, 2H); LC-MS (Method 2): *t*_R = 5.73 min, *m/z* (M+H)⁺ = 509.

Example 248. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(2,3-difluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 248)

**Cpd 248**

[0533] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (2,3-difluorophenyl)boronic acid following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.71 (t, *J* = 57.9 Hz, 1H), 7.56 – 7.38 (m, 5H), 7.34 – 7.14 (m, 3H), 6.67 (dd, *J* = 8.9, 1.8 Hz, 1H), 6.57 (d, *J* = 1.8 Hz, 1H), 6.05 (d, *J* = 7.9 Hz, 1H), 3.96 (s, 3H), 3.66 – 3.58 (m, 3H), 3.30 – 3.19 (m, 2H), 2.14 – 2.06 (m, 2H), 1.70 (q, *J* = 10.2 Hz, 2H); LC-MS (Method 2): *t*_R = 5.42 min, *m/z* (M+H)⁺ = 509.

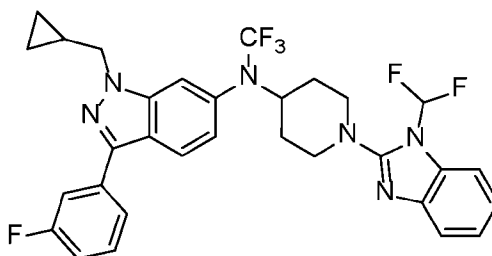
Example 249. N-(1-(1-cyclopropyl-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-(2,2-difluoroethyl)-3-(3-fluorophenyl)-1H-indazol-6-amine (Cpd 249)



Cpd 249

[0534] The title compound was prepared from 1-(2,2-difluoroethyl)-3-(3-fluorophenyl)-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl and 2-chloro-1-cyclopropyl-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.79 – 7.69 (m, 2H), 7.63 (ddd, *J* = 10.4, 2.7, 1.5 Hz, 1H), 7.52 (td, *J* = 8.0, 6.2 Hz, 1H), 7.35 – 7.26 (m, 2H), 7.20 (td, *J* = 8.7, 2.6 Hz, 1H), 7.07 – 6.99 (m, 2H), 6.72 (dt, *J* = 4.4, 2.1 Hz, 2H), 6.44 (tt, *J* = 55.1, 3.9 Hz, 1H), 6.09 (d, *J* = 8.1 Hz, 1H), 4.83 (td, *J* = 15.0, 3.9 Hz, 2H), 3.96 (d, *J* = 12.7 Hz, 2H), 3.70 – 3.54 (m, 1H), 3.36 (tt, *J* = 7.0, 3.7 Hz, 1H), 3.16 (t, *J* = 11.9 Hz, 2H), 2.12 (d, *J* = 12.6 Hz, 2H), 1.64 (q, *J* = 10.7 Hz, 2H), 1.15 (dt, *J* = 7.1, 3.5 Hz, 2H), 0.91 (dd, *J* = 4.7, 2.1 Hz, 2H); LC-MS (Method 2): *t*_R = 5.12 min, *m/z* (M+H)⁺ = 531.

Example 250. 1-(cyclopropylmethyl)-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-N-(trifluoromethyl)-1H-indazol-6-amine (Cpd 250)

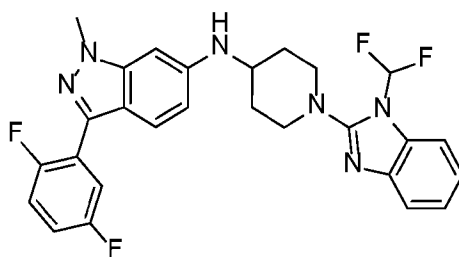


Cpd 250

[0535] To a mixture of 1-(cyclopropylmethyl)-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-1H-indazol-6-amine (106 mg, 0.2 mmol) and tetramethylammonium trifluoromethanethiolate (70.1 mg, 0.40 mmol) was added MeCN (1 ml). The mixture was stirred at rt for overnight. Then, silver(I) fluoride (101 mg, 0.80 mmol) was added and stirred at rt for another 4 hr. The mixture was poured into EtOAc/H₂O (15 mL/15 mL). The organic layer was washed with H₂O (15 mL), dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography (12g column) using 0-

35% EtOAc/hexane as the eluent to give 1-(cyclopropylmethyl)-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-N-(trifluoromethyl)-1H-indazol-6-amine (61 mg, 0.102 mmol, 51.0 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.13 (d, *J* = 8.7 Hz, 1H), 7.85 – 7.78 (m, 1H), 7.75 (d, *J* = 1.7 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.58 – 7.53 (m, 2H), 7.45 – 7.39 (m, 2H), 7.24 (td, *J* = 8.6, 2.7 Hz, 1H), 7.21 – 7.09 (m, 3H), 4.41 (d, *J* = 7.0 Hz, 2H), 3.82 (td, *J* = 11.9, 5.9 Hz, 1H), 3.52 (d, *J* = 12.5 Hz, 2H), 3.19 – 3.09 (m, 2H), 2.03 (d, *J* = 11.6 Hz, 2H), 1.81 – 1.68 (m, 2H), 1.29 (ddt, *J* = 10.0, 7.3, 3.8 Hz, 1H), 0.53 – 0.39 (m, 4H); LC-MS (Method 2): *t*_R = 6.95 min, *m/z* (M+H)⁺ = 599.

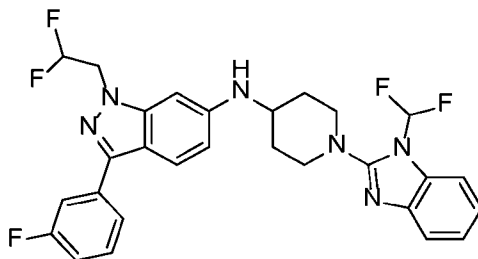
Example 251. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(2,5-difluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 251)



Cpd 251

[0536] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (2,5-difluorophenyl)boronic acid following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.71 (t, *J* = 57.9 Hz, 1H), 7.52 – 7.44 (m, 3H), 7.44 – 7.34 (m, 2H), 7.30 – 7.16 (m, 3H), 6.67 (dd, *J* = 8.9, 1.8 Hz, 1H), 6.56 (d, *J* = 1.9 Hz, 1H), 6.04 (d, *J* = 7.9 Hz, 1H), 3.96 (s, 3H), 3.71 – 3.53 (m, 3H), 3.30 – 3.18 (m, 2H), 2.10 (d, *J* = 12.7 Hz, 2H), 1.77 – 1.64 (m, 2H); LC-MS (Method 2): *t*_R = 5.43 min, *m/z* (M+H)⁺ = 509.

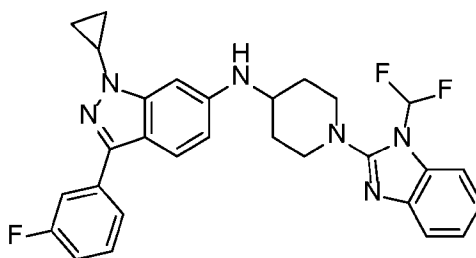
Example 252. 1-(2,2-difluoroethyl)-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-1H-indazol-6-amine (Cpd 252)



Cpd 252

[0537] The title compound was prepared from 1-(2,2-difluoroethyl)-3-(3-fluorophenyl)-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.79 – 7.73 (m, 2H), 7.71 (t, J = 57.4 Hz, 1H), 7.63 (ddd, J = 10.4, 2.7, 1.5 Hz, 1H), 7.56 – 7.45 (m, 3H), 7.25 – 7.16 (m, 3H), 6.76 – 6.68 (m, 2H), 6.44 (tt, J = 55.1, 4.0 Hz, 1H), 6.12 (d, J = 7.9 Hz, 1H), 4.82 (td, J = 14.9, 3.9 Hz, 2H), 3.60 (dd, J = 13.4, 4.2 Hz, 3H), 3.24 (dd, J = 20.4, 8.9 Hz, 2H), 2.10 (d, J = 12.5 Hz, 2H), 1.70 (q, J = 11.2 Hz, 2H); LC-MS (Method 2): t_R = 5.72 min, m/z ($M+H$) $^+$ = 541.

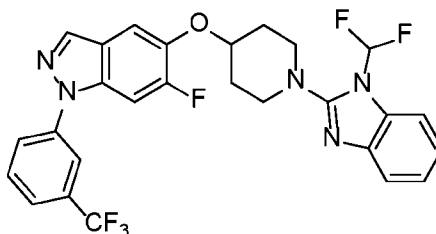
Example 253. 1-cyclopropyl-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-1H-indazol-6-amine (Cpd 253)



Cpd 253

[0538] The title compound was prepared from 1-cyclopropyl-3-(3-fluorophenyl)-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.74 – 7.71 (m, 2H), 7.70 (t, J = 57.4 Hz, 1H), 7.60 (dt, J = 10.3, 2.1 Hz, 1H), 7.54 – 7.44 (m, 3H), 7.27 – 7.12 (m, 3H), 6.72 (dd, J = 8.9, 1.9 Hz, 1H), 6.64 (d, J = 1.9 Hz, 1H), 6.10 (d, J = 7.8 Hz, 1H), 3.70 – 3.54 (m, 4H), 3.23 (d, J = 10.7 Hz, 2H), 2.15 – 2.07 (m, 2H), 1.78 – 1.66 (m, 2H), 1.13 – 1.05 (m, 4H); LC-MS (Method 2): t_R = 5.81 min, m/z ($M+H$) $^+$ = 517.

Example 254. 5-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazole (Cpd 254)



Cpd 254

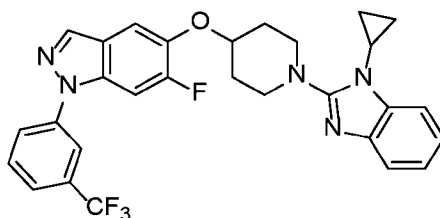
STEP 1: Synthesis of 6-fluoro-5-(piperidin-4-yloxy)-1-(3-(trifluoromethyl)phenyl)-1H-indazole, HCl

[0539] The material, 6-fluoro-5-(piperidin-4-yloxy)-1-(3-(trifluoromethyl)phenyl)-1H-indazole, HCl, was prepared from 6-fluoro-1H-indazol-5-ol and 1-bromo-3-trifluoromethylbenzene following a similar procedure as described in **Example 223** (STEP 1 to STEP 3). LC-MS (Method 1): t_R = 3.00 min, m/z (M+H)⁺ = 380.

STEP 2: Synthesis of 5-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazole (Cpd 254)

[0540] The title compound was prepared from 6-fluoro-5-(piperidin-4-yloxy)-1-(3-(trifluoromethyl)phenyl)-1H-indazole, HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.37 (d, J = 0.9 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.06 (s, 1H), 7.91 – 7.78 (m, 3H), 7.78 – 7.73 (m, 3H), 7.54 – 7.49 (m, 2H), 7.28 – 7.18 (m, 3H), 4.74 (t, J = 3.8 Hz, 1H), 3.53 (q, J = 10.4 Hz, 2H), 2.25 – 2.15 (m, 2H), 2.02 – 1.94 (m, 2H); LC-MS (Method 2): t_R = 6.22 min, m/z (M+H)⁺ = 546.

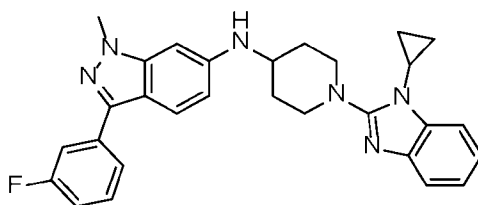
Example 255. 5-((1-(1-(cyclopropyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazole (Cpd 255)



Cpd 255

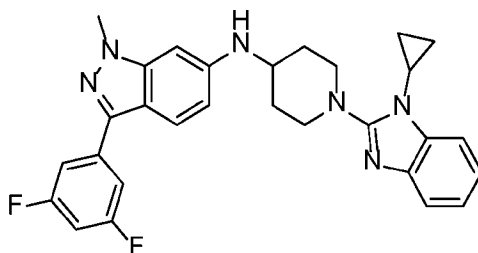
[0541] The title compound was prepared from 6-fluoro-5-(piperidin-4-yloxy)-1-(3-(trifluoromethyl)phenyl)-1H-indazole, HCl and 2-chloro-1-cyclopropyl-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.37 (d, J = 0.9 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.06 (s, 1H), 7.91 – 7.78 (m, 3H), 7.78 – 7.73 (m, 3H), 7.54 – 7.49 (m, 2H), 7.28 – 7.18 (m, 3H), 4.74 (t, J = 3.8 Hz, 1H), 3.53 (q, J = 10.4 Hz, 2H), 2.25 – 2.15 (m, 2H), 2.02 – 1.94 (m, 2H); LC-MS (Method 2): t_R = 5.53 min, m/z (M+H)⁺ = 536.

Example 256. N-(1-(1-(cyclopropyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 256)

**Cpd 256**

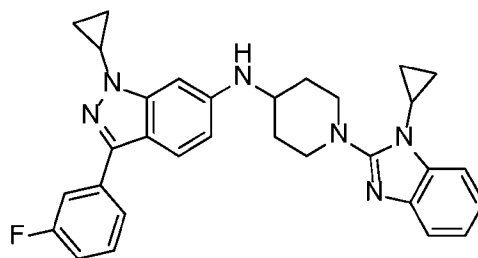
[0542] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl and 2-chloro-1-cyclopropyl-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.78 – 7.69 (m, 2H), 7.62 (ddd, *J* = 10.6, 2.7, 1.5 Hz, 1H), 7.50 (td, *J* = 8.0, 6.2 Hz, 1H), 7.31 (dt, *J* = 6.5, 2.6 Hz, 2H), 7.21 – 7.11 (m, 1H), 7.09 – 6.99 (m, 2H), 6.69 (dd, *J* = 8.9, 1.9 Hz, 1H), 6.57 (d, *J* = 1.9 Hz, 1H), 6.02 (d, *J* = 8.1 Hz, 1H), 3.99 – 3.95 (m, 5H), 3.72 – 3.55 (m, 1H), 3.35 (dq, *J* = 6.9, 3.5 Hz, 1H), 3.17 (t, *J* = 11.9 Hz, 2H), 2.12 (d, *J* = 12.5 Hz, 2H), 1.64 (q, *J* = 9.6 Hz, 2H), 1.16 (tt, *J* = 7.0, 3.9 Hz, 2H), 0.91 (p, *J* = 4.6 Hz, 2H); LC-MS (Method 2): *t*_R = 4.94 min, *m/z* (M+H)⁺ = 481.

Example 257. N-(1-(1-cyclopropyl-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3,5-difluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 257)

**Cpd 257**

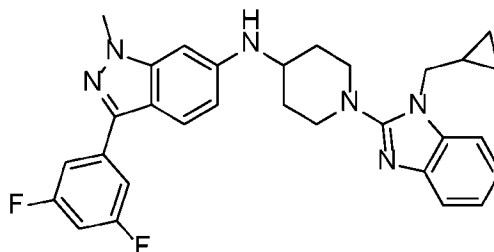
[0543] The title compound was prepared from 3-(3,5-difluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl and 2-chloro-1-cyclopropyl-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.76 (d, *J* = 8.9 Hz, 1H), 7.53 (qd, *J* = 6.9, 3.4 Hz, 2H), 7.36 – 7.25 (m, 2H), 7.19 (tt, *J* = 9.3, 2.4 Hz, 1H), 7.09 – 6.98 (m, 2H), 6.71 (dd, *J* = 8.9, 1.8 Hz, 1H), 6.58 (d, *J* = 1.9 Hz, 1H), 6.06 (d, *J* = 8.1 Hz, 1H), 3.99 – 3.94 (m, 5H), 3.72 – 3.59 (m, 1H), 3.35 (tt, *J* = 7.0, 3.7 Hz, 1H), 3.22 – 3.11 (m, 2H), 2.16 – 2.08 (m, 2H), 1.64 (q, *J* = 9.7 Hz, 2H), 1.15 (td, *J* = 7.2, 5.1 Hz, 2H), 0.95 – 0.86 (m, 2H); LC-MS (Method 2): *t*_R = 5.13 min, *m/z* (M+H)⁺ = 499.

Example 258. 1-cyclopropyl-N-(1-(1-cyclopropyl-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-1H-indazol-6-amine (Cpd 258)

**Cpd 258**

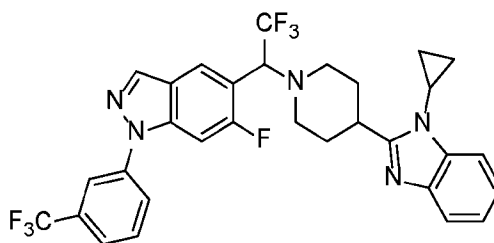
[0544] The title compound was prepared from 1-cyclopropyl-3-(3-fluorophenyl)-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl and 2-chloro-1-cyclopropyl-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.76 – 7.68 (m, 2H), 7.60 (ddd, *J* = 10.5, 2.7, 1.5 Hz, 1H), 7.49 (td, *J* = 8.0, 6.2 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.22 – 7.12 (m, 1H), 7.06 – 7.00 (m, 2H), 6.71 (dd, *J* = 8.9, 1.9 Hz, 1H), 6.65 (d, *J* = 1.9 Hz, 1H), 6.08 (d, *J* = 8.1 Hz, 1H), 3.95 (d, *J* = 12.7 Hz, 2H), 3.68 – 3.63 (m, 2H), 3.36 (dt, *J* = 6.8, 3.3 Hz, 1H), 3.19 (t, *J* = 11.9 Hz, 2H), 2.13 (d, *J* = 12.6 Hz, 2H), 1.66 (q, *J* = 10.0 Hz, 2H), 1.19 – 1.05 (m, 6H), 0.91 (p, *J* = 4.7 Hz, 2H); LC-MS (Method 2): *t*_R = 5.21 min, *m/z* (M+H)⁺ = 507.

Example 259. N-(1-(1-(cyclopropylmethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3,5-difluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 259)

**Cpd 259**

[0545] The title compound was prepared from 3-(3,5-difluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl and 2-chloro-1-(cyclopropylmethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.76 (d, *J* = 8.9 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.47 – 7.37 (m, 2H), 7.19 (tt, *J* = 9.3, 2.4 Hz, 1H), 7.14 – 7.03 (m, 2H), 6.71 (dd, *J* = 8.9, 1.9 Hz, 1H), 6.57 (d, *J* = 1.9 Hz, 1H), 6.06 (d, *J* = 8.2 Hz, 1H), 3.99 – 3.94 (m, 5H), 3.69 – 3.58 (m, 1H), 3.52 (dd, *J* = 10.1, 6.7 Hz, 2H), 3.18 – 3.07 (m, 2H), 2.11 (dd, *J* = 12.8, 3.8 Hz, 2H), 1.71 – 1.57 (m, 2H), 1.27 – 1.13 (m, 1H), 0.54 – 0.44 (m, 2H), 0.40 (qd, *J* = 5.0, 2.2 Hz, 2H); LC-MS (Method 2): *t*_R = 5.34 min, *m/z* (M+H)⁺ = 513.

Example 260. 5-(1-(4-(1-cyclopropyl-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)-2,2,2-trifluoroethyl)-6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazole, TFA (Cpd 260)

**Cpd 260**STEP 1: Synthesis of methyl 6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carboxylate

[0546] The material, methyl 6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carboxylate, was prepared from methyl 6-fluoro-1H-indazole-5-carboxylate and 1-bromo-3-trifluoromethylbenzene following a similar procedure as described in the synthesis of **Int-71** (STEP 1). LC-MS (Method 1): $t_R = 3.58$ min, m/z ($M+H$)⁺ = 339.

STEP 2: Synthesis of 6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carbaldehyde

[0547] The material, 6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carbaldehyde, was prepared from methyl 6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carboxylate following a similar procedure as described in the synthesis of **Int-30**. LC-MS (Method 1): $t_R = 3.525$ min, m/z ($M+H$)⁺ = 309.

STEP 3: Synthesis of 2,2,2-trifluoro-1-(6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-yl)ethan-1-ol

[0548] The material, 2,2,2-trifluoro-1-(6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-yl)ethan-1-ol, was prepared from 6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazole-5-carbaldehyde following a similar procedure as described in the synthesis of **Int-38**. LC-MS (Method 1): $t_R = 3.56$ min, m/z ($M+H$)⁺ = 379.

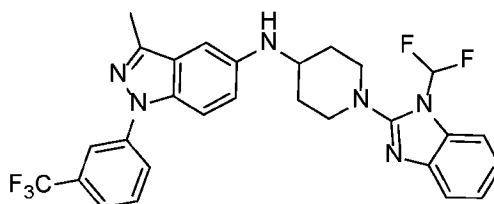
STEP 4: Synthesis of 2,2,2-trifluoro-1-(6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-yl)ethyl methanesulfonate

[0549] The material, 2,2,2-trifluoro-1-(6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-yl)ethyl methanesulfonate, was prepared from 2,2,2-trifluoro-1-(6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-yl)ethan-1-ol and methanesulfonyl chloride following a similar procedure as described in the synthesis of **Int-68**. LC-MS (Method 1): $t_R = 3.67$ min, m/z ($M+H$)⁺ = 457.

STEP 5: Synthesis of 5-(1-(4-(1-cyclopropyl-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)-2,2,2-trifluoroethyl)-6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazole, TFA (Cpd 260)

[0550] The title compound was prepared from 2,2,2-trifluoro-1-(6-fluoro-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-yl)ethyl methanesulfonate and 1-cyclopropyl-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 197**. LC-MS (Method 2): t_R = 5.96 min, m/z (M+H)⁺ = 602.

Example 261. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-amine (Cpd 261)



Cpd 261

STEP 1: Synthesis of 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-amine

[0551] The material, 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-amine, was prepared from 3-methyl-1H-indazol-5-amine and 1-bromo-3-trifluoromethylbenzene following a similar procedure as described in the synthesis of **Int-71** (STEP 1). LC-MS (Method 1): t_R = 2.785 min, m/z (M+H)⁺ = 292.

STEP 2: Synthesis of 3-methyl-N-(piperidin-4-yl)-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-amine, 2HCl

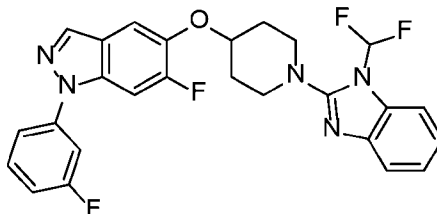
[0552] The material, 3-methyl-N-(piperidin-4-yl)-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-amine, 2HCl, was prepared from 3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-amine and tert-butyl 4-oxopiperidine-1-carboxylate following a similar procedure as described in the synthesis of **Int-52**. LC-MS (Method 1): t_R = 3.46 min, m/z (M+H)⁺ = 375.

STEP 3: Synthesis of N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-methyl-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-amine (Cpd 261)

[0553] The title compound was prepared from 3-methyl-N-(piperidin-4-yl)-1-(3-(trifluoromethyl)phenyl)-1H-indazol-5-amine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.06 (d, J = 8.3 Hz, 1H), 7.99 (s, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.72 – 7.66

(m, 1H), 7.63 – 7.56 (m, 1H), 7.50 (dd, $J = 7.4, 1.5$ Hz, 2H), 7.29 – 7.15 (m, 3H), 7.03 (dd, $J = 9.1, 2.1$ Hz, 1H), 6.85 (d, $J = 2.1$ Hz, 1H), 3.60 (d, $J = 13.2$ Hz, 3H), 3.24 (t, $J = 11.7$ Hz, 3H), 2.52 (s, 3H), 2.10 (d, $J = 12.7$ Hz, 2H), 1.69 (d, $J = 11.1$ Hz, 2H).; LC-MS (Method 2): $t_R = 5.54$ min, m/z ($M+H$) $^+ = 541$.

Example 262. 5-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-6-fluoro-1-(3-fluorophenyl)-1H-indazole, TFA (Cpd 262)



Cpd 262

STEP 1: Synthesis of 6-fluoro-1-(3-fluorophenyl)-1H-indazol-5-ol

[0554] The material, 6-fluoro-1-(3-fluorophenyl)-1H-indazol-5-ol, was prepared from 6-fluoro-1H-indazol-5-ol and 1-bromo-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-71** (STEP 1). LC-MS (Method 1): $t_R = 3.10$ min, m/z ($M+H$) $^+ = 247$.

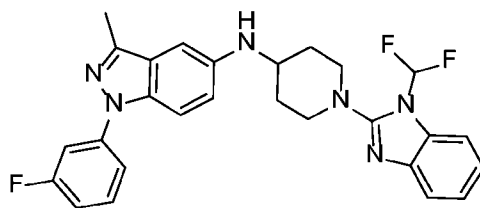
STEP 2: Synthesis of 6-fluoro-1-(3-fluorophenyl)-5-(piperidin-4-yloxy)-1H-indazole, 1HCl

[0555] The material, 6-fluoro-1-(3-fluorophenyl)-5-(piperidin-4-yloxy)-1H-indazole, 1HCl, was prepared from 6-fluoro-1-(3-fluorophenyl)-1H-indazol-5-ol and tert-butyl 4-hydroxypiperidine-1-carboxylate following a similar procedure as described in the synthesis of **Int-61** (STEP 1 and STEP 3). LC-MS (Method 1): $t_R = 2.83$ min, m/z ($M+H$) $^+ = 330$.

STEP 3: Synthesis of 5-((1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)oxy)-6-fluoro-1-(3-fluorophenyl)-1H-indazole, TFA (Cpd 262)

[0556] The title compound was prepared from 6-fluoro-1-(3-fluorophenyl)-5-(piperidin-4-yloxy)-1H-indazole, HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. LC-MS (Method 2): $t_R = 6.07$ min, m/z ($M+H$) $^+ = 496$.

Example 263. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-(3-fluorophenyl)-3-methyl-1H-indazol-5-amine (Cpd 263)

**Cpd 263****STEP 1: Synthesis of 1-(3-fluorophenyl)-3-methyl-1H-indazol-5-amine**

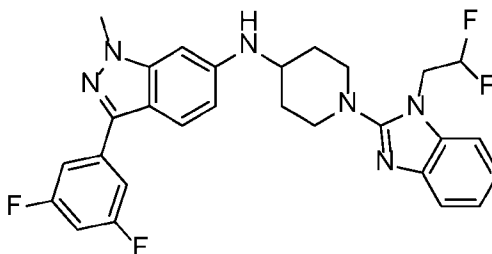
[0557] The material, 1-(3-fluorophenyl)-3-methyl-1H-indazol-5-amine, was prepared from 3-methyl-1H-indazol-5-amine and 1-bromo-3-fluorobenzene following a similar procedure as described in the synthesis of **Int-71** (STEP 1). LC-MS (Method 1): $t_R = 2.51$ min, m/z ($M+H$)⁺ = 242.

STEP 2: Synthesis of 1-(3-fluorophenyl)-3-methyl-N-(piperidin-4-yl)-1H-indazol-5-amine, 2HCl

[0558] The material, 1-(3-fluorophenyl)-3-methyl-N-(piperidin-4-yl)-1H-indazol-5-amine, 2HCl, was prepared from 1-(3-fluorophenyl)-3-methyl-1H-indazol-5-amine and tert-butyl 4-oxopiperidine-1-carboxylate following a similar procedure as described in the synthesis of **Int-52**. LC-MS (Method 1): $t_R = 2.58$ min, m/z ($M+H$)⁺ = 325.

