FLUORINATED CYCLIC DERIVATIVES OF SULFONAMIDES AND SULFONES, AND COMPOSITIONS AND METHODS THEREOF

Priority Claims and Related Patent Applications

[0001] This application claims the benefit of priority from U.S. Provisional Application Serial Nos. 63/460,744, filed on April 20, 2023, and 63/546,566, filed on October 31, 2023, the entire content of each of which is incorporated herein by reference in its entirety.

Technical Field of the Invention

[0002] The invention generally relates to novel compounds and therapeutic uses thereof. More particularly, the invention provides novel fluorinated cyclic derivatives of sulfonamides and sulfones, their salts, solvates, hydrates and polymorphs thereof as transient receptor potential cation channel, mucolipin subfamily (TRPML) modulators. The invention also provides pharmaceutical compositions comprising a compound of the invention and methods thereof for treating various diseases and disorders associated with or related to TRPML activities such as neurodegenerative diseases, lysosome storage diseases, muscular dystrophy, reactive oxygen species (ROS) or oxidative stress related diseases, metabolic diseases, metastatic cancer, and aging.

Background of the Invention

[0003] The lysosome, the cell's recycling center, can mediate the degradation of a variety of biomaterials (proteins, lipids, and membranes) into smaller molecules or building blocks, which will be subsequently transported out of lysosomes for re-utilization or energy (see, *e.g.*, de Duve **2005** *Nat Cell Biol* 7(9): 847-9; Parkinson-Lawrence, *et al.* **2010** *Physiology (Bethesda)* 25(2): 102-15). Problems in either the degradation step (due to lack of hydrolytic enzymes) or the transport step may lead to lysosome storage (of accumulated materials) and more than 50 human diseases collectively called lysosome storage diseases (LSDs). Lysosome storage can in turn affect lysosomal degradation and membrane transport/trafficking, making a positive feedback loop and a vicious cycle. Because lysosome storage is also seen in common neurodegenerative diseases such as Alzheimer's and Parkinson's, understanding the mechanisms underlying the positive feedback loop may provide therapeutic approaches not only for LSDs, but also for

common sporadic neurodegenerative diseases. A lysosome-localized Ca^{2+} channel, TRPML1, has been recently identified as a key regulator of most membrane trafficking processes in the lysosome. Human mutations of TRPML1 cause lysosomal trafficking defects, lysosome storage, and neurodegenerative and retinal diseases.

[0004] TRPML1 (also abbreviated as ML1), a member of the TRP-type Ca^{2+} channel superfamily, is the principle Ca^{2+} channel in the lysosome (see, *e.g.*, Cheng, *et al.* **2010** *FEBS Lett* 584(10): 2013-21). Loss-of-function mutations in the human TRPML1 gene cause Type IV Mucolipidosis (ML4), a lysosome storage neurodegenerative disease. $TRPML1^{-/-}$ (abbreviated as $ML1^{-/-}$) skin fibroblasts from ML4 patients are characterized by the accumulation of enlarged endosomal/lysosomal compartments (vacuoles) in which lipids and other biomaterials build up, suggestive of trafficking defects. Analyses of trafficking kinetics suggest that the primary defects are in the late endocytic pathways. First, ML1 is likely required for the formation of transport vesicles from the late endosome and lysosome (LEL) to the Trans-Golgi Network (TGN) (LEL-to-TGN retrograde trafficking). Second, fusion of lysosomes with the plasma membrane (referred to as lysosomal exocytosis), a process that is important in cellular waste elimination, membrane repair, and phagocytosis, is defective in ML4 cells. Defects in either of these trafficking steps could lead to lysosome storage. Because the release of Ca^{2+} from lysosomes (lysosomal Ca^{2+} release) is essential for both trafficking steps, it is hypothesized that ML1 is indeed the Ca^{2-} release channel that regulates lysosomal trafficking.

[0005] $PI(3,5)P_2$, a low-abundance phosphoinositide, is the primary activator of ML1 and a positive regulator of lysosomal trafficking. Both TRPML1-lacking and $PI(3,5)P_2$-deficient cells exhibit defects in LEL-to-Golgi retrograde trafficking and autophagosome–lysosome fusion, suggesting that the TRPML1-$PI(3,5)P_2$ system represents a common signaling pathway essential for late endocytic trafficking.

[0006] Due to the function of lysosome in lysosomal trafficking, lysosomes are required for quality-control regulation of mitochondria, the "power house" of the cell and the major source of endogenous ROS (reactive oxygen species). Damaged mitochondria causes oxidative stress, which is a common feature of most LSDs, neurodegenerative diseases, and aging (Xu, *et al.* **2015** *Annu Rev Physiol* 77, 57-80). Recent studies suggest that mitochondria are localized in close physical proximity to lysosomes (Elbaz-Alon, *et al.* **2014** *Dev Cell* 30, 95-102; Li, *et al.* **2015** *Cell Mol Neurobiol* 35, 615-621). Hence, the lysosomal membrane is potentially an

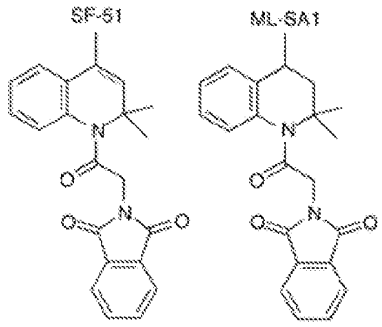
accessible and direct target of ROS signaling. Given that ROS reportedly regulates ion channels (Bogeski, *et al.* **2014** *Antioxid Redox Signal* 21, 859-862), it is possible that lysosomal conductances, particularly through lysosomal Ca^{2+} channels such as TRPML1, may mediate ROS-regulation of lysosomal function. Indeed, electrophysiological studies revealed that whole-endolysosome TRPML1 currents were directly activated by ROS.