STEP 3: Synthesis of N-(1-(1-(3-fluorophenyl)-3-methyl-1H-indazol-5-yl)piperidin-4-yl)-1-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 263)

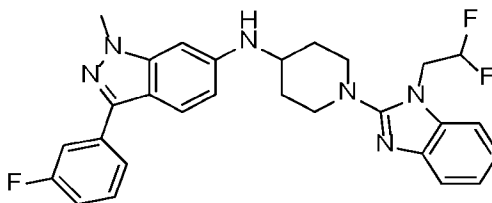
[0559] The title compound was prepared from 1-(3-fluorophenyl)-3-methyl-N-(piperidin-4-yl)-1H-indazol-5-amine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.78 – 7.64 (m, 2H), 7.65 – 7.43 (m, 6H), 7.22 (dtd, $J = 18.5, 7.5, 1.4$ Hz, 2H), 7.14 – 7.04 (m, 1H), 7.01 (dd, $J = 9.1, 2.2$ Hz, 1H), 6.83 (d, $J = 2.1$ Hz, 1H), 5.62 (d, $J = 8.2$ Hz, 1H), 3.60 (d, $J = 12.4$ Hz, 3H), 3.24 (t, $J = 11.5$ Hz, 2H), 2.10 (d, $J = 12.5$ Hz, 2H), 1.99 (s, 1H), 1.69 (q, $J = 9.8$ Hz, 2H), 1.17 (t, $J = 7.1$ Hz, 1H); LC-MS (Method 2): $t_R = 5.09$ min, m/z ($M+H$)⁺ = 491.

Example 264. N-(1-(1-(2,2-difluoroethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3,5-difluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 264)

Cpd 264

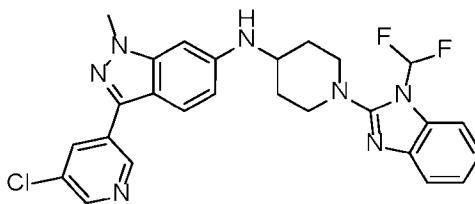
[0560] The title compound was prepared from 3-(3,5-difluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl and 2-chloro-1-(2,2-difluoroethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.76 (d, *J* = 8.9 Hz, 1H), 7.58 – 7.41 (m, 4H), 7.27 – 7.08 (m, 3H), 6.72 (dd, *J* = 8.9, 1.9 Hz, 1H), 6.57 (d, *J* = 1.8 Hz, 1H), 6.47 (tt, *J* = 54.9, 3.8 Hz, 1H), 6.06 (d, *J* = 8.0 Hz, 1H), 4.54 (td, *J* = 15.1, 3.8 Hz, 2H), 3.95 (s, 3H), 3.71 – 3.57 (m, 1H), 3.50 (dd, *J* = 10.6, 6.6 Hz, 2H), 3.20 – 3.06 (m, 2H), 2.16 – 2.06 (m, 2H), 1.74 – 1.60 (m, 2H); LC-MS (Method 2): *t*_R = 5.11 min, *m/z* (M+H)⁺ = 523.

Example 265. N-(1-(1-(2,2-difluoroethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 265)

**Cpd 265**

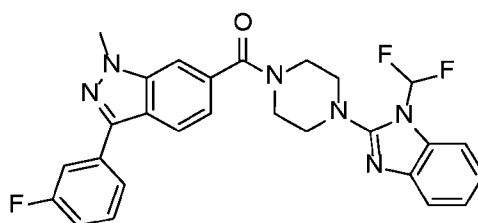
[0561] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl and 2-chloro-1-(2,2-difluoroethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.75 – 7.71 (m, 2H), 7.62 (ddd, *J* = 10.6, 2.7, 1.5 Hz, 1H), 7.55 – 7.41 (m, 3H), 7.21 – 7.08 (m, 3H), 6.70 (dd, *J* = 8.9, 1.9 Hz, 1H), 6.56 (d, *J* = 1.8 Hz, 1H), 6.47 (tt, *J* = 54.9, 3.8 Hz, 1H), 6.02 (d, *J* = 8.1 Hz, 1H), 4.54 (td, *J* = 15.1, 3.8 Hz, 2H), 3.95 (s, 3H), 3.63 (d, *J* = 9.7 Hz, 1H), 3.50 (dd, *J* = 10.2, 6.6 Hz, 2H), 3.19 – 3.08 (m, 2H), 2.10 (dd, *J* = 13.1, 3.9 Hz, 2H), 1.73 – 1.61 (m, 2H); LC-MS (Method 2): *t*_R = 4.85 min, *m/z* (M+H)⁺ = 505.

Example 266. 3-(5-chloropyridin-3-yl)-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine (Cpd 266)

**Cpd 266**

[0562] The title compound was prepared from 3-bromo-N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-6-amine and (5-chloropyridin-3-yl)boronic acid following a similar procedure as described in **Example 15**. ¹H NMR (400 MHz, DMSO-d₆) δ 9.05 (d, *J* = 1.8 Hz, 1H), 8.59 (d, *J* = 2.4 Hz, 1H), 8.27 (t, *J* = 2.1 Hz, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.71 (t, *J* = 57.9 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.21 (dtd, *J* = 18.3, 7.5, 1.3 Hz, 2H), 6.73 (dd, *J* = 8.9, 1.9 Hz, 1H), 6.59 (d, *J* = 1.8 Hz, 1H), 6.11 (d, *J* = 7.9 Hz, 1H), 3.97 (s, 3H), 3.73 – 3.53 (m, 3H), 3.29 – 3.19 (m, 2H), 2.10 (d, *J* = 12.7 Hz, 2H), 1.77 – 1.64 (m, 2H); LC-MS (Method 2): *t*_R = 5.32 min, *m/z* (M+H)⁺ = 508.

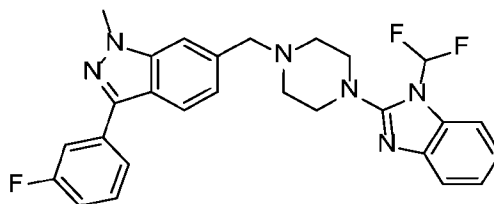
Example 267. (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 267)



Cpd 267

[0563] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 1-(difluoromethyl)-2-(piperazin-1-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.17 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.89 – 7.82 (m, 2H), 7.80 (t, *J* = 57.7 Hz, 1H), 7.72 (ddd, *J* = 10.4, 2.7, 1.5 Hz, 1H), 7.62 – 7.47 (m, 3H), 7.33 – 7.17 (m, 4H), 4.15 (s, 3H), 3.89 (br s, 2H), 3.61 (br s, 2H), 3.32 (br s, 4H); LC-MS (Method 2): *t*_R = 5.68 min, *m/z* (M+H)⁺ = 505.

Example 268. 6-((4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)methyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 268)

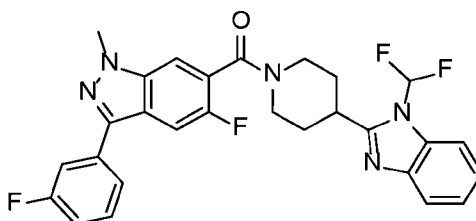


Cpd 268

[0564] The title compound was prepared from 3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carbaldehyde and 1-(difluoromethyl)-2-(piperazin-1-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 53**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.05 (d, *J* =

8.4 Hz, 1H), 7.82 (dt, $J = 7.8, 1.2$ Hz, 1H), 7.73 – 7.45 (m, 6H), 7.28 – 7.16 (m, 4H), 4.10 (s, 3H), 3.73 (s, 2H), 3.30 – 3.28 (m, 4H), 2.64 (t, $J = 4.8$ Hz, 4H); LC-MS (Method 2): $t_R = 4.75$ min, m/z (M+H)⁺ = 491.

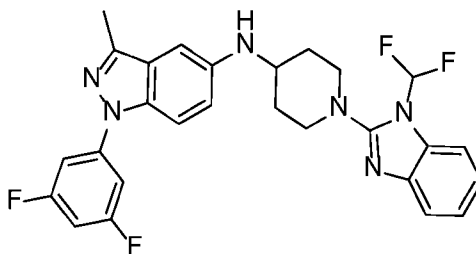
Example 269. (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(5-fluoro-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)methanone (Cpd 269)



Cpd 269

[0565] The title compound was prepared from 5-fluoro-3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl following a similar procedure as described in **Example 1**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.21 (t, $J = 57.4$ Hz, 1H), 8.03 (d, $J = 10.0$ Hz, 1H), 7.97 – 7.79 (m, 2H), 7.76 – 7.62 (m, 3H), 7.54 (td, $J = 8.1, 6.2$ Hz, 1H), 7.37 – 7.28 (m, 2H), 7.27 – 7.19 (m, 1H), 4.67 (d, $J = 13.0$ Hz, 1H), 4.14 (s, 3H), 3.59 (d, $J = 13.6$ Hz, 1H), 3.54 – 3.45 (m, 1H), 3.30 – 3.23 (m, 1H), 3.05 (td, $J = 12.8, 2.8$ Hz, 1H), 2.18 – 1.69 (m, 4H); LC-MS (Method 2): $t_R = 5.91$ min, m/z (M+H)⁺ = 522.

Example 270. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-(3,5-difluorophenyl)-3-methyl-1H-indazol-5-amine, TFA (Cpd 270)



Cpd 270

STEP 1: Synthesis of 1-(3,5-difluorophenyl)-3-methyl-1H-indazol-5-amine

[0566] The material, 1-(3,5-difluorophenyl)-3-methyl-1H-indazol-5-amine, was prepared from 3-methyl-1H-indazol-5-amine and (3,5-difluorophenyl)boronic acid following a similar procedure as described in the synthesis of **Int-24** (STEP 1). LC-MS (Method 1): $t_R = 2.64$ min, m/z (M+H)⁺ = 260.

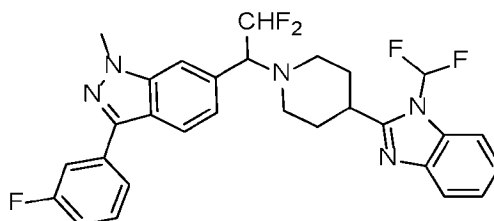
STEP 2: Synthesis of 1-(3,5-difluorophenyl)-3-methyl-N-(piperidin-4-yl)-1H-indazol-5-amine, 2HCl

[0567] The material, 1-(3,5-difluorophenyl)-3-methyl-N-(piperidin-4-yl)-1H-indazol-5-amine, 2HCl, was prepared from 1-(3,5-difluorophenyl)-3-methyl-1H-indazol-5-amine and tert-butyl 4-oxopiperidine-1-carboxylate following a similar procedure as described in the synthesis of **Int-52**. LC-MS (Method 1): $t_R = 2.78$ min, m/z ($M+H$)⁺ = 343.

STEP 3: Synthesis of N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-(3,5-difluorophenyl)-3-methyl-1H-indazol-5-amine, TFA (Cpd 270)

[0568] The title compound was prepared from 1-(3,5-difluorophenyl)-3-methyl-N-(piperidin-4-yl)-1H-indazol-5-amine, 2HCl and 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 102**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.92 – 7.55 (m, 2H), 7.53 – 7.44 (m, 5H), 7.29 – 7.19 (m, 3H), 7.15 (t, $J = 9.3$ Hz, 2H), 3.64 (dd, $J = 16.6$, 12.6 Hz, 3H), 3.23 (t, $J = 12.0$ Hz, 2H), 2.53 (s, 3H), 2.13 – 2.02 (m, 2H), 1.76 (d, $J = 11.7$ Hz, 2H); LC-MS (Method 2): $t_R = 5.35$ min, m/z ($M+H$)⁺ = 509.

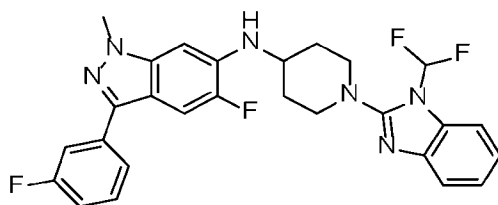
Example 271. 6-(1-(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)-2,2-difluoroethyl)-3-(3-fluorophenyl)-1-methyl-1H-indazole (Cpd 271)



Cpd 271

[0569] The title compound was prepared from 2,2-difluoro-1-(3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)ethyl 4-nitrobenzenesulfonate and 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole following a similar procedure as described in **Example 202**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.11 (d, $J = 8.5$ Hz, 1H), 8.06 (t, $J = 57.4$ Hz, 1H), 7.84 (dt, $J = 7.7$, 1.2 Hz, 1H), 7.77 – 7.53 (m, 5H), 7.33 – 7.19 (m, 4H), 6.76 (td, $J = 55.2$, 5.8 Hz, 1H), 4.24 – 4.11 (m, 5H), 3.16 – 3.07 (m, 2H), 2.97 – 2.95 (m, 1H), 2.36 (dt, $J = 11.3$, 5.8 Hz, 1H), 2.17 – 1.78 (m, 4H); LC-MS (Method 2): $t_R = 5.23$ min, m/z ($M+H$)⁺ = 540.

Example 272. N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-5-fluoro-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 272)

**Cpd 272****STEP 1: Synthesis of 5-fluoro-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine**

[0570] To a suspension of 5-fluoro-3-(3-fluorophenyl)-1-methyl-1H-indazole-6-carboxylic acid (288 mg, 1 mmol) in 1,4-dioxane (6 ml) was added tBuOH (0.765 ml, 8.0 mmol), Et₃N (0.558 ml, 4.0 mmol), and then diphenyl phosphorazidate (303 mg, 1.10 mmol). The mixture was stirred at 95 °C for 4 hr. After cooling to rt, the mixture with some salt precipitation was filtered through celite and eluted with EtOAc. The filtrate was concentrated and dried *in vacuo* for 1 hr. Then, to the crude product was added CH₂Cl₂ (1 mL) and TFA (3 mL) to remove the Boc group. After completion by LCMS, the mixture was concentrated to remove most of solvent and TFA. The crude residue was diluted with EtOAc/H₂O (15 mL/15 mL) and Na₂CO₃ (aq) was added dropwise until the pH of aqueous layer is > 8. The layer were separated and the aqueous layer was extracted with EtOAc (15 mL). The combined organic layer was dried (Na₂SO₄) and filtered. The filtrate was concentrated and some solid formed with low solubility in CH₂Cl₂. The crude product was then triturated with 20% CH₂Cl₂/hexane and filtered. The solid collected was the side product 1-(5-fluoro-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-ylurea (50 mg, 0.095 mmol, 9.50 % yield). The filtrate contained the designed product was concentrated and then was purified by silica gel chromatography using 10-40%EtOAc/hexane as the eluent to give 5-fluoro-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine (150 mg, 0.579 mmol, 57.9 % yield). LC-MS (Method 1): *t*_R = 3.30 min, *m/z* (M+H)⁺ = 260.

STEP 2: Synthesis of tert-butyl 4-((5-fluoro-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)amino)piperidine-1-carboxylate

[0571] To a mixture of 5-fluoro-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine (0.15 g, 0.579 mmol) and tert-butyl 4-oxopiperidine-1-carboxylate (0.231 g, 1.157 mmol) was added CH₂Cl₂ (3 ml). The mixture was stirred at rt for 5-10 min and then sodium triacetoxyborohydride (0.429 g, 2.025 mmol) was added portionwise. The mixture was stirred at rt for 36 hr. Then H₂O (5 mL) was added. Then, saturated Na₂CO₃ (aq) was added dropwise and slowly until the pH of aqueous layer is ca. 8. The mixture was stirred for 10 min and extracted with CH₂Cl₂ (5 mL x 2). The combined

organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 5-40% EtOAc/hexane as the eluent to give tert-butyl 4-((5-fluoro-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)amino)piperidine-1-carboxylate (226 mg, 0.511 mmol, 88 % yield). LC-MS (Method 1): *t_R* = 3.86 min, *m/z* (M+H)⁺ = 443.

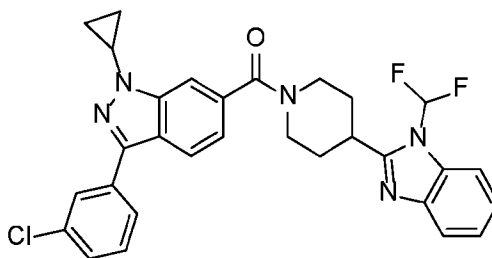
STEP 3: Synthesis of 5-fluoro-3-(3-fluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2 HCl

[0572] To a solution of tert-butyl 4-((5-fluoro-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-yl)amino)piperidine-1-carboxylate (226 mg, 0.51 mmol) in CH₂Cl₂ (4 ml) was added HCl (4M in dioxane, 4.90 mmol, 1.02 mL, 8 equiv). The mixture was stirred at rt for 1.5 hr. Then, hexane (20 mL) was added slowly and was stirred for 10 min. Carefully removed the solvent and repeated adding/removal of hexane for 3 times. The residue was dried *in vacuo* to give 5-fluoro-3-(3-fluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl (208 mg, 0.50 mmol, 98 % yield). The product was pure by LCMS and was used in the next step without further purification. LC-MS (Method 1): *t_R* = 2.89 min, *m/z* (M+H)⁺ = 343.

STEP 4: Synthesis of N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-5-fluoro-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine (Cpd 272)

[0573] To a mixture of 5-fluoro-3-(3-fluorophenyl)-1-methyl-N-(piperidin-4-yl)-1H-indazol-6-amine, 2HCl (0.205 g, 0.494 mmol) in DMSO (1.5 ml) was added 2-chloro-1-(difluoromethyl)-1H-benzo[d]imidazole (0.130 g, 0.642 mmol) and Hunig's base (0.345 ml, 1.974 mmol). The mixture was sealed and heated at 150 °C for 1 hr. After cooling to rt, the mixture was diluted with EtOAc (15 mL) and washed with H₂O (15 mL x3). The organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 10-55% EtOAc/hexane (40g gold column) as the eluent to give N-(1-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-5-fluoro-3-(3-fluorophenyl)-1-methyl-1H-indazol-6-amine (202.7 mg, 0.399 mmol, 81 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.75 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.72 (t, *J* = 57.4 Hz, 1H), 7.70 (s, 1H), 7.63 (ddd, *J* = 10.5, 2.7, 1.5 Hz, 1H), 7.57 – 7.45 (m, 3H), 7.27 – 7.11 (m, 3H), 6.86 (d, *J* = 7.2 Hz, 1H), 5.67 (dd, *J* = 8.2, 2.8 Hz, 1H), 4.00 (s, 3H), 3.79 – 3.67 (m, 1H), 3.66 – 3.57 (m, 2H), 3.31 – 3.19 (m, 2H), 2.09 (dd, *J* = 13.3, 3.7 Hz, 2H), 1.89 – 1.75 (m, 2H); LC-MS (Method 2): *t_R* = 5.98 min, *m/z* (M+H)⁺ = 509.

Example 389. (3-(3-chlorophenyl)-1-cyclopropyl-1H-indazol-6-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, TFA (Cpd. 389)

**Cpd. 389****STEP-1: Synthesis of 3-bromo-1-cyclopropyl-1H-indazole-6-carboxylic acid**

[0574] To a suspension of methyl 3-bromo-1-cyclopropyl-1H-indazole-6-carboxylate (443 mg, 1.5 mmol) in THF (6 ml)/MeOH (1 ml) was added 1N NaOH(aq) (6 mL, 6 mmol, 4 equiv). The mixture was heated at 50-55 °C for 1 hr. After cooling to rt, 1N HCl(aq) was added dropwise until the pH of aqueous layer is ca. 3. Then, the mixture was concentrated by blowing air to remove most of THF. The yellow solid was filtered, washed with H₂O (5 mL x 2), and then dried to give 3-bromo-1-cyclopropyl-1H-indazole-6-carboxylic acid (420 mg, 1.494 mmol, 100 % yield). LC-MS (Method 1): tR = 3.22 min, m/z (M+H)⁺ = 281.

STEP-2: Synthesis of (3-bromo-1-cyclopropyl-1H-indazol-6-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone

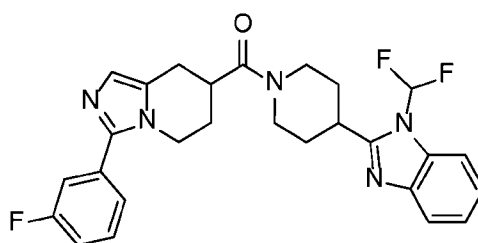
[0575] To a mixture of 3-bromo-1-cyclopropyl-1H-indazole-6-carboxylic acid (422 mg, 1.5 mmol), 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (486 mg, 1.50 mmol), and HATU (741 mg, 1.95 mmol) was added DMF (4.5 ml) and then Hunig's base (1.31 ml, 7.50 mmol). The mixture was stirred at rt for 1 hr. The mixture was diluted with EtOAc (30 mL) and then washed with H₂O (30 mL x 2). The organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 80-100% EtOAc/hexane as the eluent to give (3-bromo-1-cyclopropyl-1H-indazol-6-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (744 mg, 1.446 mmol, 96 % yield). LC-MS (Method 1): tR = 3.51 min, m/z (M+H)⁺ = 516.

STEP-3: Synthesis of (3-(3-chlorophenyl)-1-cyclopropyl-1H-indazol-6-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, TFA (Cpd. 389)

[0576] In a flask was placed (3-bromo-1-cyclopropyl-1H-indazol-6-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (51.4 mg, 0.1 mmol), (3-chlorophenyl)boronic acid (23.46 mg, 0.15 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (8.17 mg, 10.0 μmol), and K₂CO₃ (62.2 mg, 0.45 mmol). The air was removed and re-filled with N₂ (repeat for 3 times). Then, 1,4-dioxane (1.5 ml)/water (0.5 ml) was added and the mixture was stirred at 85

°C for 1.5 hr. After cooling to rt, the organic layer was separated. The water layer was extracted with EtOAc (3 mL x 2). The combined organic layer was dried (Na₂SO₄) and filtered through PL-Thiol MP Resin and eluted with EtOAc and MeOH. After removal of solvent, the product was submitted for purification by semi-preparative HPLC to give (3-(3-chlorophenyl)-1-cyclopropyl-1H-indazol-6-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, TFA (28.9 mg, 0.044 mmol, 43.8 % yield). LC-MS (Method 2): tR = 6.69 min, m/z (M+H)⁺ = 546.

Example 403. (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-7-yl)methanone, TFA (Cpd. 403)



Cpd. 403

[0577] STEP-1: Synthesis of (3-bromo-5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-7-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone

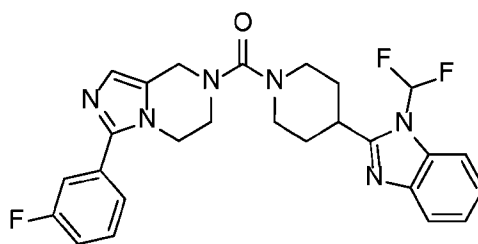
To a mixture of 3-bromo-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-7-carboxylic acid (368 mg, 1.5 mmol), 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (486 mg, 1.50 mmol), and HATU (741 mg, 1.95 mmol) was added DMF (4.5 ml) and then Hunig's base (1.31 ml, 7.50 mmol). The mixture was stirred at rt for 1 hr. The mixture was diluted with EtOAc (30 mL) and then washed with H₂O (30 mL x 2). The organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-10-15% MeOH/EtOAc as the eluent to give (3-bromo-5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-7-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (665 mg, 1.390 mmol, 93 % yield). LC-MS (Method 1): tR = 2.75 min, m/z (M+H)⁺ = 480.

STEP-2: Synthesis of (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-7-yl)methanone, TFA (Cpd. 403)

[0578] In a flask was placed (3-bromo-5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-7-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (71.8 mg, 0.15 mmol), (3-fluorophenyl)boronic acid (31.5 mg, 0.225 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (12.25 mg,

0.015 mmol), and K₂CO₃ (93 mg, 0.675 mmol). The air was removed and re-filled with N₂ (repeat for 3 times). Then, 1,4-dioxane (1.5 ml)/water (0.5 ml) was added and the mixture was stirred at 85 °C for 1.5 hr. After cooling to rt, the organic layer was separated. The water layer was extracted with EtOAc (3 mL x 2). The combined organic layer was dried (Na₂SO₄) and filtered through PL-Thiol MP Resin and eluted with EtOAc and MeOH. After removal of solvent, the product was submitted for purification by semi-preparative HPLC to give (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-7-yl)methanone, TFA (30.9 mg, 0.051 mmol, 33.9 % yield). LC-MS (Method 2): tR = 4.23 min, m/z (M+H)⁺ = 494.

Example 406. (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone, TFA (Cpd. 406)



Cpd. 406

STEP-1: Synthesis of (3-bromo-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone

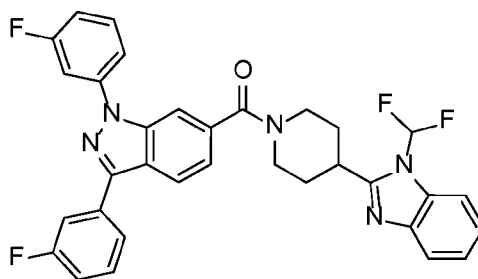
[0579] To a mixture of 3-bromo-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine, HCl (239 mg, 1 mmol) and 4-nitrophenyl carbonochloridate (202 mg, 1.000 mmol) in CH₂Cl₂ (4 mL) at 0 °C was added slowly Hunig's base (0.43 mL, 2.5 mmol). The mixture was allowed to warm to rt and stirred for another 1 hr. The mixture was blowing down to give a crude mixture. To the crude mixture was added 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (324 mg, 1.0 mmol), then DMF (3 ml) and Hunig's base (0.68 mL, 4 mmol). The mixture was heated at 80 °C for overnight. The mixture was diluted with EtOAc (30 mL) and washed with H₂O (60 mL x 3). The organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-10-12% MeOH/EtOAc as the eluent to give (3-bromo-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (ca. 55% purity, 245 mg, 0.281 mmol, 28.1 % yield). The

product, ca. 55% purity, contained impurity and was used for next step without further purification. LC-MS (Method 1): $t_R = 2.84$ min, m/z (M+H) $^{+} = 481$.

STEP-2: Synthesis of (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone, TFA (Cpd. 406)

[0580] In a flask was placed (3-bromo-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone (87 mg, 0.1 mmol), (3-fluorophenyl)boronic acid (20.99 mg, 0.15 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (8.17 mg, 10.0 μ mol), and K₂CO₃ (62.2 mg, 0.450 mmol). The air was removed and re-filled with N₂ (repeat for 3 times). Then, 1,4-dioxane (1.5 ml)/water (0.5 ml) was added and the mixture was stirred at 85 °C for 1.5 hr. After cooling to rt, the organic layer was separated. The water layer was extracted with EtOAc (3 mL x 2). The combined organic layer was dried (Na₂SO₄) and filtered through PL-Thiol MP Resin and eluted with EtOAc and MeOH. After removal of solvent, the product was submitted for purification by semi-preparative HPLC to give (4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(3-(3-fluorophenyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone, TFA (17.1 mg, 0.028 mmol, 28.1 % yield). LC-MS (Method 2): $t_R = 4.22$ min, m/z (M+H) $^{+} = 495$.

Example 409. (1,3-bis(3-fluorophenyl)-1H-indazol-6-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, TFA (Cpd. 409)



Cpd. 409

STEP-1: Synthesis of methyl 1,3-bis(3-fluorophenyl)-1H-indazole-6-carboxylate

[0581] To a mixture of methyl 3-(3-fluorophenyl)-1H-indazole-6-carboxylate (270 mg, 1 mmol), (3-fluorophenyl)boronic acid (280 mg, 2.0 mmol), copper (II) acetate (182 mg, 1.0 mmol), 2,2'-bipyridine (156 mg, 1.0 mmol), and Na₂CO₃ (212 mg, 2.0 mmol) was added 1,2-Dichloroethane (20 ml). The mixture was opened to air and stirred at 65 °C for overnight. After cooling to rt, the mixture was diluted with EtOAc (20 mL), filtered through celite and eluted with EtOAc. The filtrate was concentrated and then purified by silica gel chromatography using 10-30%

EtOAc/hexane as the eluent to give methyl 1,3-bis(3-fluorophenyl)-1H-indazole-6-carboxylate (113 mg, 0.310 mmol, 31.0 % yield). LC-MS (Method 1): tR = 3.99 min, m/z (M+H)+ = 365.

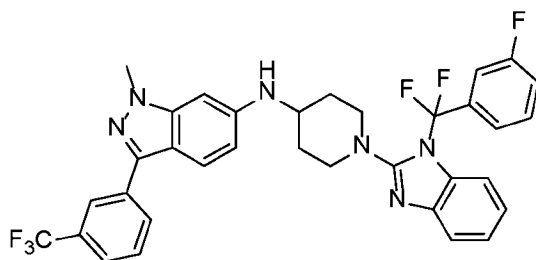
STEP-2: Synthesis of 1,3-bis(3-fluorophenyl)-1H-indazole-6-carboxylic acid

[0582] To a solution of methyl 1,3-bis(3-fluorophenyl)-1H-indazole-6-carboxylate (113 mg, 0.31 mmol) in THF (3 ml)/MeOH (0.3 ml) was added 1N NaOH(aq) (1.24 mL, 1.24 mmol, 4 equiv). The mixture was heated at 50 °C for 1 hr. After cooling to rt, 1N HCl(aq) was added dropwise until the pH of aqueous layer is ca. 3. Then, the mixture was concentrated to remove most of THF. Then, the solid was filtered, washed with H₂O (5 mL x 2), and then dried to give 1,3-bis(3-fluorophenyl)-1H-indazole-6-carboxylic acid (104 mg, 0.297 mmol, 96 % yield). The product was used for next step without further purification. LC-MS (Method 1): tR = 3.66 min, m/z (M+H)+ = 351.

STEP-3: Synthesis of (1,3-bis(3-fluorophenyl)-1H-indazol-6-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, TFA (Cpd. 409)

[0583] To a mixture of 1,3-bis(3-fluorophenyl)-1H-indazole-6-carboxylic acid (52.5 mg, 0.15 mmol), 1-(difluoromethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole, 2HCl (48.6 mg, 0.150 mmol), and HATU (74.1 mg, 0.195 mmol) was added DMF (1 ml) and then hunig's base (0.131 ml, 0.750 mmol). The mixture was stirred at rt for 1 hr. The mixture was filtered and submitted for purification by semi-preparative HPLC to give (1,3-bis(3-fluorophenyl)-1H-indazol-6-yl)(4-(1-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)methanone, TFA (38.2 mg, 0.055 mmol, 36.5 % yield). LC-MS (Method 2): tR = 6.72 min, m/z (M+H)+ = 584.

Example 437. N-(1-(1-(difluoro(3-fluorophenyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-3-(3-(trifluoromethyl)phenyl)-1H-indazol-6-amine, TFA (Cpd. 437)



Cpd. 437

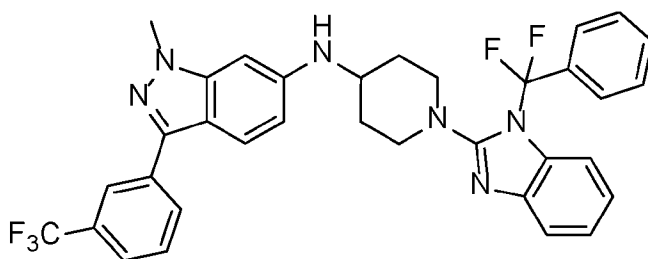
STEP-1: Synthesis of 2-chloro-1-(difluoro(3-fluorophenyl)methyl)-1H-benzo[d]imidazole

[0584] To a mixture of 2-chloro-1H-benzo[d]imidazole (153 mg, 1 mmol) and Cs₂CO₃ (326 mg, 1.0 mmol) in microwave tube was added DMF (1 ml). The mixture was stirred at rt for 3-5 min and 1-(bromodifluoromethyl)-3-fluorobenzene (225 mg, 1.0 mmol) was added. The tube was sealed and heated at 70 °C for overnight. The mixture was then diluted with EtOAc (5 mL) and washed with H₂O (5 mL x 3). The organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography (24g gold column) using 5-20% EtOAc/hexane as the eluent to give 2-chloro-1-(difluoro(3-fluorophenyl)methyl)-1H-benzo[d]imidazole (65 mg, 0.219 mmol, 21.91 % yield) as a colorless oil. LC-MS (Method 1): tR = 3.66 min, m/z (M+H)⁺ = 297.

STEP-2: Synthesis of N-(1-(1-(difluoro(3-fluorophenyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-3-(3-(trifluoromethyl)phenyl)-1H-indazol-6-amine, TFA (Cpd. 437)

In a microwave was placed 1-methyl-N-(piperidin-4-yl)-3-(3-(trifluoromethyl)phenyl)-1H-indazol-6-amine, 2HCl (0.045 g, 0.1 mmol) and 2-chloro-1-(difluoro(3-fluorophenyl)methyl)-1H-benzo[d]imidazole (0.031 g, 0.105 mmol). The, DMSO (1 ml) and Hunig's base (0.070 ml, 0.400 mmol) were added. The tube was sealed and heated at 150 °C for overnight. The mixture was filtered and submitted for purification by semi-preparative HPLC to give N-(1-(1-(difluoro(3-fluorophenyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-3-(3-(trifluoromethyl)phenyl)-1H-indazol-6-amine, TFA. LC-MS (Method 1): tR = 3.84 min, m/z (M+H)⁺ = 635.

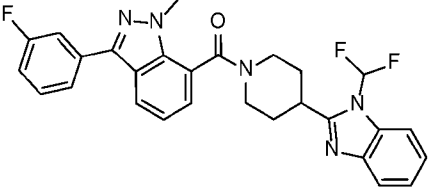
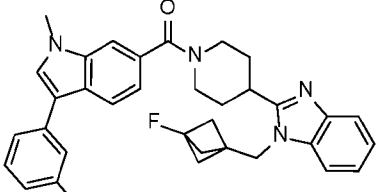
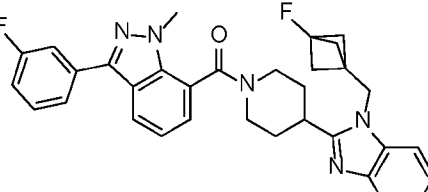
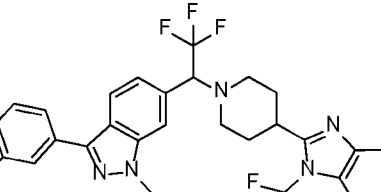
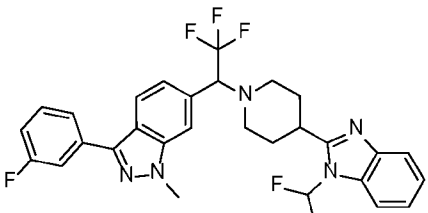
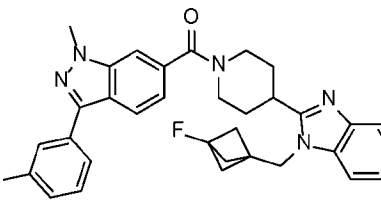
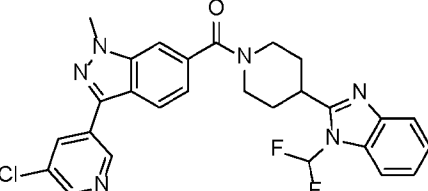
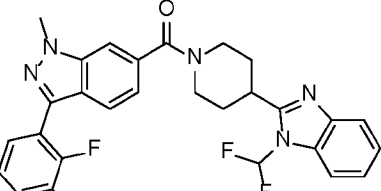
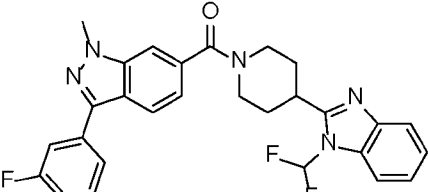
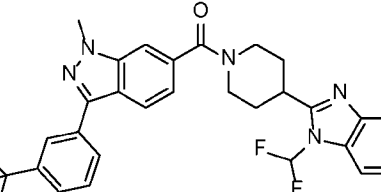
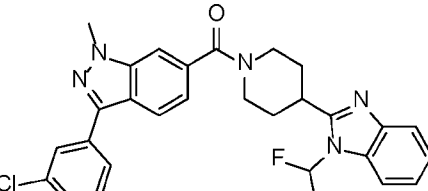
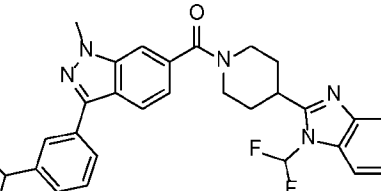
[0585] Example 440. N-(1-(1-(difluoro(phenyl)methyl)-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)-1-methyl-3-(3-(trifluoromethyl)phenyl)-1H-indazol-6-amine

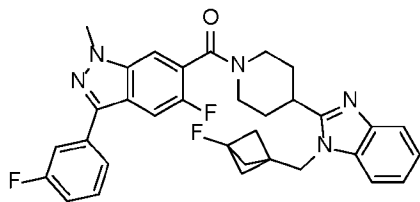
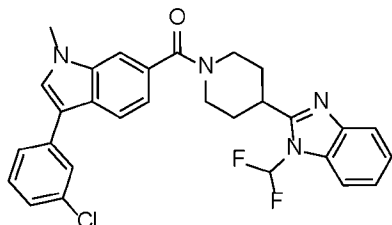
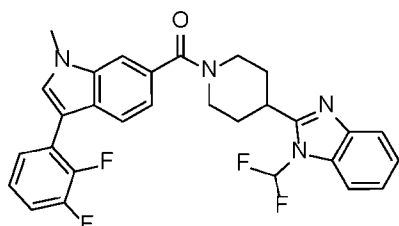
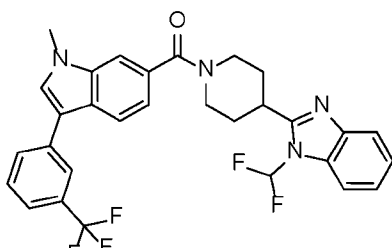
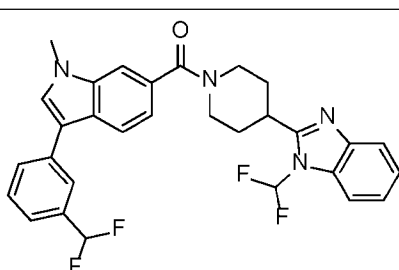
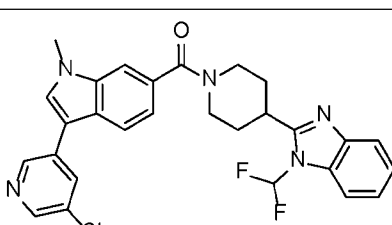
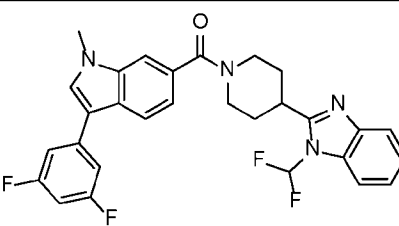
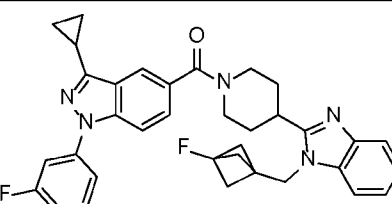
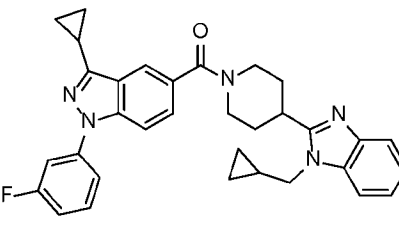
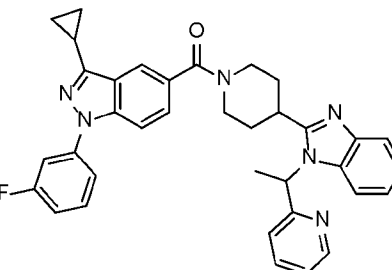
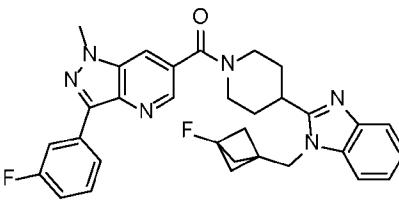
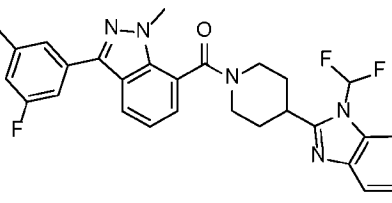


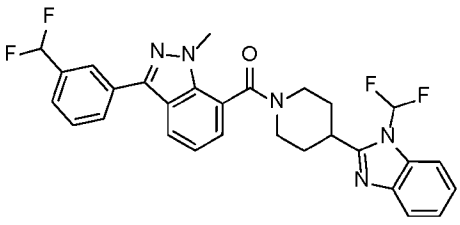
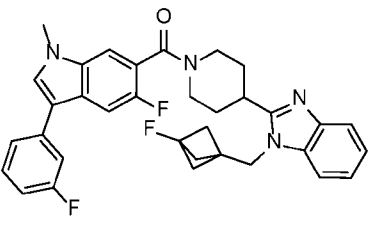
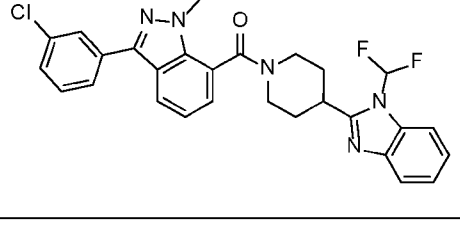
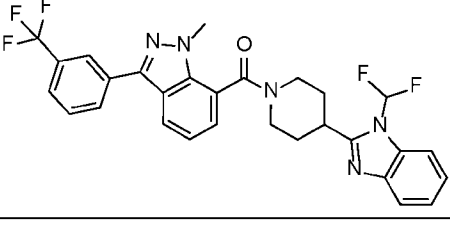
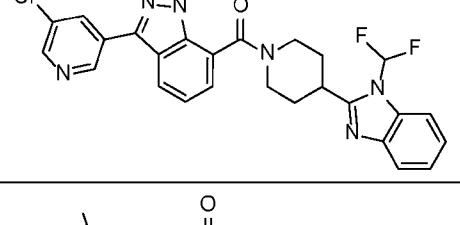
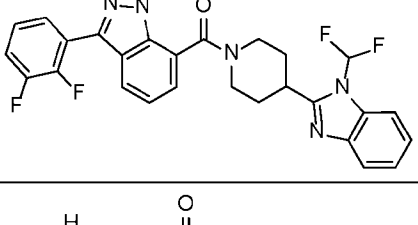
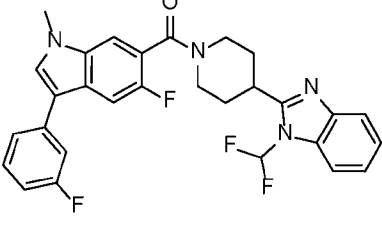
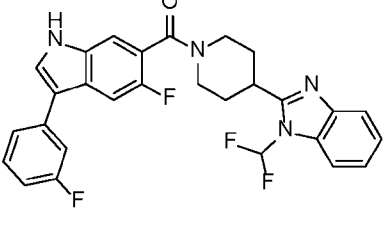
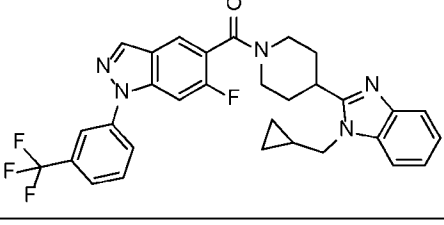
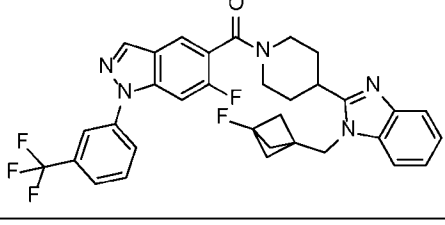
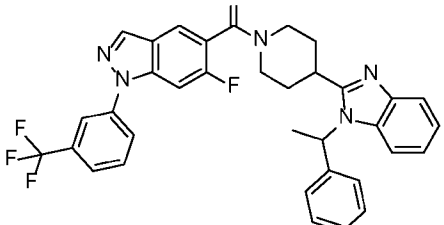
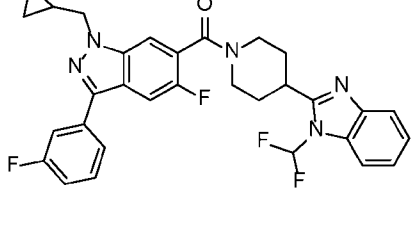
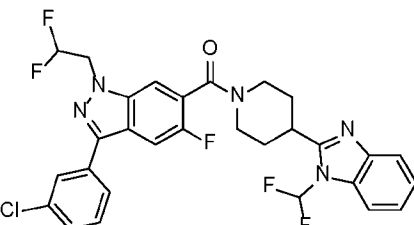
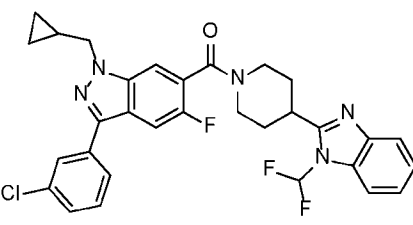
Cpd. 440

[0586] Table 4 shows additional compounds that were synthesized using similar procedures as described herein.

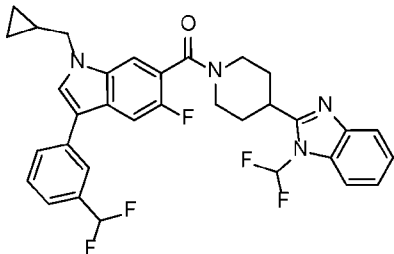
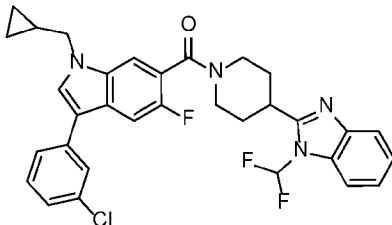
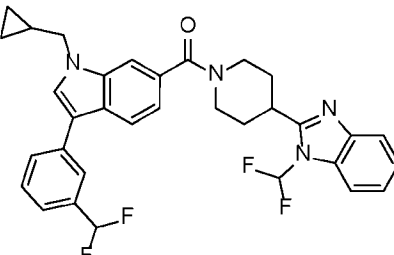
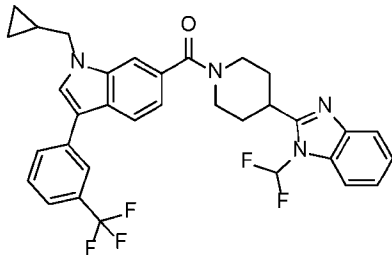
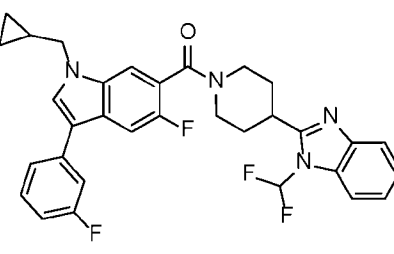
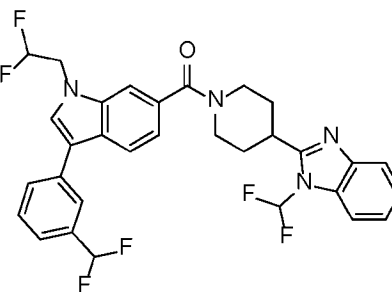
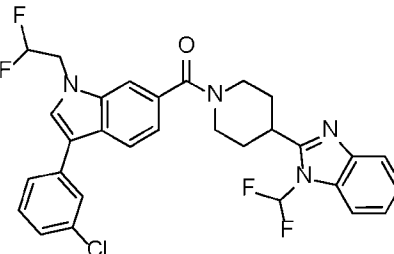
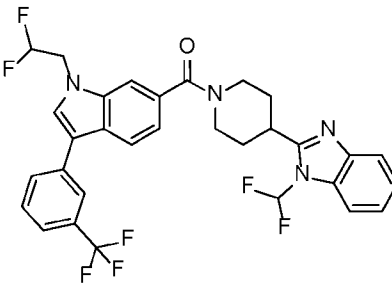
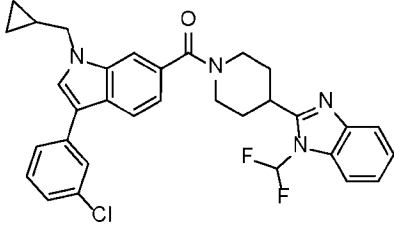
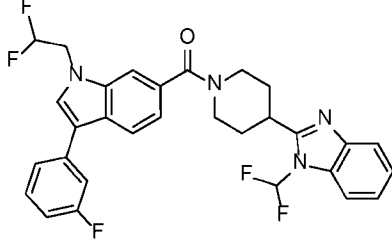
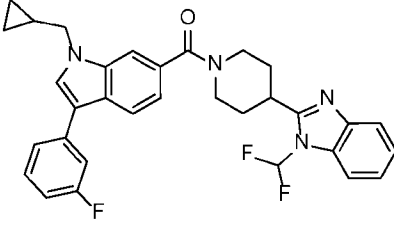
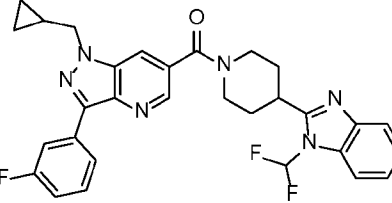
Table 4

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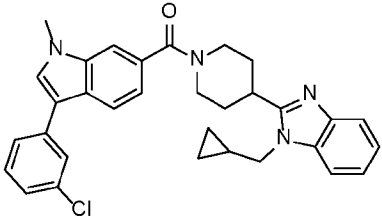
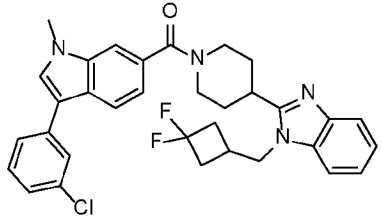
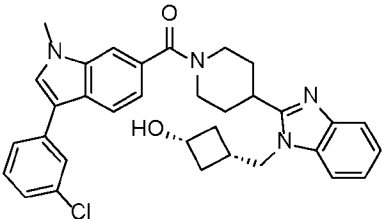
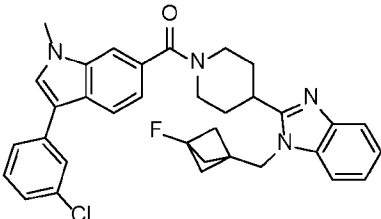
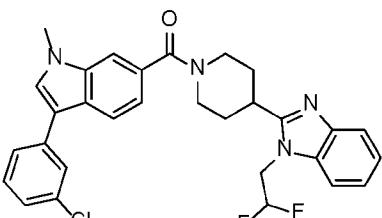
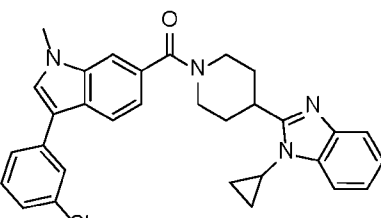
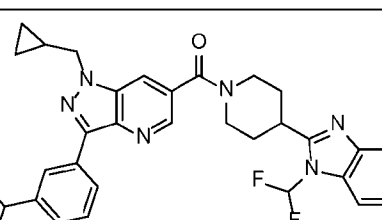
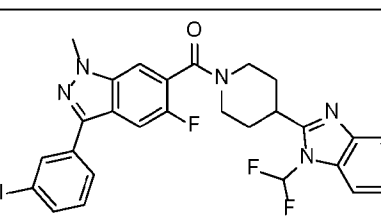
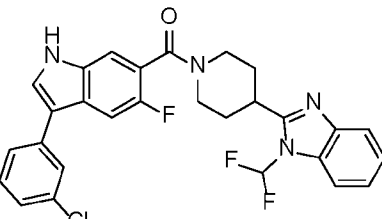
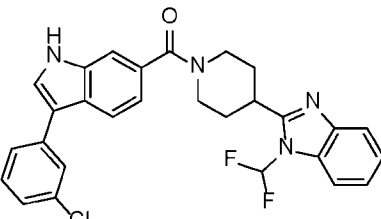
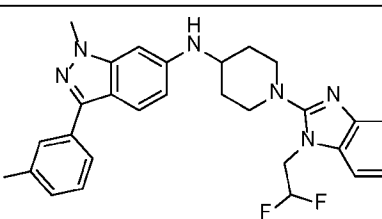
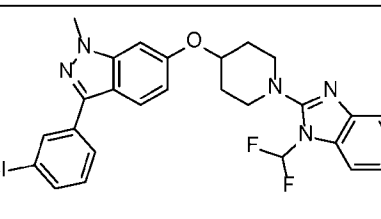
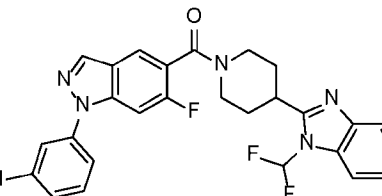
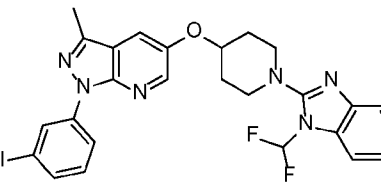
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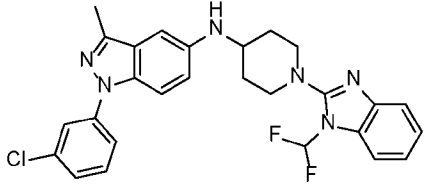
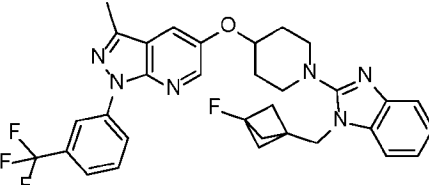
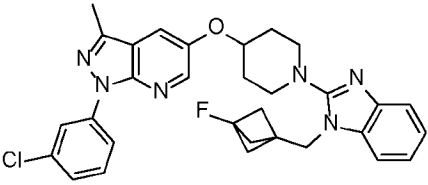
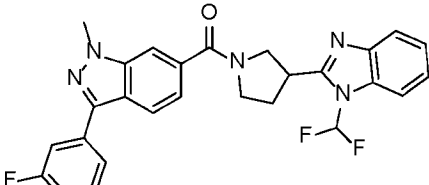
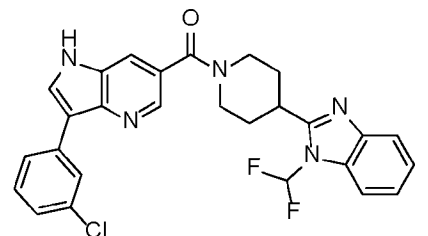
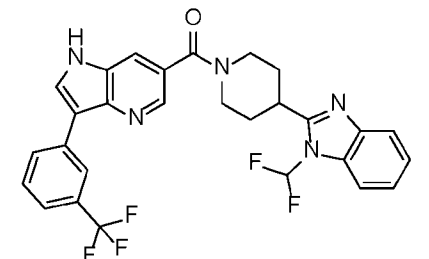
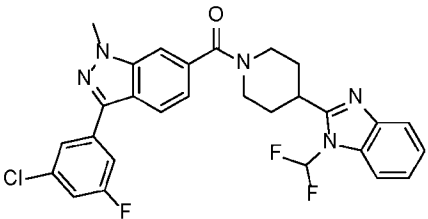
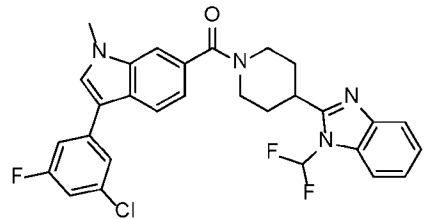
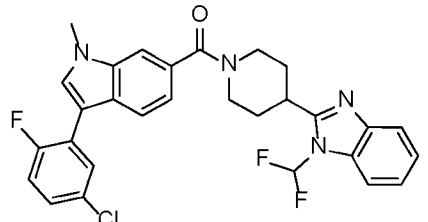
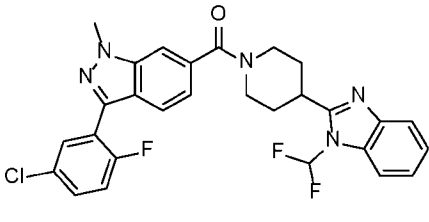
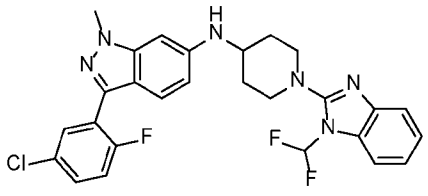
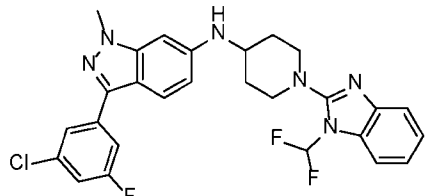
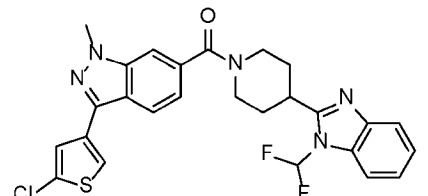
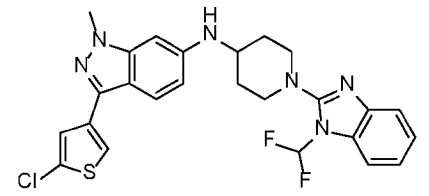
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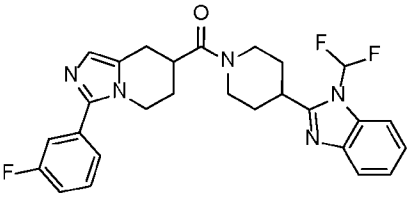
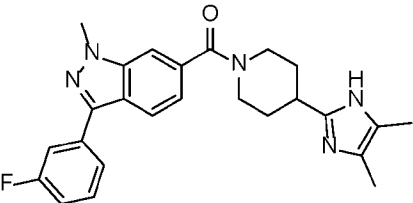
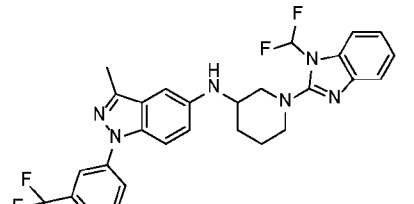
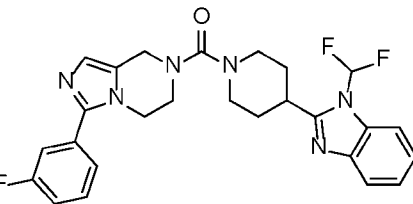
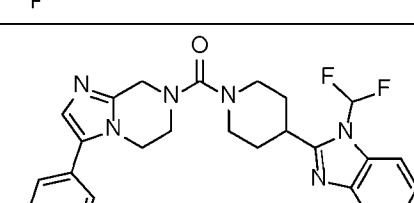
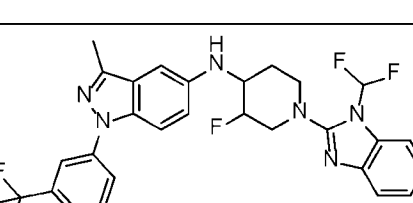
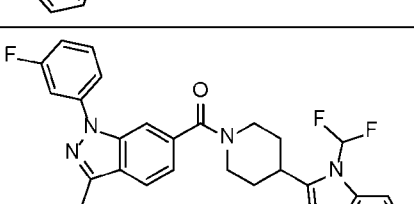
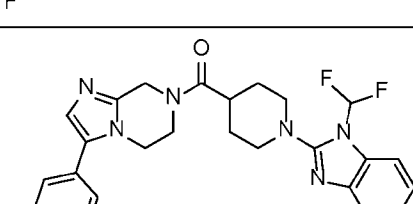
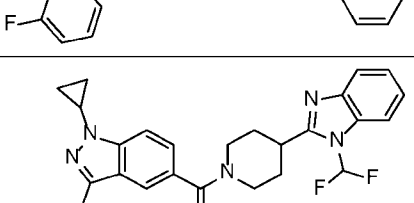
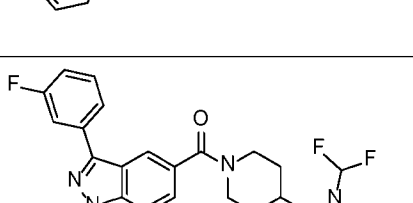
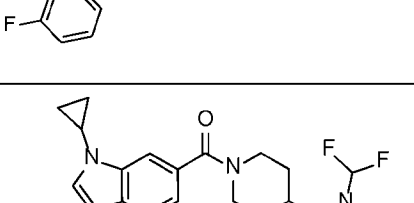
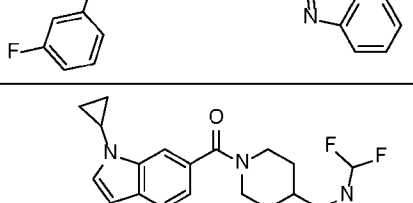
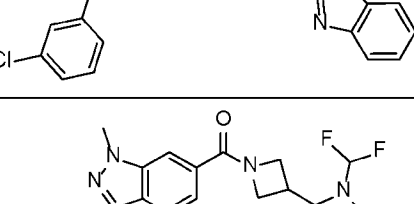
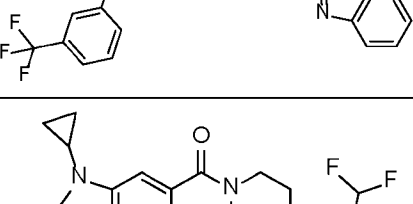
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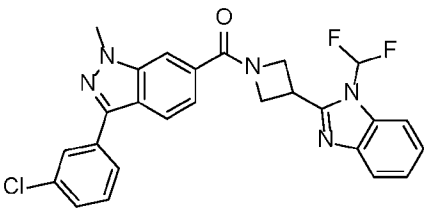
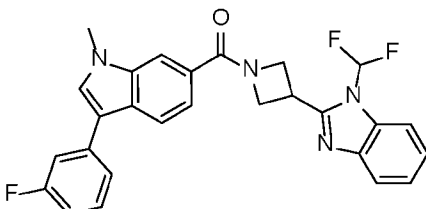
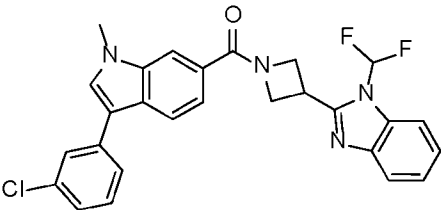
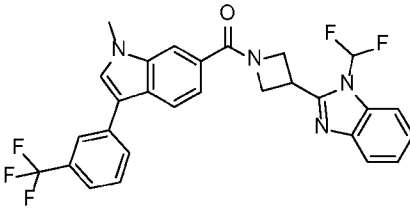
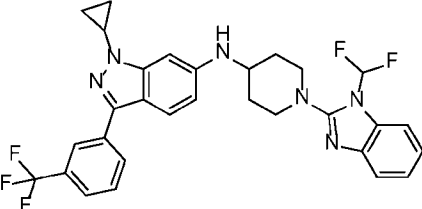
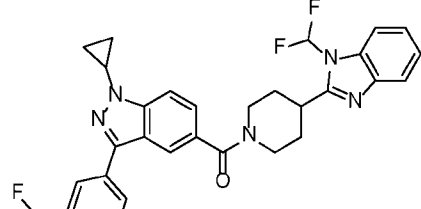
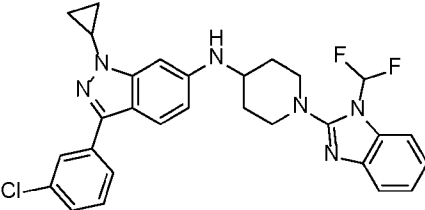
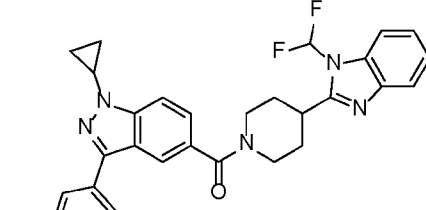
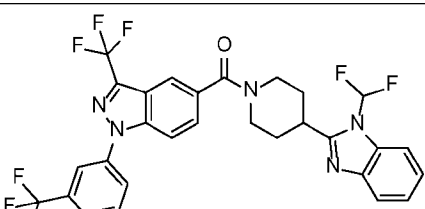
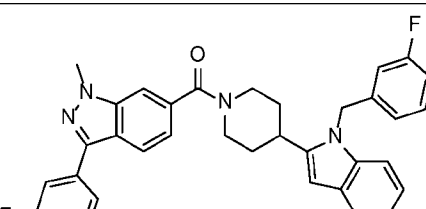
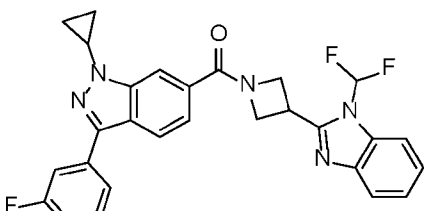
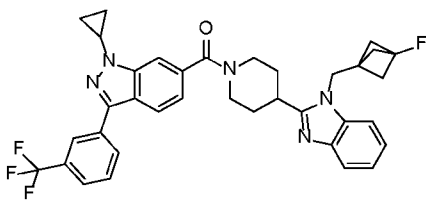
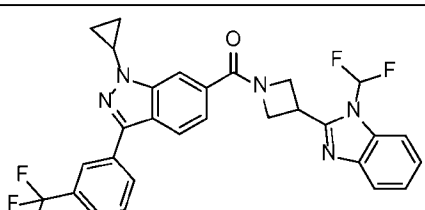
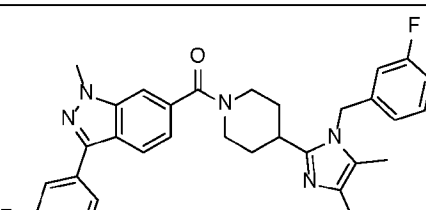
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Biological Studies of Compounds

[0587] Spared nerve injury in mice: SNI was performed as described (Nelson TS, Sinha GP, Santos DFS, Jukkola P, Prasoon P, Winter MK, et al. Spinal neuropeptide Y Y1 receptor-expressing neurons are a pharmacotherapeutic target for the alleviation of neuropathic pain. *Proc Natl Acad Sci U S A*. 2022;119(46):e2204515119). Mice were anesthetized with inhaled isoflurane (5% for induction, 2% for maintenance). The hind left limb was shaved and aseptitized with three alternating wipes of 70% ethanol and 2% chlorhexidine gluconate. A small incision was made in the skin of the hind left leg, and the underlying muscle was separated via blunt dissection to expose the sciatic nerve branches. The peroneal and tibial nerves were ligated with 6-0 silk sutures and carefully transected, ensuring the sural nerve was left intact. After nerve

manipulation, the muscle tissue was loosely sutured using 5-0 nylon sutures, and the skin was closed with 9 mm wound clips. A topical triple antibiotic ointment (Neosporin) was applied to the wound. Wound clips were removed approximately 10 days post-surgery, with behavioral experiments starting 21 days after surgery. Sham surgeries followed the same procedure, including nerve exposure, but without ligation or transection.

[0588] Compounds administration. Intraperitoneal. Intraperitoneal delivery was carried out using a 30-gauge, 0.3-inch needle, inserted into the lower left quadrant of the abdomen. The needle was positioned parallel to the backbone at a 45° angle to the abdominal wall. Behavioral assessments were conducted at 1-, 2-, 3-, 4-, 5-, and 6-hours following administration to measure paw withdrawal threshold and cold aversion time.

Example 273. High-throughput rDRG calcium assay

Preparation of culture of primary rat dorsal root ganglion (rDRG) neurons

[0589] Primary rat dorsal root ganglion (rDRG) neurons were purchased from Cell Application, Inc. (#R8820NK-10) and were prepared according to the manufacturer's protocol. In brief, a 384-well flat, clear-bottom microplate (Corning #3770) was coated with 10 µL/well Neuron Coating Solution II (Cell Application, Inc., #029-05) and incubated at 37 °C overnight. After coating, the plate was rinsed twice with sterile phosphate-buffered saline (PBS) to remove the unbound coating solution, and then the plate was allowed to air dry before seeding. Two vials (2 x 10⁶) of cryopreserved rDRG neurons were thawed and resuspended in 10 mL plating medium (Cell Application, Inc., #R823P-10). rDRG neurons were then centrifuged at 1000 rpm for 5 min to remove trace amount of DMSO. The resulting cell pellet was resuspended in 10 mL plating medium supplemented with nerve growth factor (NGF, 100 ng/mL) and rat glial cell line-derived neurotrophic factor (rGDNF, 25 ng/mL). 20 µL/well cell suspension was dispensed into each well of the pre-coated 384-well plate. The seeded plate was stood at room temperature (RT) for 15 min and then incubated at 37 °C under 5% CO₂ overnight. After overnight incubation, the plating medium was carefully changed to fresh Rat Ganglion Neuron Culture Medium (Cell Application, Inc., #R823K-100) supplemented with NGF (100 ng/mL) and rGDNF (25 ng/mL). The whole culture medium was refreshed on days 3 and 5, and half of the medium was changed every 3 to 4 days afterward. Cell death occurred during the first few days after plating. The remaining pure rDRG neurons arborized and formed a complex neurite network in one week. Seeded rDRG neurons were cultured for a total of two weeks to allow neurite network maturation before assay.

High-throughput rDRG calcium assay

[0590] The rDRG culture plate was refreshed with 20 μ L/well Rat Ganglion Neuron Culture Medium 24 hr before assay. 60 nL of a test compound was dosed into each well using an Echo® acoustic liquid handler (Beckman Coulter), and Digitonin (Sigma #D141) was dosed into selected wells as a negative control for viability. After dosing, the plate was returned to a 37 °C, 5% CO₂ humidified incubator for 16 hr. 20 μ L/well of Calbryte™ 520 AM dye-loading solution (AAT Bioquest# 36319) was dispensed into the assay plate, and then the plate was incubated in a 37 °C, 5% CO₂ humidified incubator for 30 min. The plate was removed from the incubator and incubated at RT in the dark for 15 min. A calcium flux assay was performed by a FLIPR® Penta high-throughput cellular screening system (Molecular Devices) by monitoring the fluorescence intensity at Ex/Em = 490/525 nm at 1 sec/frame. The baseline was allowed to establish for 10 sec, and then 50 nL of the sodium channel activator 1K α PMTX (Alomone Labs # P-172) (100 μ M final conc.) was dispensed into the read plate using a FLIPR® 384 pin tool. Measurement was continued for an additional 5 minutes after 1K α PMTX addition (310 frames total). Fluorescence intensity at 525 nm was extracted for each well and timepoint using the ScreenWorks® 5.0 software (Molecular Devices). The maximum and minimum intensity values from each well were obtained, and the response of the rDRG neurons was calculated by subtracting the minimum signal from the maximum signal (Max – Min). The response values were averaged for all wells under the same treatment conditions, and the data were then normalized to wells without stimulant (0%) and with stimulant only (100%).

[0591] Table 5 shows the results of the high-throughput rDRG calcium assay for Compounds 1-379. The results are expressed as the ratio of the IC₅₀ of a test compound for a single run, or the average IC₅₀ of a test compound for multiple runs, in the rDRG assay to the average IC₅₀ of a reference indirect Na_V1.7 inhibitor, **AZ194** [compound **194** disclosed in Braden *et al.*, *Neurobiol. Pain*, **11**:100082 (2022)], for multiple runs in the rDRG assay. In Table 5, the plus symbols denote the following with respect to the **IC₅₀ ratio**, IC₅₀ test compound/IC₅₀ AZ194: ++++ = IC₅₀ ratio $\leq$ 1; +++ = IC₅₀ ratio > 1 and $\leq$ 2; ++ = IC₅₀ ratio > 2 and $\leq$ 3; and + = IC₅₀ ratio > 3.

Table 5

Cpd	IC ₅₀ ratio	Cpd	IC ₅₀ ratio	Cpd	IC ₅₀ ratio	Cpd	IC ₅₀ ratio	Cpd	IC ₅₀ ratio
1	++	2	+	3	++	4	+++	5	+++

6	++++	7	++	8	+	9	+++	10	+++
11	++++	12	++++	13	++	14	++++	15	++++
16	+++	17	+	18	++++	19	+	20	++++
21	+++	22	++++	23	+++	24	+	25	++++
26	+++	27	+++	28	++++	29	+++	30	++
31	+++	32	++++	33	+	34	++++	35	+
36	++++	37	++++	38	++	39	++++	40	+++
41	++++	42	+++	43	++	44	+	45	++++
46	++++	47	+++	48	+	49	+++	50	++++
51	++++	52	++++	53	++++	54	++++	55	++++
56	+++	57	++++	58	++++	59	+++	60	+++
61	+++	62	+++	63	+++	64	++++	65	+++
66	+++	67	+++	68	+++	69	++	70	+++
71	++++	72	+++	73	++	74	++++	75	++++
76	+++	77	+++	78	++++	79	+++	80	++++
81	++++	82	++++	83	+++	84	++++	85	+++
86	++++	87	++++	88	+++	89	++++	90	+++
91	++++	92	++++	93	++++	94	++++	95	++++
96	+++	97	+++	98	++++	99	++++	100	++++
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106	++	107	++++	108	++++	109	++	110	++++
111	++	112	+++	113	++++	114	++++	115	++++
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191	+++	192	++++	193	++++	194	++++	195	++++
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206	++++	207	+++	208	+++	209	++++	210	++++
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221	+++	222	++++	223	++++	224	++	225	+++
226	+++	227	++++	228	+++	229	+++	230	+++
231	+++	232	+++	233	+++	234	+++	235	+++
236	+	237	+++	238	++	239	++	240	+++
241	+	242	++	243	+	244	++++	245	+++
246	++++	247	++++	248	+++	249	++++	250	+++
251	+++	252	++++	253	++++	254	+++	255	++++
256	+++	257	+++	258	++++	259	++++	260	++++
261	++++	262	+++	263	++	264	++++	265	++++
266	++++	267	+++	268	++++	269	++++	270	++++
271	++++	272	++++	273	++++	274	+++	275	++++
276	++++	277	++++	278	++++	279	+++	280	+++
281	++++	282	++++	283	+++	284	++++	285	+++
286	++++	287	+++	288	++++	289	++++	290	++
291	+++	292	++++	293	++++	294	++++	295	+++
296	+++	297	++	298	+++	299	+++	300	++++
301	+	302	++++	303	+++	304	++++	305	++++
306	++++	307	+++	308	++++	309	++++	310	++
311	+	312	+++	313	++++	314	+++	315	++++
316	++++	317	++++	318	++++	319	+++	320	++
321	+++	322	++++	323	++++	324	++++	325	++++
326	++++	327	+	328	++++	329	++++	330	++++
331	++++	332	++++	333	++++	334	++++	335	++++

336	++++	337	++++	338	+++	339	+++	340	+++
341	++++	342	+++	343	+++	344	++++	345	++++
346	++++	347	++++	348	+++	349	+	350	++++
351	+++	352	++++	353	++++	354	++++	355	++
356	+++	357	++++	358	++++	359	+++	360	++++
361	+++	362	++++	363	+	364	+++	365	+++
366	++++	367	++	368	+++	369	+++	370	++++
371	+++	372	+++	373	+++	374	++++	375	+++
376	++++	377	+++	378	++++	379	++	380	++++
381	++++	382	++++	383	+++	384	+	385	+++
386	++++	387	++++	388	++++	389	++++	390	++++
391	++++	392	++++	393	++++	394	++++	395	++++
396	+++	397	++++	398	++	399	++++	400	+
401	++++	402	+++	403	+++	404	++	405	+++
406	++++	407	++++	408	++++	409	++++	410	+++
411	++++	412	++++	413	++++	414	+++	415	++++
416	++++	417	+	418	+	419	+++	420	+++
421	+++	422	++++	423	++++	424	++++	425	++++
426	++++	427	++++	428	++++	429	++++	430	++++
431	N/A	432	N/A	433	N/A	434	N/A	435	N/A
436	N/A	437	N/A	438	N/A	439	N/A	440	N/A

Example 274. Analgesic effects of indirect Nav1.7 inhibitors in a murine model of neuropathic pain

[0592] Indirect Nav1.7 inhibitors disclosed herein were tested in a murine model of neuropathic pain. Neuropathic pain was induced by ligation and cutting of tibial and peritoneal nerves in 8 week-old, male and female C57BL/6J mice. 14 days after nerve injury, independent animal groups received an intraperitoneal (i.p.) administration of varying doses of a test compound, and the effects of the test compound on the behavior of the animal with respect to tactile allodynia and cold allodynia were measured for 6 hr post administration. Tactile allodynia is represented as the mechanical force to produce a withdrawal of the damage paw, so that a value closer to zero represents more pain and a value farther from zero represents less pain. Cold allodynia is

represented as the time an animal spends flicking, licking and shaking the damaged paw, so that a longer withdrawal duration represents more pain and vice versa. In **Figs. 1A-D**, 10 mg/kg of test compounds was i.p. administered to male mice. Compound **194** is a reference indirect Nav1.7 inhibitor disclosed in Braden *et al.*, *Neurobiol. Pain*, **11**:100082 (2022), and is also known as **AZ194**. **Figs. 1A-D** show that 10 mg/kg of i.p. administered Compound **193** and Compound **215** markedly reduced both tactile allodynia (**Figs. 1A** and **B**) and cold allodynia (**Figs. 1C** and **D**) in male mice. **Fig. 1A**) effect of i.p. administered test compounds on tactile allodynia; **Fig. 1B**) area under the curve of the anti-tactile allodynic effect of test compounds; **Fig. 1C**) effect of i.p. administered test compounds on cold allodynia; **Fig. 1D**) area under the curve of the anti-cold allodynic effect of test compounds. Data are presented as the mean $\pm$ SEM (n = 8 animals per group). In **Figs. 1B** and **1D**, ***P<0.001 vs vehicle group, as determined by one-way ANOVA followed by the Dunnett's test.

[0593] In **Figs. 2A-D**, 10 mg/kg of test compounds was i.p. administered to female mice. Compound **194** is the reference indirect Nav1.7 inhibitor **AZ194**. **Figs. 2A-D** show that 10 mg/kg of i.p. administered Compound **193** markedly reduced both tactile allodynia (**Figs. 2A** and **B**) and cold allodynia (**Figs. 2C** and **D**) in female mice. **Fig. 2A**) effect of i.p. administered test compounds on tactile allodynia; **Fig. 2B**) area under the curve of the anti-tactile allodynic effect of test compounds; **Fig. 2C**) effect of i.p. administered test compounds on cold allodynia; **Fig. 2D**) area under the curve of the anti-cold allodynic effect of test compounds. Data are presented as the mean $\pm$ SEM (n = 8 animals per group). In **Figs. 2B** and **2D**), ***P<0.001 vs vehicle group, as determined by one-way ANOVA followed by the Dunnett's test.

[0594] In **Figs. 3A-D**, 1 mg/kg, 3 mg/kg or 10 mg/kg of Compound **193** was i.p. administered to male mice. **Figs. 3A-D** show that i.p. administered Compound **193** reduced both tactile allodynia (**Figs. 3A** and **B**) and cold allodynia (**Figs. 3C** and **D**) in male mice in a dose-dependent manner. **Fig. 3A**) effect of i.p. administered Compound **193** on tactile allodynia; **Fig. 3B**) area under the curve of the anti-tactile allodynic effect of Compound **193**; **Fig. 3C**) effect of i.p. administered Compound **193** on cold allodynia; **Fig. 3D**) area under the curve of the anti-cold allodynic effect of Compound **193**. Data are presented as the mean $\pm$ SEM (n = 8 animals per group). In **Figs. 3B** and **3D**), ***P<0.001 vs vehicle group, as determined by one-way ANOVA followed by the Dunnett's test.

[0595] In **Figs. 4A** and **B**, 3 mg/kg, 10 mg/kg or 30 mg/kg of Compound **215** was i.p. administered to male mice. **Figs. 4A** and **B** show that i.p. administered Compound **215** reduced

cold allodynia (**Fig. 4B**) in male mice in a dose-dependent manner while its effect on tactile allodynia (**Fig. 4A**) was less dose-dependent. Data are presented as the mean $\pm$ SEM (n = 8 animals per group).

[00596] In **Figs. 5A-D**, 3 mg/kg or 10 mg/kg of Compound **193** was i.p. administered to female mice. **Figs. 5A-D** show that i.p. administered Compound **193** reduced both tactile allodynia (**Figs. 5A and B**) and cold allodynia (**Figs. 5C and D**) in female mice in a dose-dependent manner. **Fig. 5A**: effect of i.p. administered Compound **193** on tactile allodynia; **Fig. 5B**: area under the curve of the anti-tactile allodynic effect of Compound **193**; **Fig. 5C**: effect of i.p. administered Compound **193** on cold allodynia; **Fig. 5D**: area under the curve of the anti-cold allodynic effect of Compound **193**. Data are presented as the mean $\pm$ SEM (n = 8 animals per group). In **Figs. B and D**), ***P<0.001 vs vehicle group, as determined by one-way ANOVA followed by the Dunnett's test.

[00597] In **Figs. 6A-D**, representative compounds reduced the tactile and cold allodynia in male neuropathic mice. **Fig. 6A**: Effect of the intraperitoneal administration of compounds on the tactile allodynia. **Fig. 6B**: Area under the curve of the antiallodynic effect induced by compounds. **Fig. 6C**: Effect of the intraperitoneal administration of compounds on the cold allodynia. **Fig. 6D**: Area under the curve of the antiallodynic effect induced by compounds. Data are presented as the mean $\pm$ SEM (n= 8 animals per group). In **Fig. 6B and Fig. 6D** ***P<0.001 vs vehicle group, as determined by one-way ANOVA followed by the Dunnett's test.

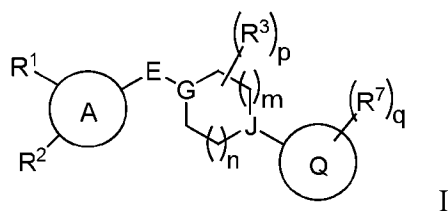
[00598] In **Figs. 7A-D**, Compound **193** and Compound **261** reduced the tactile and cold allodynia in a comparison with Gabapentin (30 mg/kg) in male neuropathic mice. **Fig. 7A**: Effect of the intraperitoneal administration of compounds on the tactile allodynia **Fig. 7B** Area under the curve of the antiallodynic effect induced by compounds. **Fig. 7C**: Effect of the intraperitoneal administration of compounds on the cold allodynia. **Fig. 7D**: Area under the curve of the antiallodynic effect induced by compounds. Data are presented as the mean $\pm$ SEM (n= 8 animals per group). In **Figs. 7B and 7D** ***P<0.001 vs vehicle group, as determined by one-way ANOVA followed by the Dunnett's test.

[0599] It is understood that, while particular embodiments have been illustrated and described, various modifications can be made thereto and are contemplated herein. It is also understood that the disclosure is not limited by the specific examples provided herein. The description and illustration of embodiments and examples of the disclosure herein are not intended to be

construed in a limiting sense. It is further understood that all aspects of the disclosure are not limited to the specific depictions, configurations or relative proportions set forth herein, which may depend upon a variety of conditions and variables. Various modifications and variations in form and detail of the embodiments and examples of the disclosure will be apparent to a person skilled in the art. It is therefore contemplated that the disclosure also covers any and all such modifications, variations and equivalents.

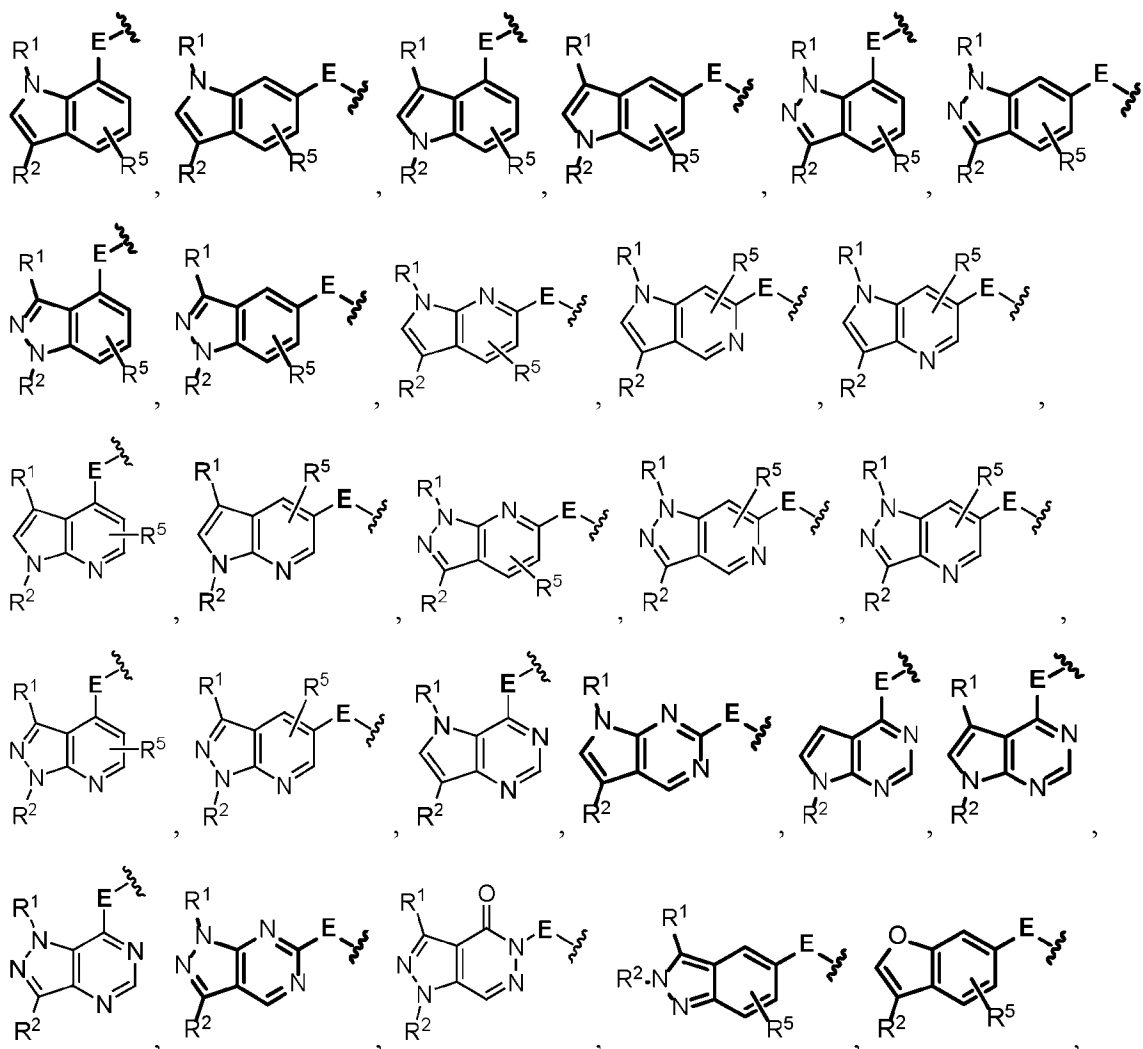
What Is Claimed Is:

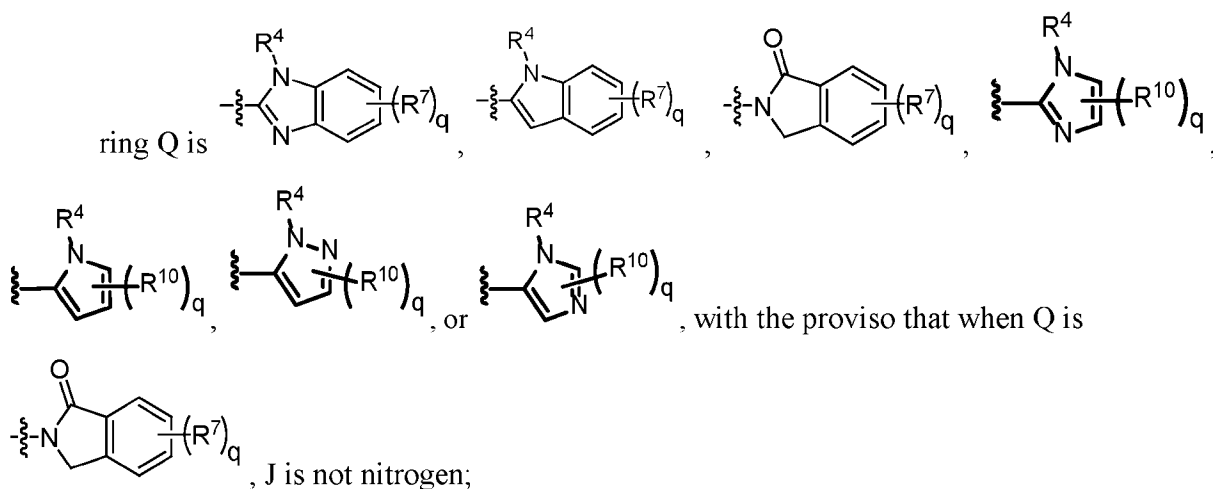
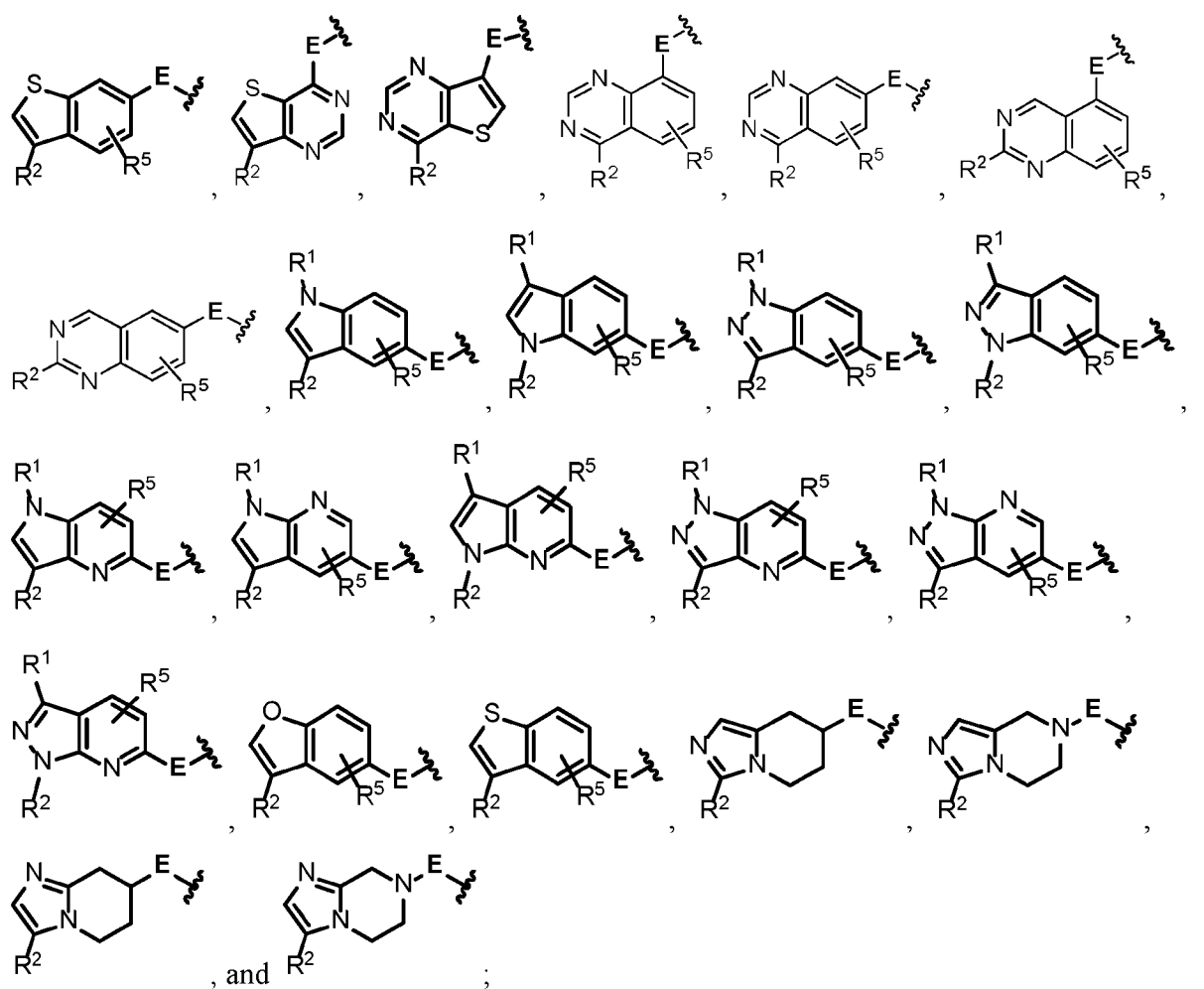
1. A compound of Formula I or a tautomer, pharmaceutically acceptable salt, solvate, hydrate, clathrate, isotopes, or isotopic forms including deuterated and tritiated forms, polymorph or stereoisomer thereof:



wherein:

ring A attached to E is selected from:

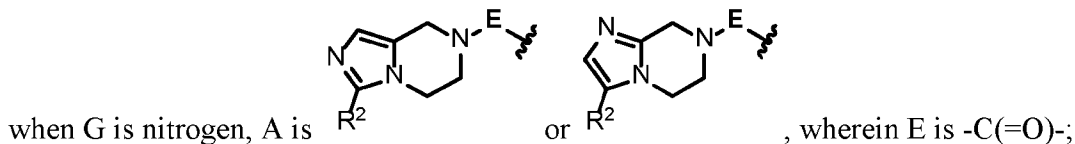




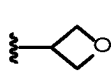
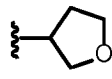
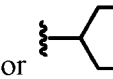
G and J independently are nitrogen or -CH-;

when G is nitrogen and J is -CH- or nitrogen, E is -C(=O)-, -CH₂-, NH, or -CHR⁶;

when G is -CH- and J is nitrogen or -CH-, E is -C(=O)-, -O-, -S-, -NH-, -N(C₁₋₄ alkyl)- [e.g., -N(methyl)- or -N(ethyl)-], or -N(C₁₋₄ haloalkyl)- (e.g., -NCHF₂- or -NCF₃-), wherein E and ring Q can be *cis* or *trans* to each other when both G and J are -CH;



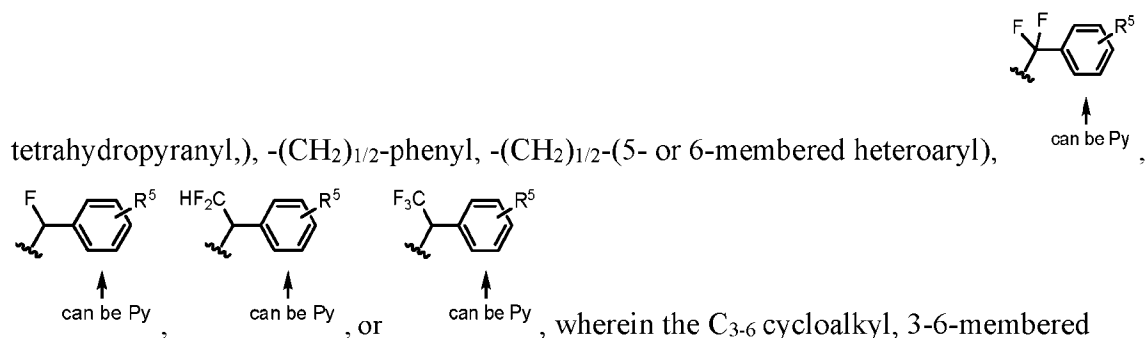
R¹ is hydrogen, C₁₋₄ alkyl (e.g., methyl, ethyl or isopropyl), C₁₋₄ haloalkyl (e.g., -CHF₂, -CF₃, -CH₂CHF₂ or -CH₂CF₃), C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclobutyl or cyclopentyl), 3-6-

membered heterocyclyl (e.g., ,  or , -CH₂-(C₃₋₆ cycloalkyl) (e.g., , -CH₂-(3-6-membered heterocyclyl), phenyl, thiophenyl, C₅₋₆ aryl, C₅₋₆ heteroaryl, or halide, wherein the C₃₋₆ cycloalkyl, 3-6-membered heterocyclyl, -CH₂-(C₃₋₆ cycloalkyl), -CH₂-(3-6-membered heterocyclyl), phenyl, thiophenyl, C₅₋₆ aryl and C₅₋₆ heteroaryl can optionally have 1, 2 or 3 substituents independently selected from halide (e.g., F and Cl), -CN, -OH, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ alkoxy (e.g., methoxy), C₁₋₄ haloalkyl (e.g., -CHF₂ and -CF₃), C₁₋₄ haloalkoxy (e.g., -OCHF₂ and -OCF₃), and -(CH₂)_{1/2}OH (e.g., -CH₂OH);

R² is 6-10-membered aryl or 5-10-membered heteroaryl, wherein the aryl or heteroaryl can be connected to ring A directly or via -CH₂-, -NH-, -NCH₃-, -O- or -S-, and wherein the aryl or heteroaryl can optionally have 1, 2 or 3 substituents independently selected from halide (e.g., F and Cl), -CN, -OH, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ alkoxy (e.g., methoxy), C₁₋₄ haloalkyl (e.g., -CHF₂ and -CF₃), C₁₋₄ haloalkoxy (e.g., -OCHF₂ and -OCF₃), -(CH₂)_{1/2}OH (e.g., -CH₂OH), -(CH₂)_{1/2}-(C₁₋₄ alkoxy) (e.g., -CH₂OCH₃), -C(=O)NH₂, -C(=O)NR⁸R⁹ (e.g., -C(=O)NHCH₃), and -SO₂R⁸ (e.g., -SO₂CH₃); and wherein R² is not connected via -NH-, -NCH₃-, -O- or -S-, to the nitrogen of ring A;

R³ in each occurrence independently is halide (e.g., F), -OH, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ haloalkyl (e.g., -CHF₂ and -CF₃), or C₁₋₄ alkoxy (e.g., methoxy), wherein R³ is not -OH or C₁₋₄ alkoxy at a carbon atom that is directly connected to a ring nitrogen atom;

R⁴ is hydrogen, C₁₋₄ alkyl (e.g., methyl or ethyl), C₁₋₄ haloalkyl (e.g., -CHF₂ or -CH₂CHF₂), C₃₋₆ cycloalkyl (e.g., cyclopropyl), 3-6-membered heterocyclyl, -(CH₂)_{1/2}-(C₃₋₆ cycloalkyl) (e.g., -CH₂-cyclopropyl), -(CH₂)_{1/2}-(3-6-membered heterocyclyl) (e.g., -CH₂-



heterocyclyl, $-(CH_2)_{1/2}$ -cycloalkyl, $-(CH_2)_{1/2}$ -heterocyclyl, $-(CH_2)_{1/2}$ -phenyl and $-(CH_2)_{1/2}$ -heteroaryl can optionally have 1, 2 or 3 substituents independently selected from halide (e.g., F and Cl), -CN, -OH, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ alkoxy (e.g., methoxy), C₁₋₄ haloalkyl (e.g., -CHF₂ and -CF₃), C₁₋₄ haloalkoxy (e.g., -OCHF₂ and -OCF₃), and $-(CH_2)_{1/2}$ OH (e.g., -CH₂OH);

R⁵ is hydrogen, halide (e.g., F or Cl), -CN, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ haloalkyl (e.g., -CHF₂ or -CF₃), C₁₋₄ alkoxy (e.g., methoxy), C₁₋₄ haloalkoxy (e.g., -OCHF₂ or -OCF₃), or $-(CH_2)_{1/2}$ OH (e.g., -CH₂OH);

R⁶ is C₁₋₄ alkyl (e.g., methyl or ethyl), C₁₋₄ haloalkyl (e.g., -CHF₂ or -CF₃), cyclopropyl or -CH₂-cyclopropyl;

R⁷ in each occurrence independently is halide (e.g., F or Cl), -CN, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ haloalkyl (e.g., -CHF₂ or -CF₃), C₁₋₄ alkoxy (e.g., methoxy), C₁₋₄ haloalkoxy (e.g., -OCHF₂ or -OCF₃), or $-(CH_2)_{1/2}$ OH (e.g., -CH₂OH);

R⁸ and R⁹ independently are hydrogen or C₁₋₄ alkyl (e.g., methyl);

R¹⁰ is H, halide, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, thiophenyl, pyridine, C₅₋₆ aryl or C₅₋₆ heteroaryl, wherein the C₃₋₆ cycloalkyl, phenyl, thiophenyl, pyridine, C₅₋₆ aryl or C₅₋₆ heteroaryl can optionally have 1, 2 or 3 substituents independently selected from halide (e.g., F or Cl), -CN, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ haloalkyl (e.g., -CHF₂ or -CF₃), C₁₋₄ alkoxy (e.g., methoxy), C₁₋₄ haloalkoxy (e.g., -OCHF₂ or -OCF₃), or $-(CH_2)_{1/2}$ OH (e.g., -CH₂OH);

m is 0, 1 or 2;

n is 0, 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2; and

a group having a stereocenter can have the (*R*)-stereochemistry or the (*S*)-stereochemistry at the stereocenter or can be racemic at the stereocenter.

2. The compound of claim 1, wherein:

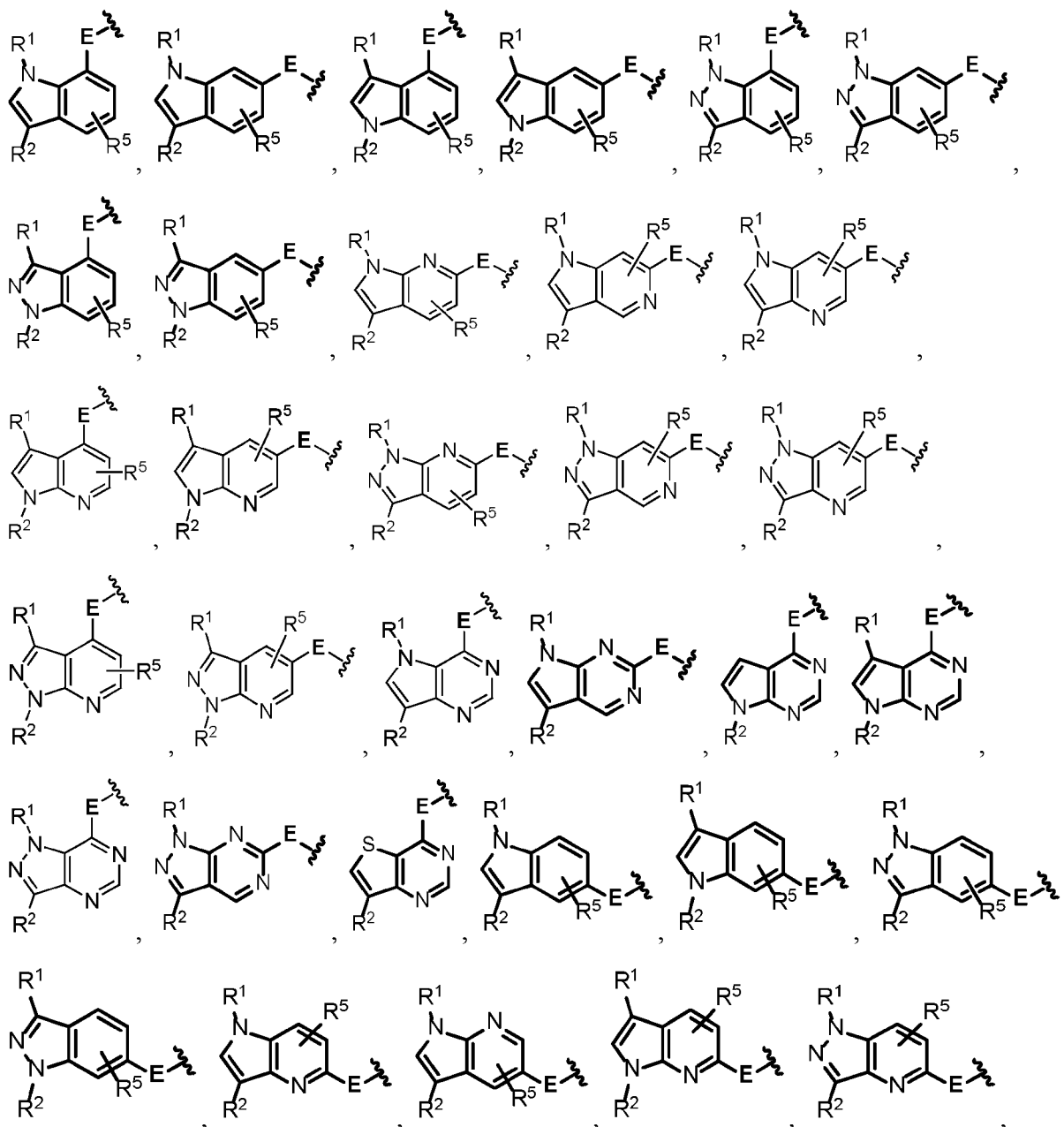
R^2 is selected from phenyl, pyrrolyl, furanyl (furyl), thiophenyl (thienyl), pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl (pyridyl), pyridazinyl, pyrimidinyl, pyrazinyl, 2-pyridinonyl, 3-pyridinonyl and 4-pyridinonyl;

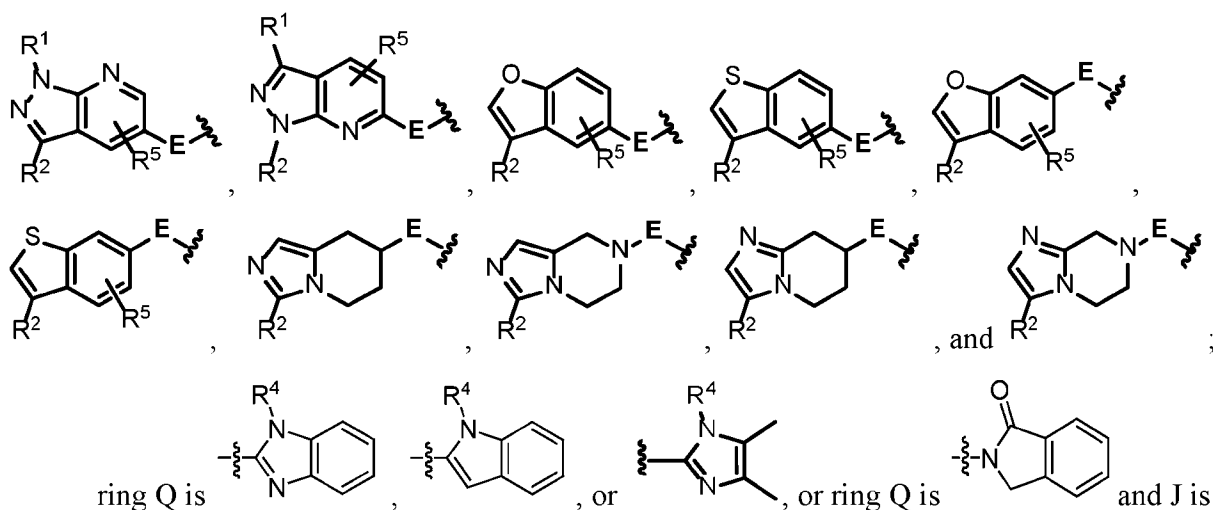
the R^2 group can be connected to ring A directly or via $-CH_2-$, $-NH-$, $-NCH_3-$, $-O-$ or $-S-$; and wherein R^2 is not connected via $-NH-$, $-NCH_3-$, $-O-$ or $-S-$, to the nitrogen of ring A;

and the R^2 group can optionally be substituted as defined in claim 1.

3. The compound of claim 1 or 2, wherein:

ring A attached to E is selected from:





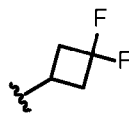
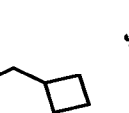
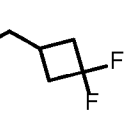
not nitrogen;

the ring containing G and J is azetidine, pyrrolidine, piperidine, homopiperidine or piperazine;

when G is nitrogen and J is -CH- or nitrogen, E is -C(=O)-, -CH₂-, -CH(CH₃)-, -CH(CHF₂)-, -CH(CF₃)-, -CH(cyclopropyl)- or -CH(CH₂-cyclopropyl)-;

when G is -CH- and J is nitrogen, E is -O-, -NH-, -NCH₃- or -NCF₃-;

R¹ is hydrogen, methyl, ethyl, isopropyl, -CHF₂, -CF₃, -CH₂CHF₂, cyclopropyl,

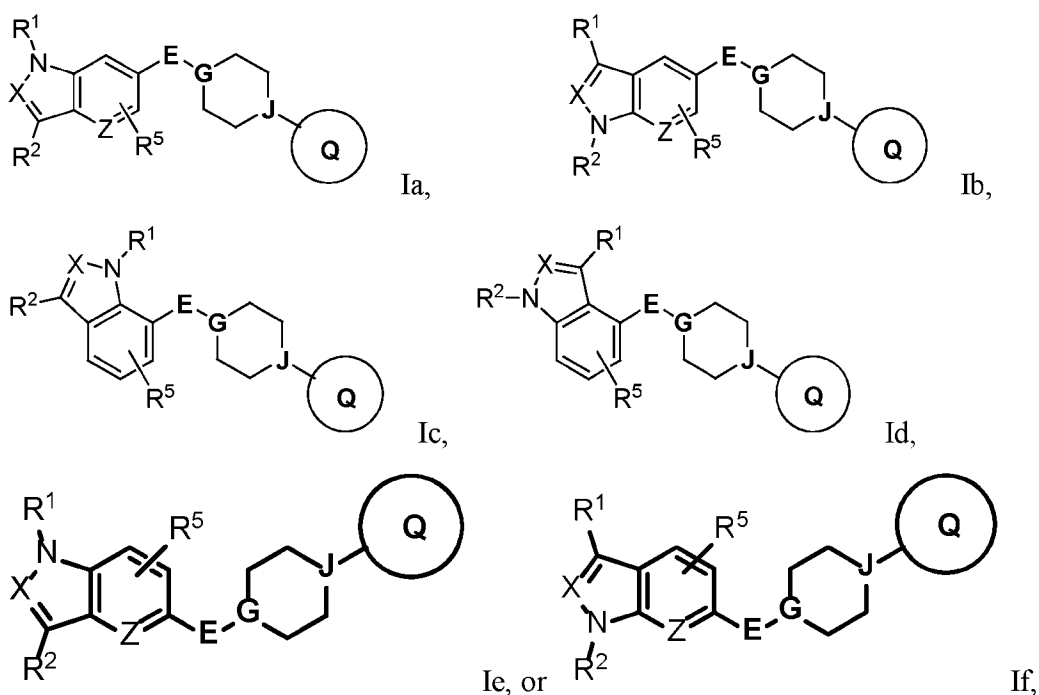
cyclobutyl, cyclopentyl, , , , or  or ;

R² is thiophenyl, phenyl or pyridinyl, wherein the thiophenyl, phenyl or pyridinyl can be connected to ring A directly or via -CH₂- or -NH-, and wherein the thiophenyl, phenyl or pyridinyl can optionally have 1 or 2 substituents independently selected from halide (e.g., F and Cl), -CN, methyl, -CHF₂, -CF₃ and methoxy; and wherein R² is not connected via -NH- to the nitrogen of ring A;

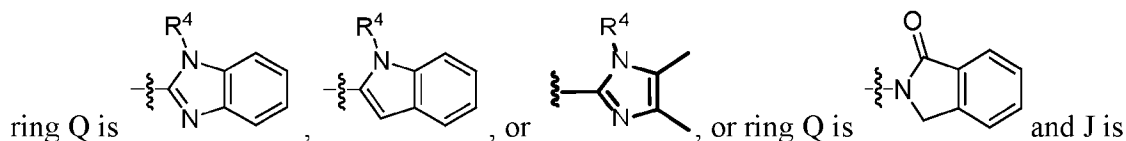
p is 0, or p is 1 and R³ is F or methyl; and

R⁵ is hydrogen, F, Cl or methyl.

4. The compound of claim 1 or 2, which has Formula Ia, Ib, Ic, Id, Ie or If, or is a tautomer, pharmaceutically acceptable salt, solvate, hydrate, clathrate, isotopes, or isotopic forms including deuterated and tritiated forms, polymorph or stereoisomer thereof:



wherein:



not nitrogen;

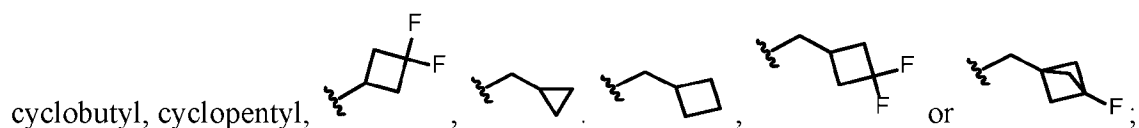
X and Z independently are carbon or nitrogen;

both G and J are not -CH-;

when G is nitrogen and J is -CH- or nitrogen, E is -C(=O)-, -CH₂-, -CH(CH₃)-, -CH(CHF₂)- or -CH(CF₃)-;

when G is -CH- and J is nitrogen, E is -O-, -NH-, -NCH₃- or -NCF₃-;

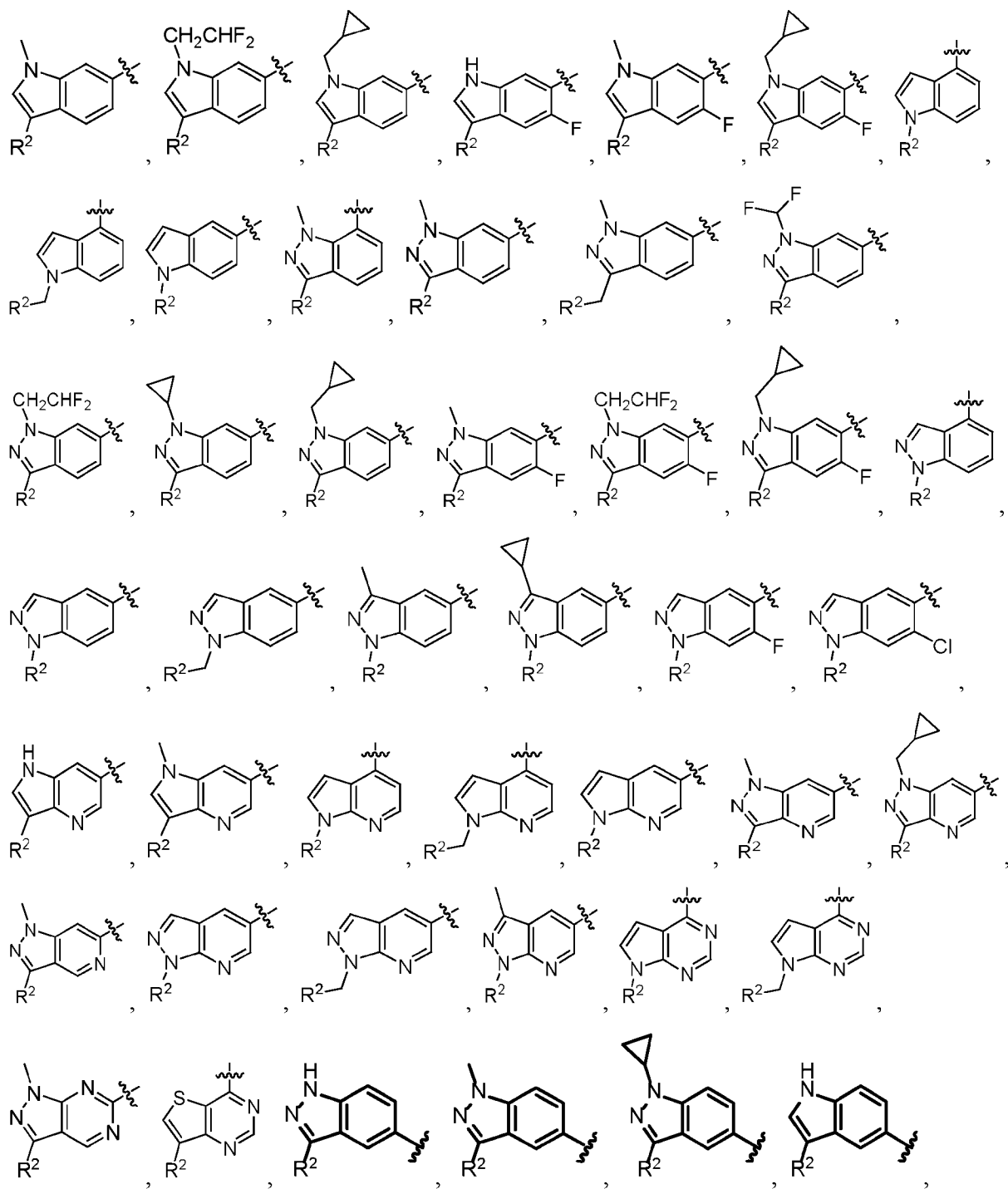
R¹ is hydrogen, methyl, ethyl, isopropyl, -CHF₂, -CF₃, -CH₂CHF₂, cyclopropyl,

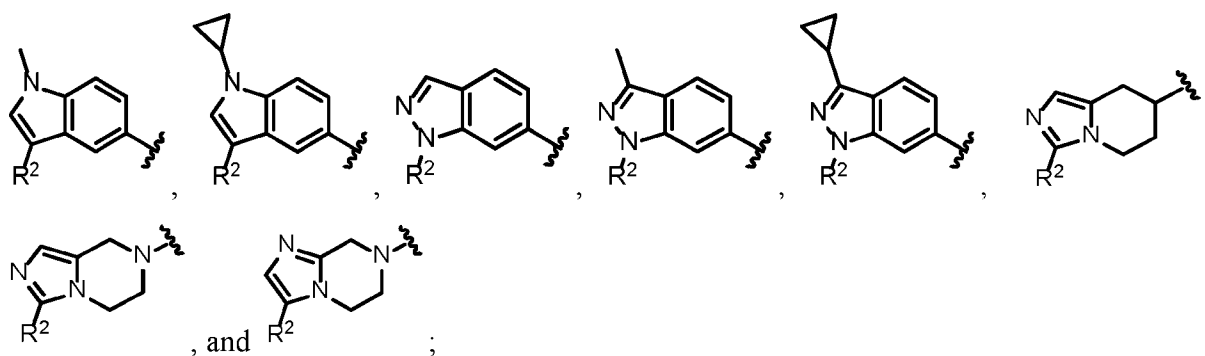


R² is thiophenyl, phenyl or pyridinyl, wherein the thiophenyl, phenyl or pyridinyl can be connected to ring A directly or via -CH₂-, and wherein the thiophenyl, phenyl or pyridinyl can optionally have 1 or 2 substituents independently selected from halide (e.g., F and Cl), -CN, methyl, -CHF₂, -CF₃ and methoxy; and

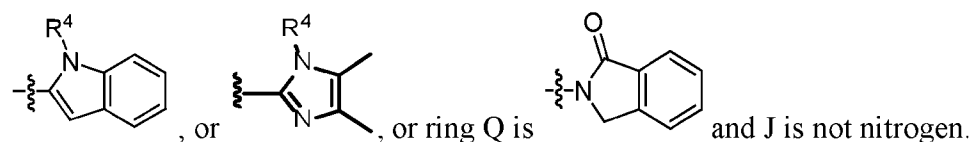
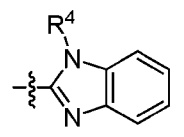
R⁵ is hydrogen, F, Cl or methyl.

5. The compound of any one of the preceding claims, wherein ring A is selected from:

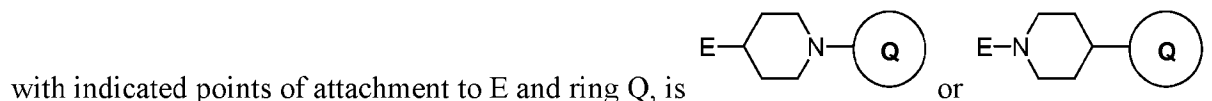




6. The compound of any one of the preceding claims, wherein ring Q is



7. The compound of any one of the preceding claims, wherein the ring containing G and J,



8. The compound of any one of the preceding claims, wherein when G is nitrogen and J is -CH- or nitrogen, E is -C(=O)-, -CH₂-, -CH(CH₃)-, -, -CH(CHF₂)-, -CH(CF₃)-, -CH(cyclopropyl)- or -CH(CH₂-cyclopropyl)-, and wherein a stereocenter can have the (*R*)-stereochemistry or the (*S*)-stereochemistry or can be racemic.

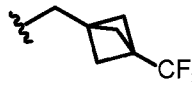
9. The compound of any one of claims 1 to 7, wherein when G is -CH- and J is nitrogen or -CH, E is -O-, -NH-, -NCH₃- or -NCF₃-.

10. The compound of any one of the preceding claims, wherein R¹ is hydrogen, methyl, -CHF₂-, -CH₂CHF₂-, cyclopropyl or -CH₂-cyclopropyl.

11. The compound of any one of the preceding claims, wherein R² is 2-F-phenyl, 2-CH₃-phenyl, 3-F-phenyl, 3-Cl-phenyl, 3-CHF₂-phenyl, 3-CF₃-phenyl, 4-F-phenyl, 2,3-diF-phenyl, 3,5-diF-phenyl, 2-F-5-Cl-phenyl, 5-Cl-thiophen-3-yl, 5-CF₃-thiophen-3-yl, 5-F-pyridin-3-yl, or 5-Cl-pyridin-3-yl, and wherein the R² group can be connected to ring A directly or via -CH₂- or -NH-; and wherein R² is not connected via -NH- to the nitrogen of ring A.

12. The compound of claim 11, wherein R² is 3-F-phenyl, 3-Cl-phenyl or 3-CF₃-phenyl.

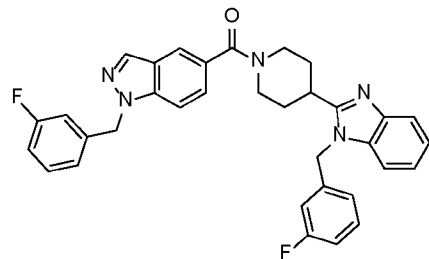
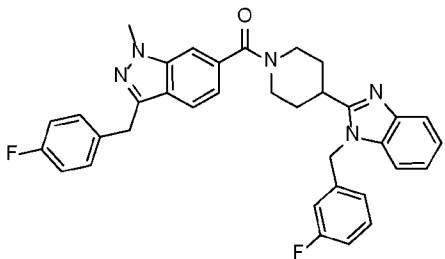
13. The compound of any one of the preceding claims, wherein p is 0.
14. The compound of any one of claims 1 to 12, wherein when p is 1 or 2, R³ in each occurrence independently is F or methyl.
15. The compound of any one of the preceding claims, wherein R⁴ is selected from -CHF₂, -CH₂CHF₂, cyclopropyl, -CH₂-cyclopropyl, -CH₂CH₂-cyclopropyl, *cis* or *trans* -CH₂-3-OH-

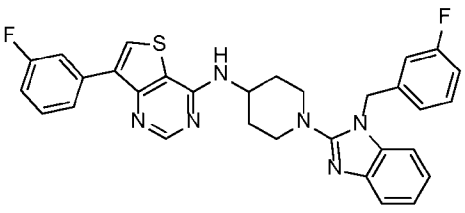
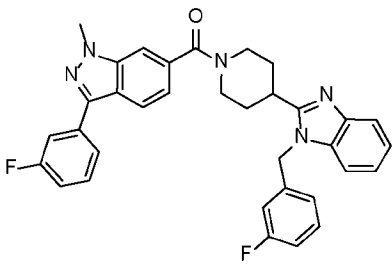
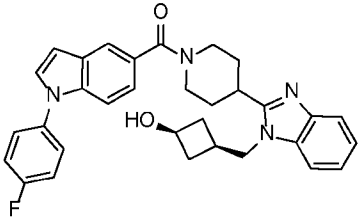
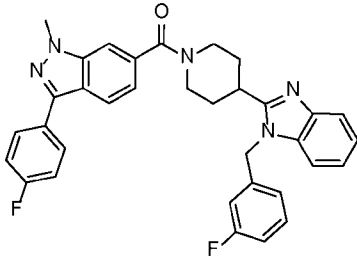
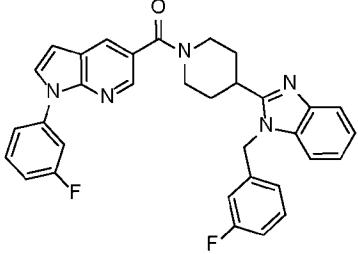
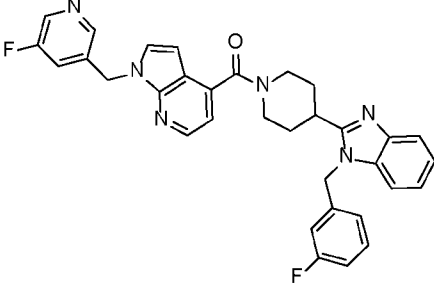
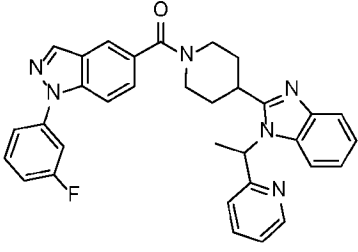
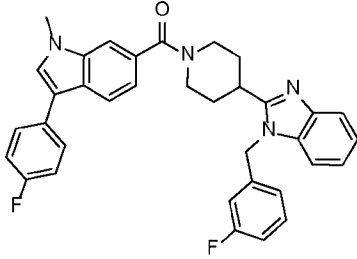
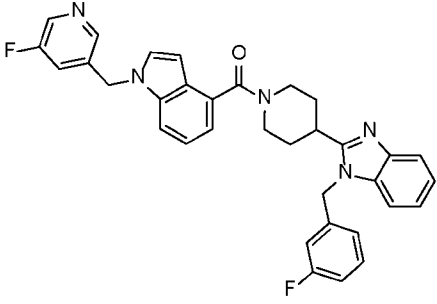
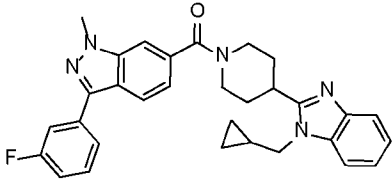
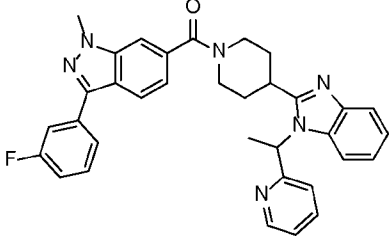
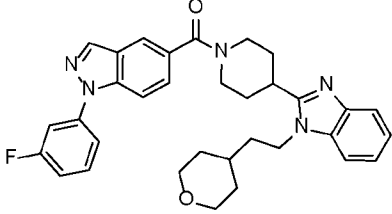
cyclobutane, -CH₂-(3,3-diF-cyclobutane), , , -CH₂-tetrahydropyran-4-yl, -CH₂CH₂-tetrahydropyran-4-yl, -CH₂-phenyl, -CH₂-(3-F-phenyl), -CH(CH₃)-phenyl, -CH(CH₃)-(3-F-phenyl), -CF₂-phenyl, -CF₂-(3-F-phenyl), -CH₂-pyridin-2-yl and -CH(CH₃)-pyridin-2-yl, and wherein a stereocenter can have the (*R*)-stereochemistry or the (*S*)-stereochemistry or can be racemic.

16. The compound of claim 15, wherein R⁴ is -CHF₂, -CH₂CHF₂, cyclopropyl, -CH₂-

cyclopropyl, -CH₂-(3-F-phenyl), -CF₂-phenyl, -CF₂-(3-F-phenyl), , -CH(CH₃)-phenyl, or -CH(CH₃)-pyridin-2-yl.

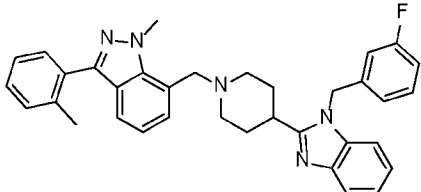
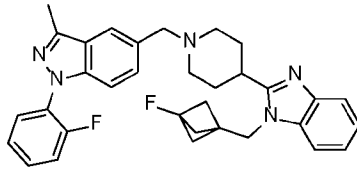
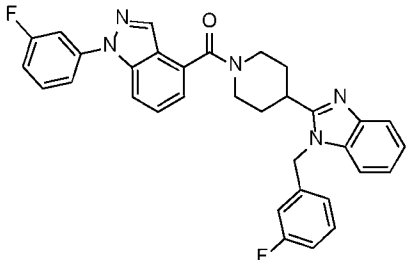
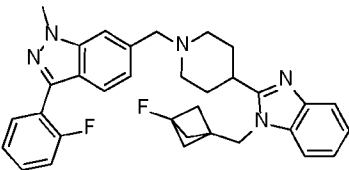
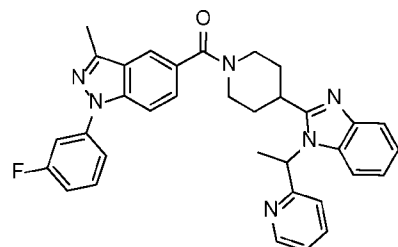
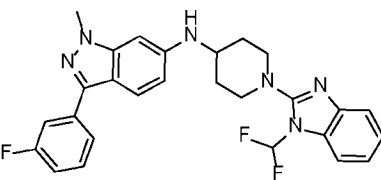
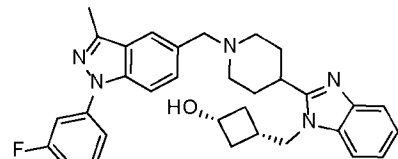
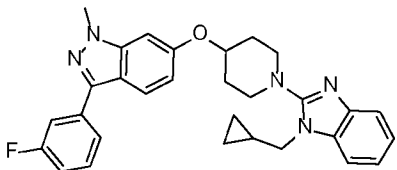
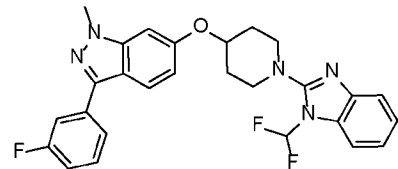
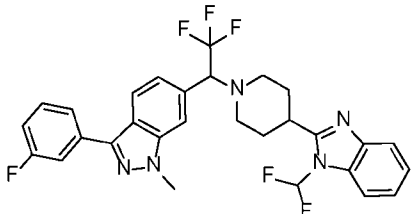
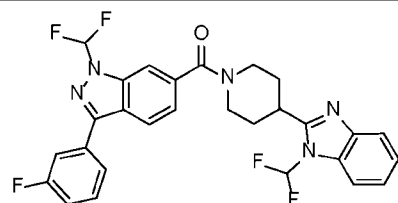
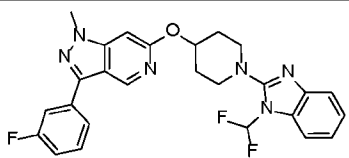
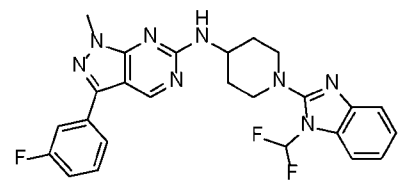
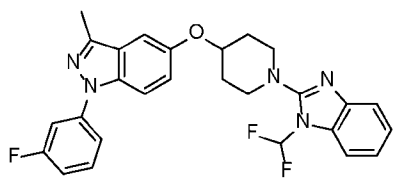
17. The compound of any one of the preceding claims, wherein R⁵ is hydrogen, F or Cl.
18. The compound of any one of the preceding claims, which is selected from Compounds **2-48** and **50-440** disclosed in the specification, and tautomers, pharmaceutically acceptable salts, solvates, hydrates, clathrates, polymorphs and stereoisomers thereof.
19. The compound of claim 18, which is selected from the following compounds, and tautomers, pharmaceutically acceptable salts, solvates, hydrates, clathrates, isotopes, or isotopic forms including deuterated and tritiated forms, polymorphs and stereoisomers thereof, wherein compounds having a stereocenter can have the (*R*)-stereochemistry or the (*S*)-stereochemistry at the stereocenter or can be racemic at the stereocenter:

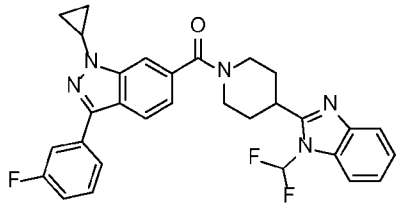
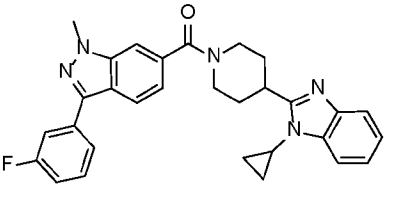
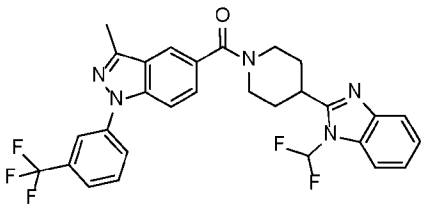
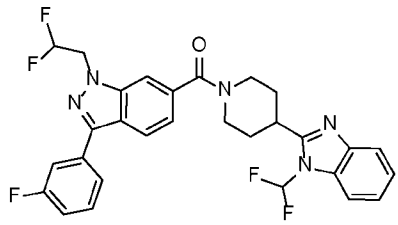
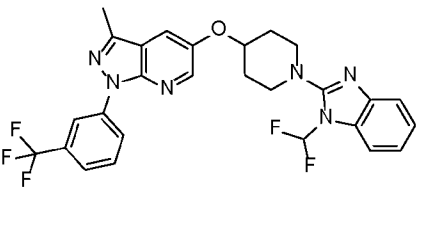
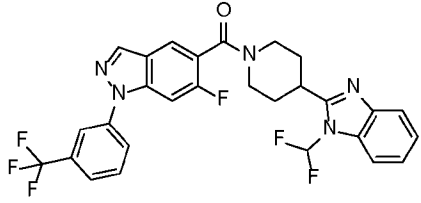
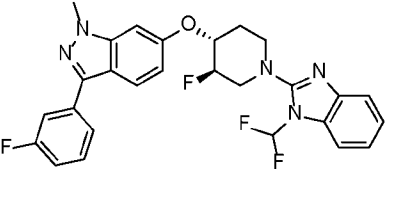
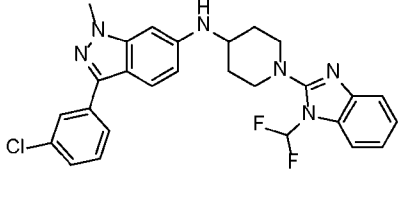
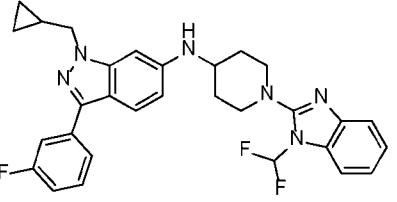
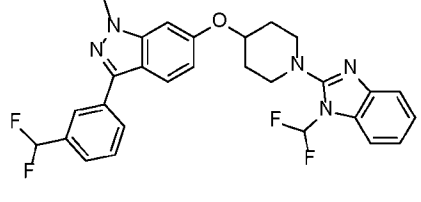
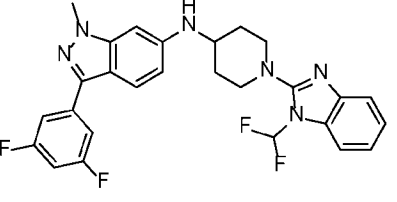
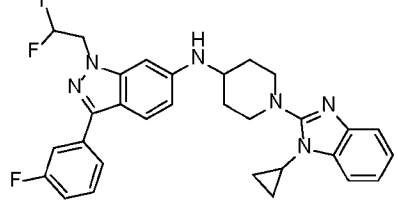
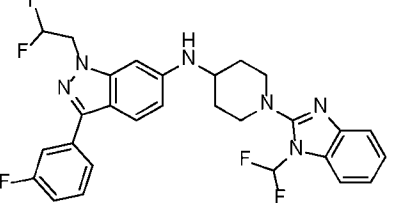
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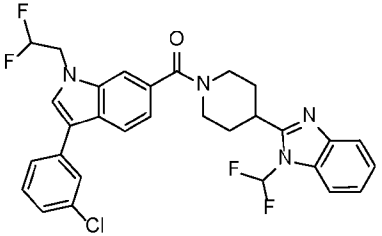
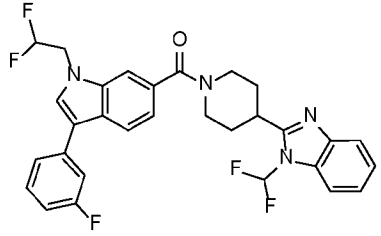
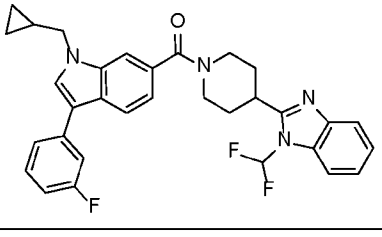
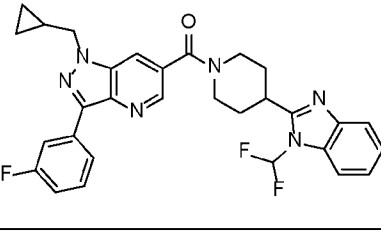
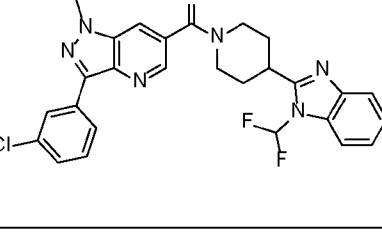
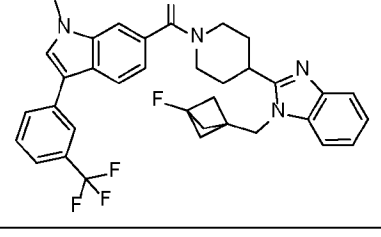
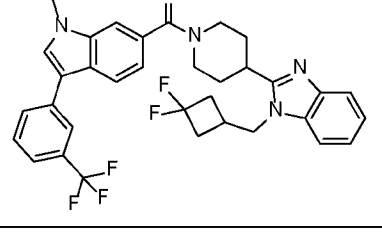
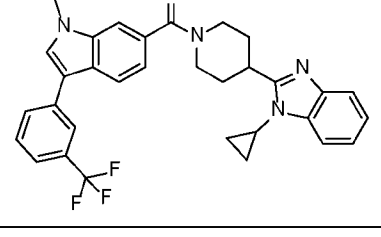
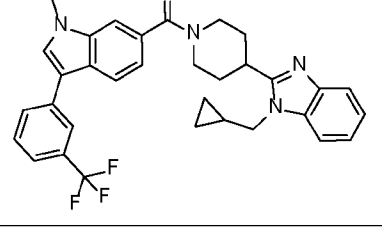
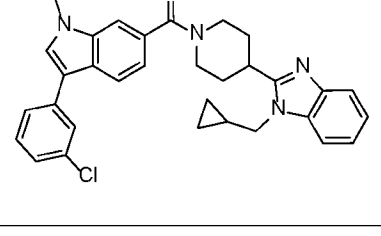
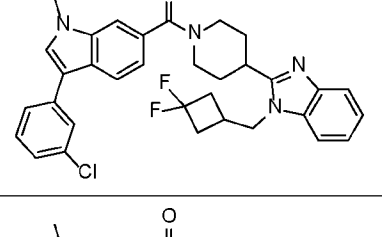
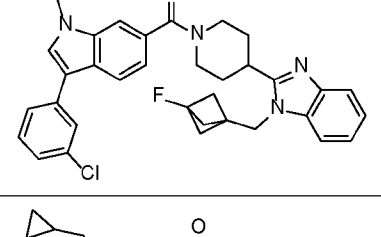
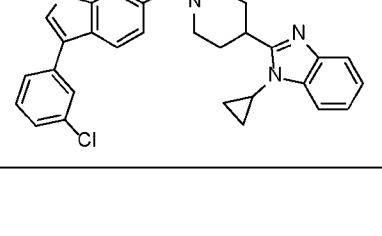
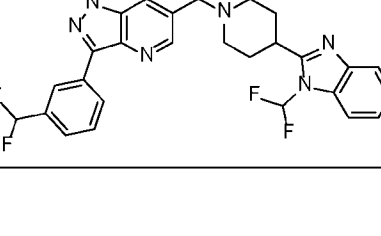
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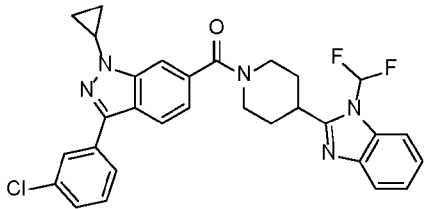
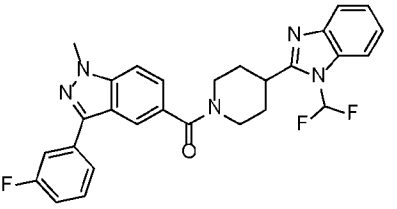
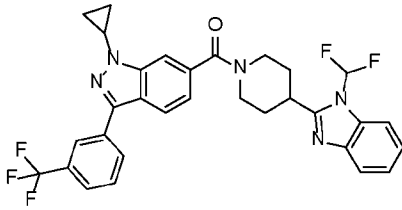
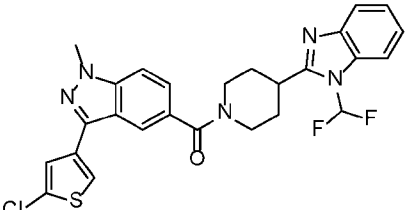
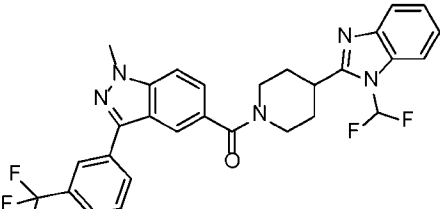
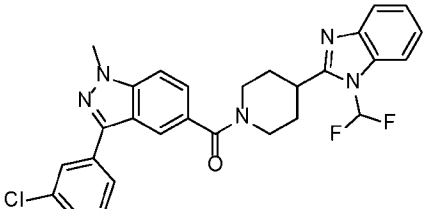
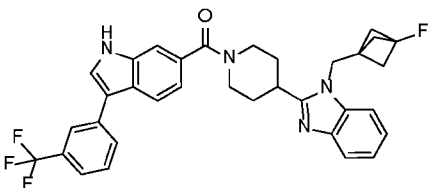
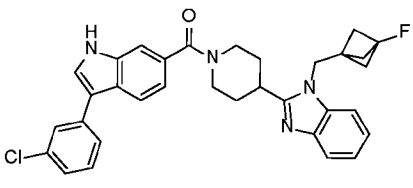
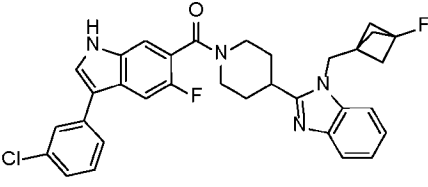
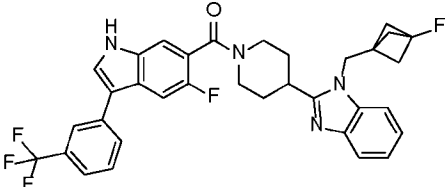
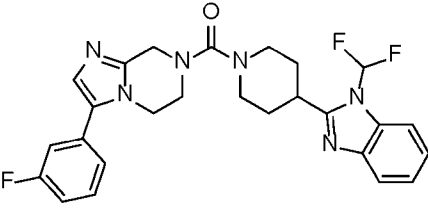
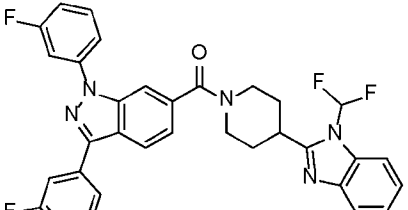
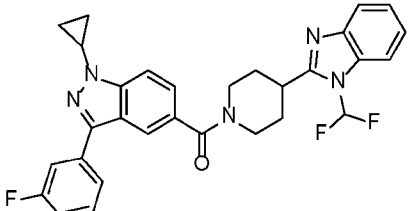
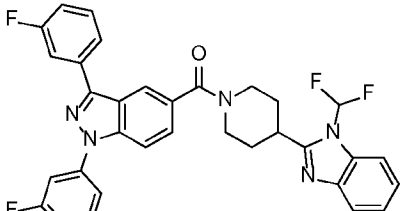
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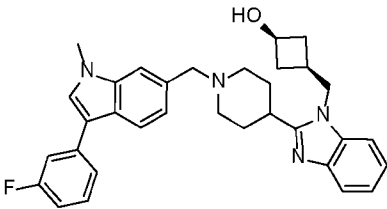
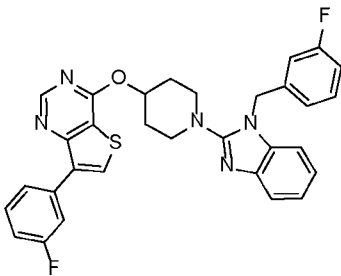
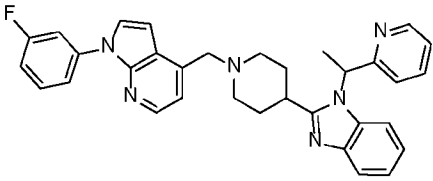
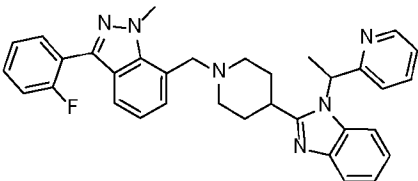
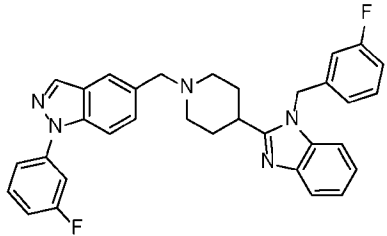
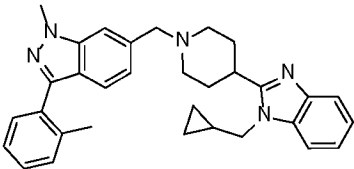
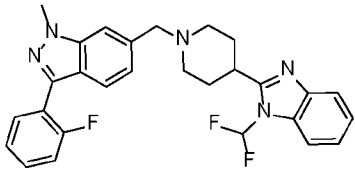
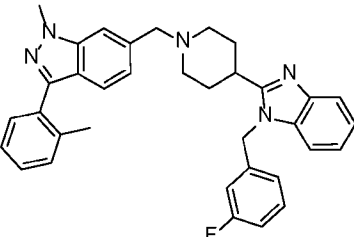
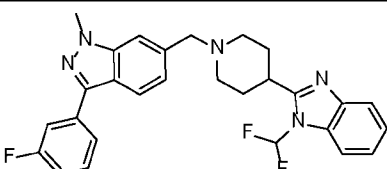
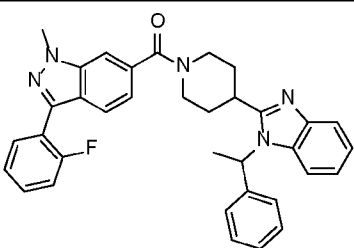
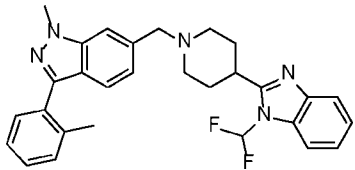
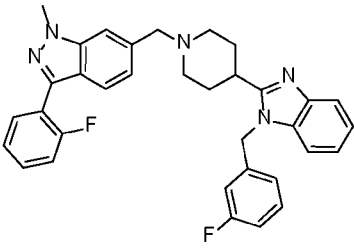
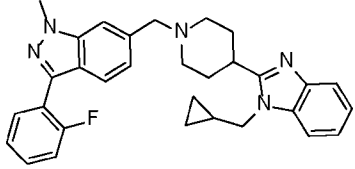
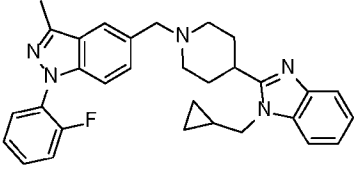
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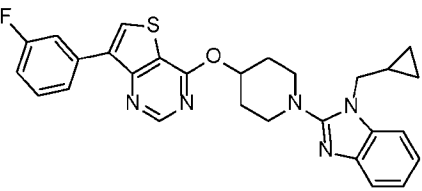
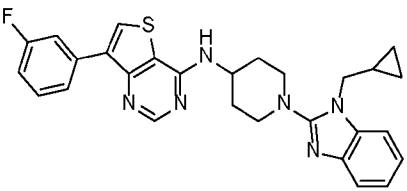
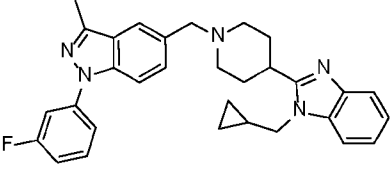
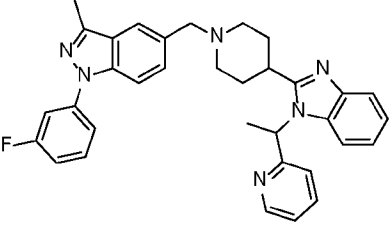
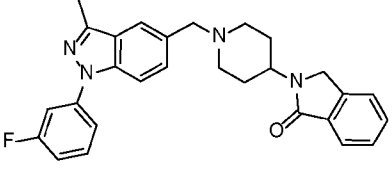
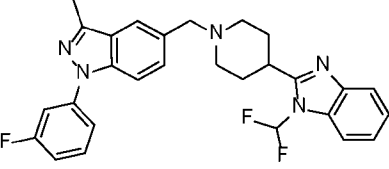
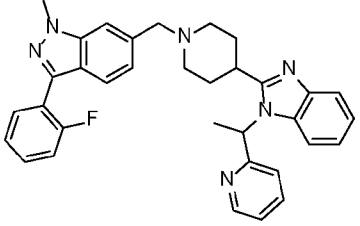
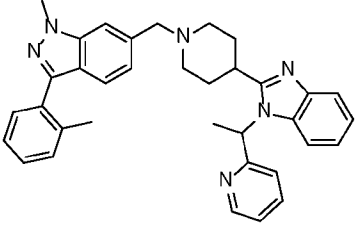
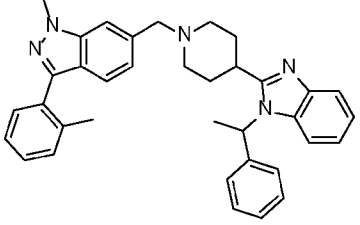
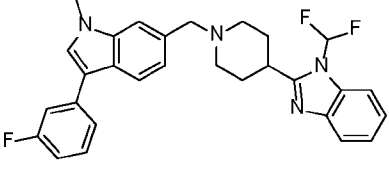
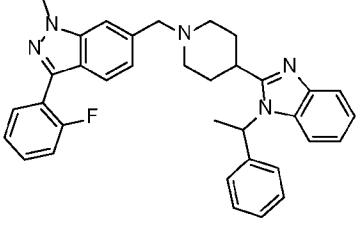
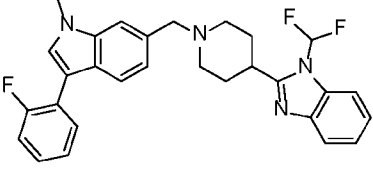
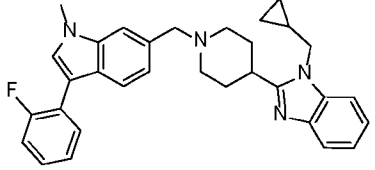
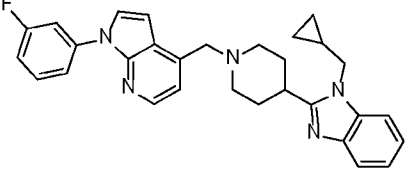
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20. The compound of claim 18, which is selected from the following compounds, and tautomers, pharmaceutically acceptable salts, solvates, hydrates, clathrates, isotopes, or isotopic forms including deuterated and tritiated forms, polymorphs and stereoisomers thereof, wherein compounds having a stereocenter can have the (*R*)-stereochemistry or the (*S*)-stereochemistry at the stereocenter or can be racemic at the stereocenter:

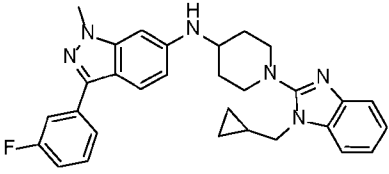
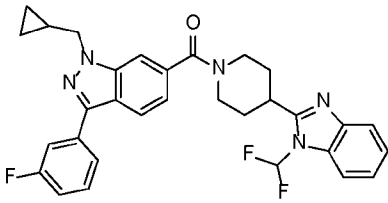
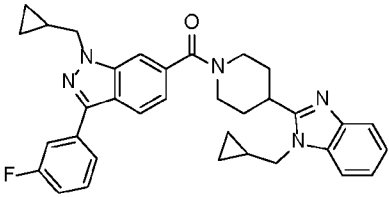
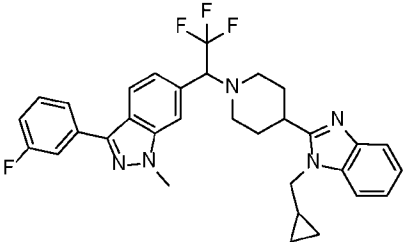
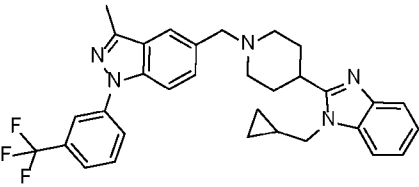
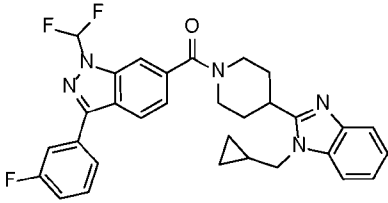
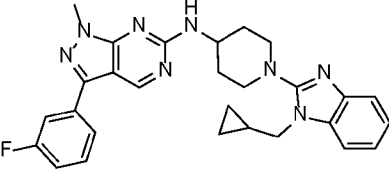
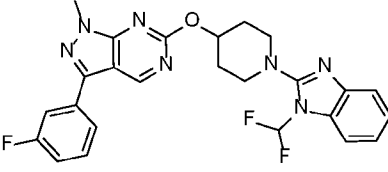
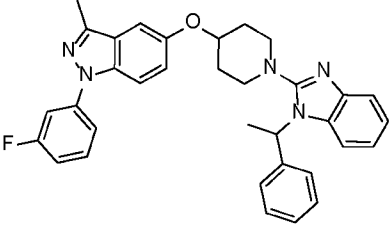
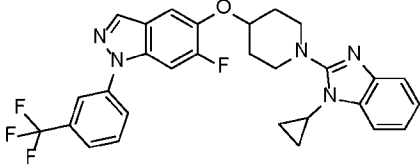
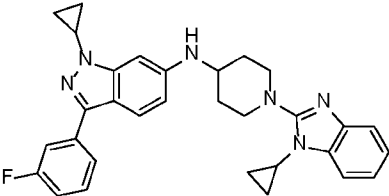
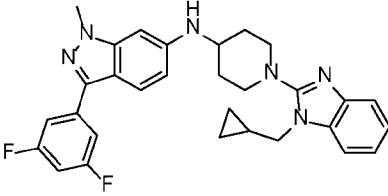
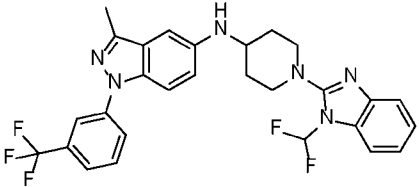
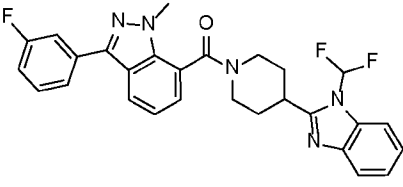
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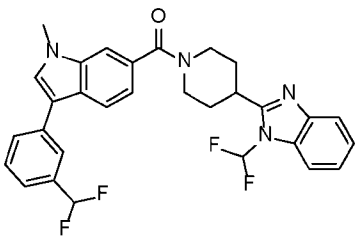
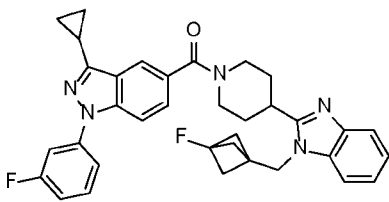
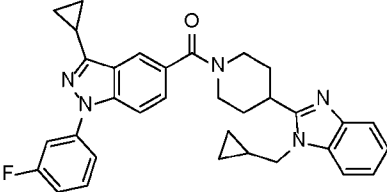
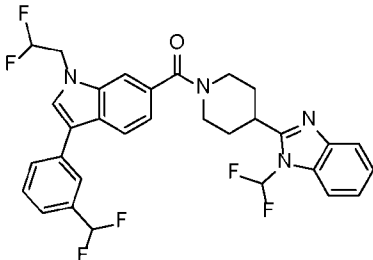
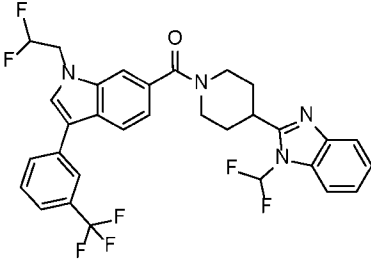
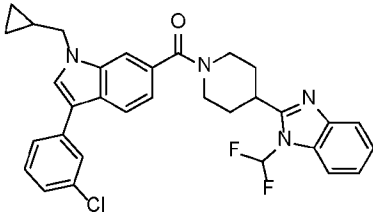
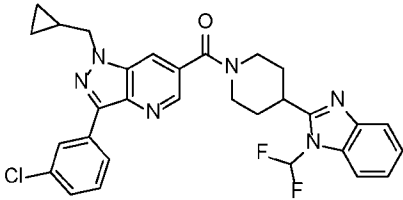
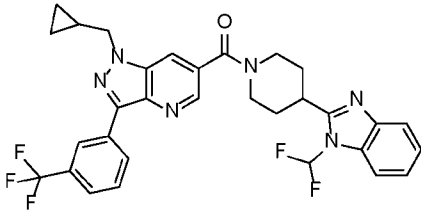
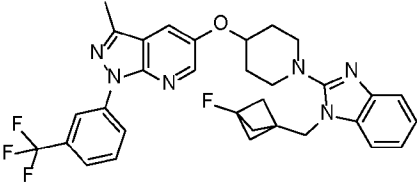
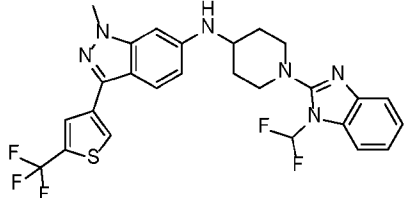
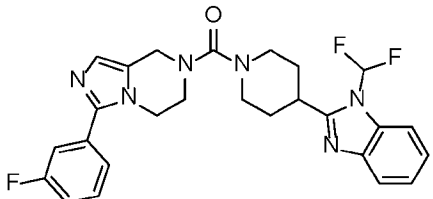
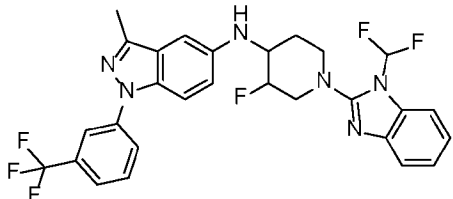
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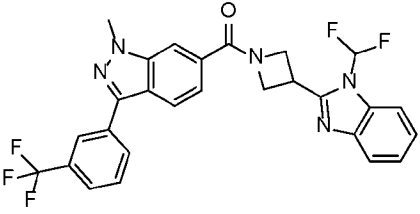
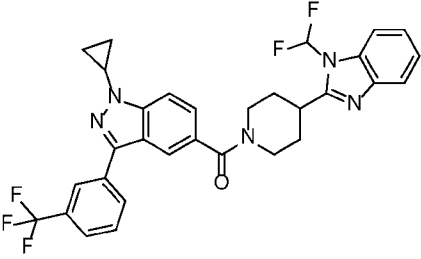
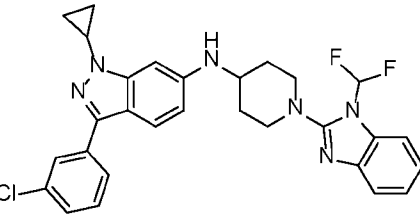
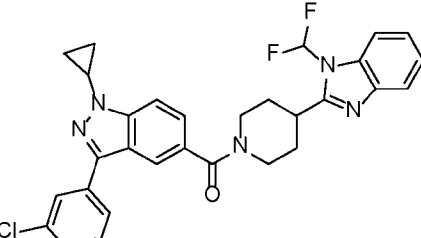
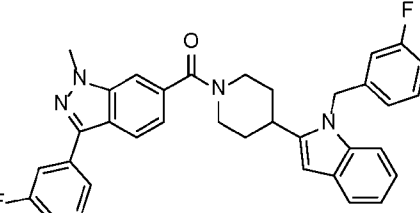
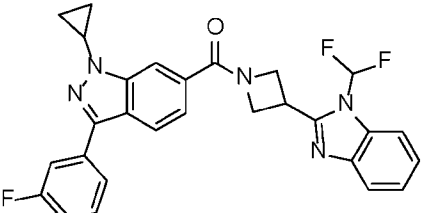
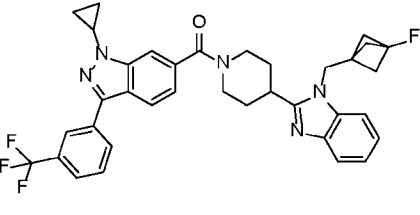
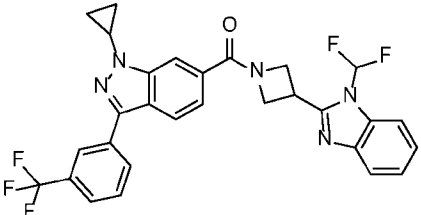
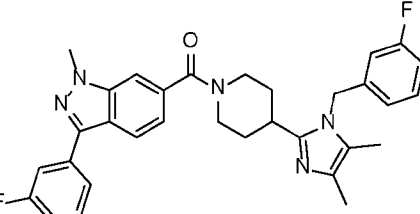
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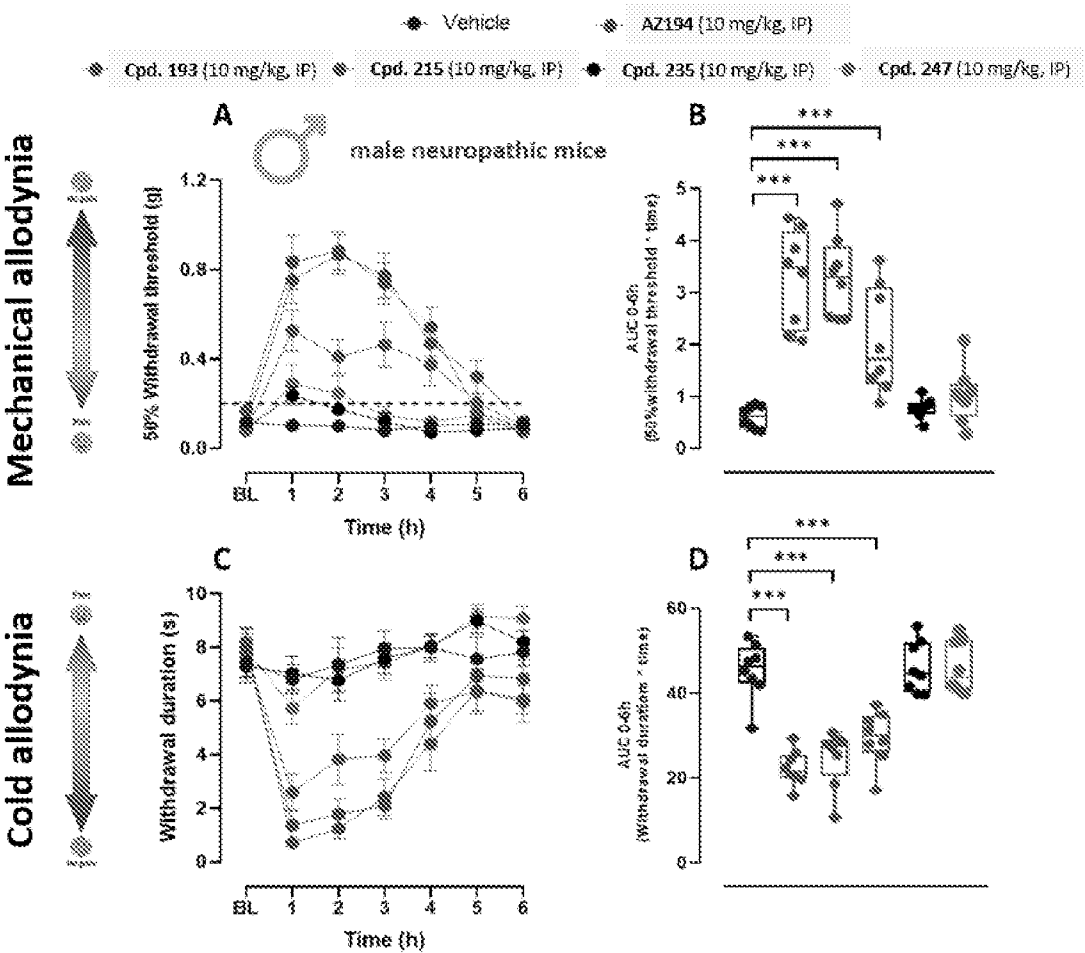
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21. A pharmaceutical composition comprising a compound of any one of the preceding claims or a tautomer, pharmaceutically acceptable salt, solvate, hydrate, clathrate, isotopes, or isotopic forms including deuterated and tritiated forms, polymorph or stereoisomer thereof, and one or more pharmaceutically acceptable excipients or carriers.

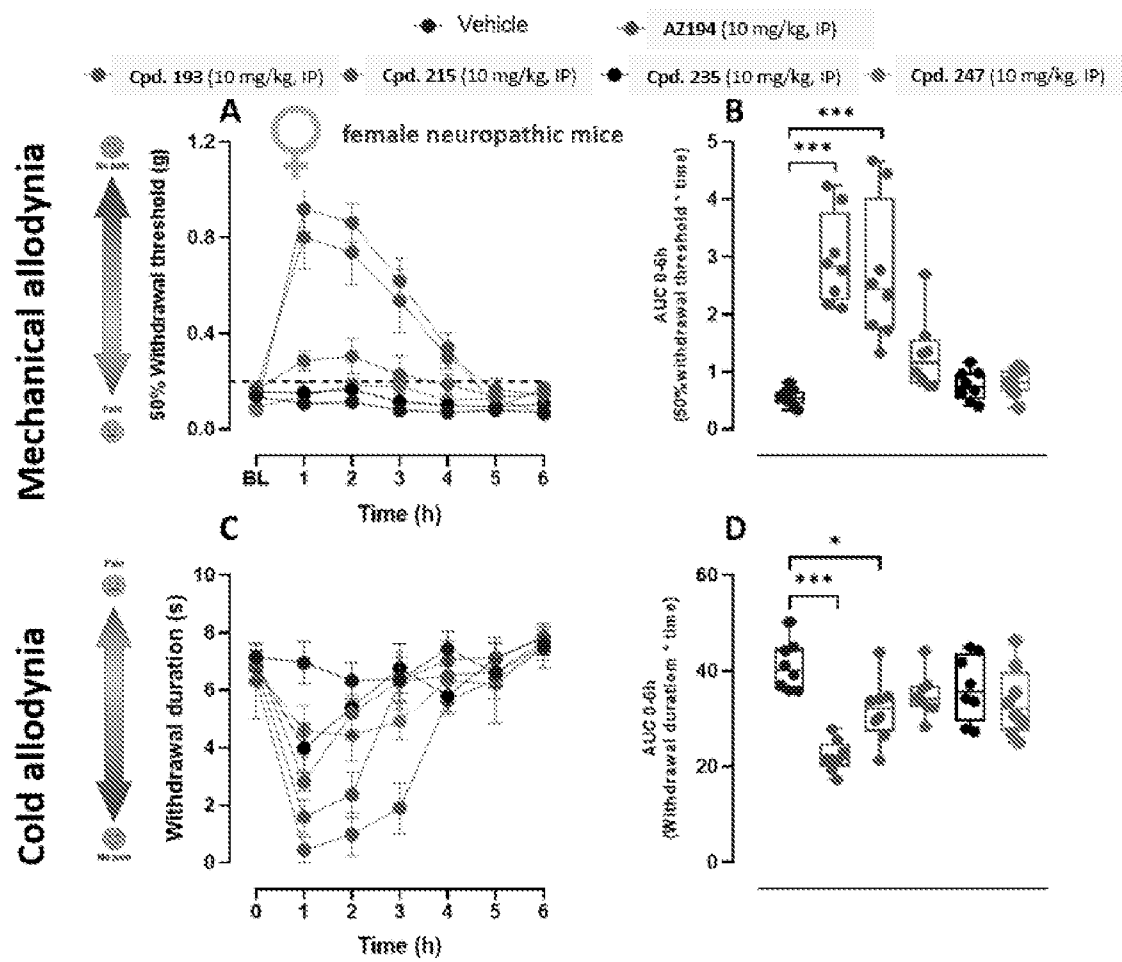
22. The pharmaceutical composition of claim 21, further comprising an additional therapeutic agent such as an additional analgesic.

23. A method of treating pain or a pain-associated disorder, comprising administering to a subject an amount of a compound of any one of claims 1 to 20, or a tautomer, pharmaceutically acceptable salt, solvate, hydrate, clathrate, isotopes, or isotopic forms including deuterated and tritiated forms, polymorph or stereoisomer thereof, effective to treat pain or a pain-associated disorder.
24. The method of claim 23, wherein the pain is acute pain, chronic pain, neuropathic pain, inflammatory pain, osteoarthritis, mechanical pain, pressure pain, tactile pain, thermal pain, cold pain, post-surgical pain, cancer pain, musculoskeletal pain (e.g., neck pain, spinal cord-related pain, lower back pain, hip pain, knee pain or joint pain), or spinal cord injury-related pain, or any combination thereof, wherein each of the preceding types of pain includes allodynia, algesia and hyperalgesia.
25. The method of claim 24, wherein the pain is acute or chronic neuropathic pain.
26. The method of claim 23, wherein the pain-associated disorder is fibromyalgia, neuralgia, a neuropathy (e.g., diabetic neuropathy), a peripheral neuropathy (e.g., PN induced by chemotherapy or nerve injury), chronic regional pain syndrome, a musculoskeletal disorder (e.g., a degenerative one such as rheumatoid arthritis, osteoarthritis or spondylosis), a headache (e.g., migraine or tension headache), or a disorder resulting from a mutation in the gene encoding Nav1.7 (e.g., primary erythromelalgia or paroxysmal extreme pain disorder).
27. The method of any one of claims 23 to 26, further comprising administering an additional therapeutic agent such as an additional analgesic.
28. The method of claim 27, wherein the compound of Formula I has a synergistic analgesic effect in combination with an additional agent or analgesic such as an opioid (e.g., morphine, oxycodone or hydrocodone) or/and an NSAID (e.g., ibuprofen, naproxen or a COX-2 inhibitor).
29. A method of inhibiting expression of voltage-gated sodium ion channel 1.7 (Nav1.7) on surface of a nerve cell, comprising contacting a nerve cell with a compound of any one of claims 1 to 20 or a tautomer, pharmaceutically acceptable salt, solvate, hydrate, clathrate, isotopes, or isotopic forms including deuterated and tritiated forms, polymorph or stereoisomer thereof.
30. The method of claim 29, wherein the compound inhibits SUMOylation of collapsin response mediator protein 2 (CRMP2).

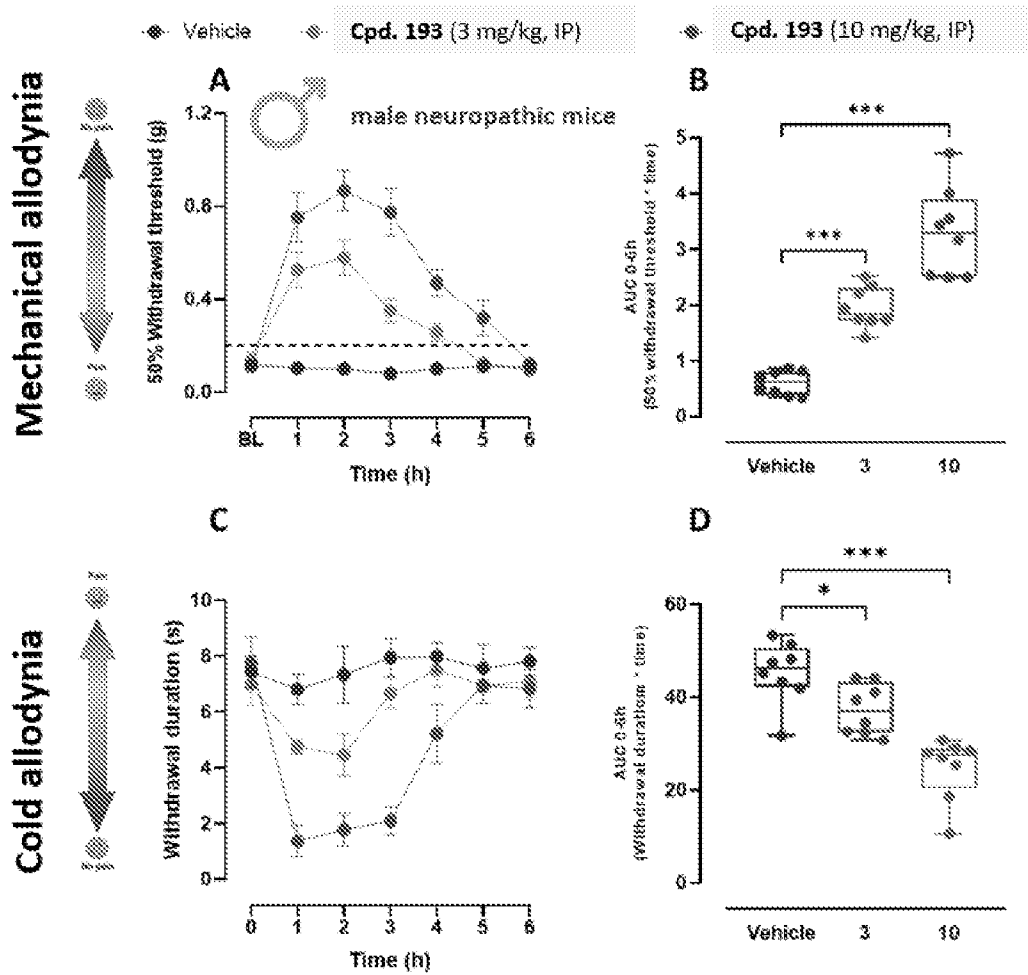
31. The method of claim 29 or 30, wherein the nerve cell is a nociceptive neuron.
32. The method of any one of claims 29 to 31, wherein the contacting occurs *in vivo* or *in vitro*.
33. The method of claim 23, wherein the subject comprises a mammal, a primate, a human, a chimpanzee, a monkey, a rodent, a rat, a mouse, a guinea pig, a gerbil or a hamster, a lagomorph, a rabbit, a bovine, a cattle, a suid, a pig, a caprine, a sheep, an equine, a horse, a canine, a dog, or a feline, and a cat.



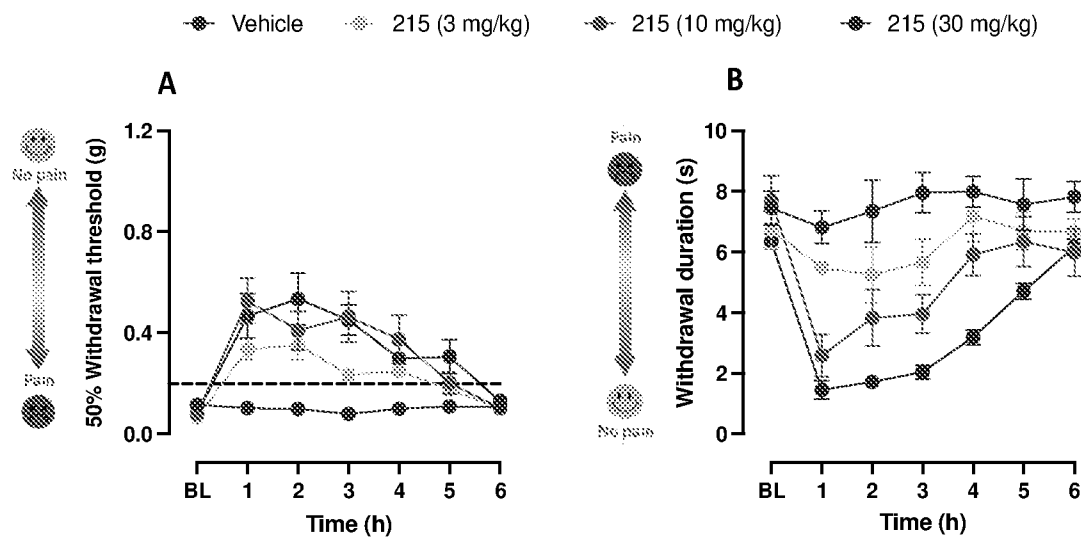
Figs. 1A-D



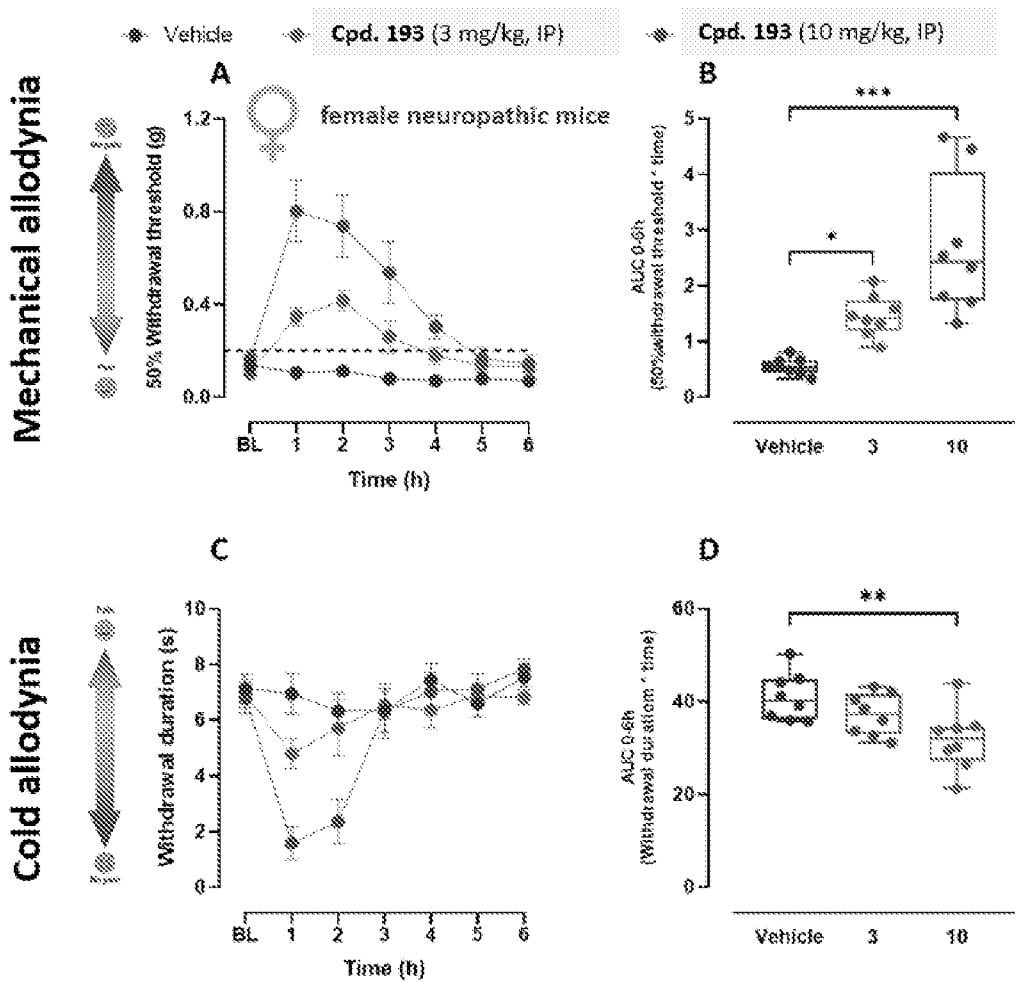
Figs. 2A-D



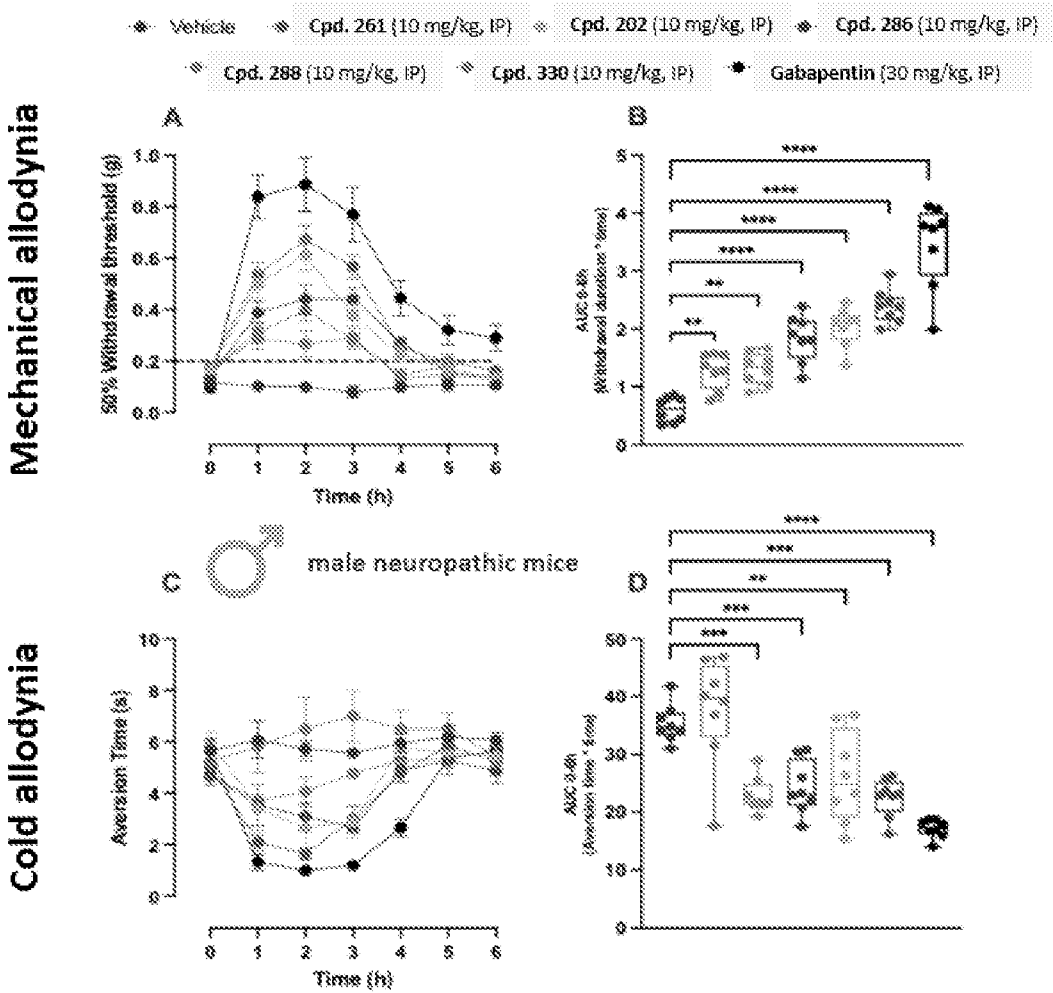
Figs. 3A-D



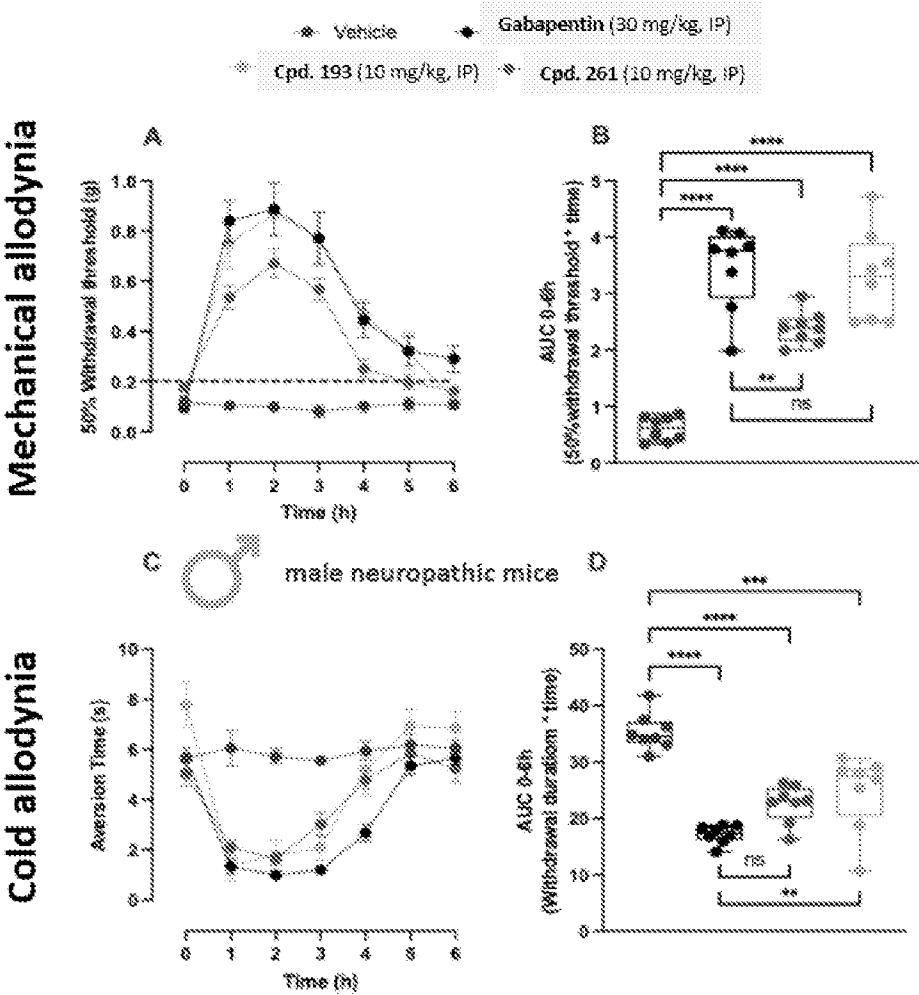
Figs. 4A and B



Figs. 5A-D



Figs. 6A-D



Figs. 7A-D

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/060335

A. CLASSIFICATION OF SUBJECT MATTER					
INV.	C07D401/14	C07D403/14	C07D409/14	C07D471/04	C07D487/04
	A61P29/00	A61K31/4439			
ADD.					
According to International Patent Classification (IPC) or to both national classification and IPC					
B. FIELDS SEARCHED					
Minimum documentation searched (classification system followed by classification symbols)					
A61P C07D					
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched					
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)					
EPO-Internal, CHEM ABS Data, WPI Data					
C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category*	Citation of document, with indication, where appropriate, of the relevant passages				Relevant to claim No.
A	WO 2018/144900 A1 (UNIV ARIZONA [US]) 9 August 2018 (2018-08-09) page 1, line 10 - line 15; claims 1-35 -----				1 - 33
☐ Further documents are listed in the continuation of Box C.					
☒ See patent family annex.					
* Special categories of cited documents :					
"A" document defining the general state of the art which is not considered to be of particular relevance			"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention		
"E" earlier application or patent but published on or after the international filing date			"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone		
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)			"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art		
"O" document referring to an oral disclosure, use, exhibition or other means			"&" document member of the same patent family		
"P" document published prior to the international filing date but later than the priority date claimed					
Date of the actual completion of the international search			Date of mailing of the international search report		
24 February 2025			07/03/2025		
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016			Authorized officer Seelmann, Ingo		

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2024/060335

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018144900 A1	09-08-2018	AU 2018215466 A1	22-08-2019
		CA 3052195 A1	09-08-2018
		CN 110381941 A	25-10-2019
		EP 3576734 A1	11-12-2019
		JP 7092776 B2	28-06-2022
		JP 2020505434 A	20-02-2020
		US 2020277271 A1	03-09-2020
		WO 2018144900 A1	09-08-2018