[0007] A regulatory imbalance can result in elevated ROS levels and oxidative stress, which are believed to underlie a variety of metabolic and neurodegenerative diseases, as well as aging (Barnham *et al.* **2004** *Nat Rev Drug Discov* 3, 205-214; Scherz-Shouval, *et al.* **2011** *Trends Biochem Sci* 36, 30-38). Given the role of TRPML1 in mediating ROS-induced autophagy, a TRPML1 agonist might be able to clear the excessive ROS, thereby ameliorating the ROS related diseases and aging, especially photo aging in the skin.

[0008] Transcription factor EB (TFEB) regulates autophagy and lysosome biogenesis. Overexpression of TFEB has been reported to induce cellular clearance in a number of lysosome storage diseases, including Pombe Disease, Cystinosis, multiple sulfatase deficiency, as well as neurodegenerative diseases, including Parkinson's disease and Huntinton's disease (Settembre, *et al.*, **2013** *Nat Rev Mol Cell Biol* 14(5), 283-96). Therefore, activation of TRPML1 by TRPML1 agonists may also lead to cellular clearance in all the aforementioned diseases, providing therapeutic targets for these devastating diseases.

[0009] Previously a potent synthetic agonist for TRPML1 has been reported (Shen, *et al.* **2012** *Nat Commun* 3, 731). This SF-51-related compound (Mucolipin Synthetic Agonist 1 or ML-SA1) could induce significant $[Ca2+]_{cyt}$ increases in HEK293 cells stably or transiently expressing ML1-4A. In electrophysiological assays, ML-SA1 robustly activated whole-cell I_{ML1-4A} and whole-endolysosome I_{ML1}. ML-SA1 also activated whole-cell I_{TRPML2} and I_{TRPML3}, but not six other related channels. ML-SA1 (10 μM) activation of whole-endolysosome I_{ML1} was comparable to the effect of the endogenous TRPML agonist PI(3,5)P2 (1μM), and these agonists were synergistic with each other. ML-SA1 activated an endogenous whole-endolysosome TRPML-like current (I_{ML-L}) in all mammalian cell types that were investigated, including Chinese Hamster Ovary (CHO), Cos-1, HEK293, skeletal muscle, pancreatic β and macrophage cells. ML-SA1 activated whole-endolysosome I_{ML-L} in wild-type (WT; $ML1^{-/+}$), but not ML4 ($ML1^{-/-}$) human fibroblasts, suggesting that although ML-SA1 targets all three TRPMLs, the expression levels of TRPML2 and TRPML3 are very low, and TRPML1 is the predominant

lysosomal TRPML channel in this cell type. These results suggest that ML-SA1 is a reasonably specific and potent agonist that can be useful for modulating the functions of TRPMLs.



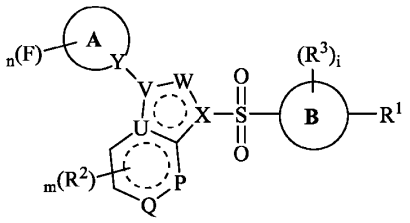
[0010] High concentration of ML-SA1 (~10 μM) is needed to effectively activate TRPMLs. Since that concentration is usually difficult to achieve *in vivo*, ML-SA1 cannot be used to treat the above TRPML-related diseases. Recently, a number of more potent TRPML1 agonists have been developed. (See, *e.g.*, WO2022076383A1). However, most of these potent agonists are highly hydrophobic molecules that are either metabolically labile and/or have or very limited brain penetrance, which in turn leads to poor oral bioavailability and limited exposure in diseased organs, especially in the brain.

[0011] There is an urgent need for orally bioavailable, highly brain-penetrant, and potent TRPML activators, in particular, compounds that are useful in treating disorders related to TRPML activities such as neurodegenerative diseases, lysosome storage diseases, muscular dystrophy, ROS or oxidative stress related diseases, metabolic diseases, metastatic cancer, and aging.

Summary of the Invention

[0012] The invention is based in part on novel fluorinated cyclic derivatives of sulfonamides and sulfones, pharmaceutical compositions thereof and methods of their preparation and use in treating or reducing various diseases or disorders. In particular, compounds, compositions and methods of the invention are useful in treating diseases or disorders mediated by or associated with TRPMLs.

[0013] In one aspect, the invention generally relates to a compound having the structure of formula (**I**):



I

or a pharmaceutically acceptable form or an isotope derivative thereof,

wherein

Ring A is a 4- to 9-membered carbocycle, or heterocycle substituted with 1-8 F's;

Ring B is a substituted or unsubstituted phenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, or thiophene, or a substituted or unsubstituted bi- or multi-cyclic carbocyclic or heterocyclic ring system;

P is CH, N or CR^2;

Q is CH, N or CR^2;

U is C or N;

V is C or N;

W is CH, N, C(=O), C(=S) or $CR^{W1}R^{W2}$, wherein each of R^{W1} and R^{W2} is independently H or C_{1-6} alkyl;

X is C or N;

Y is C, CR^Y or N, wherein R^Y is H, F or C_{1-6} alkyl;

R^1 is selected from the group consisting of F, CHF_2, $-CF_3$, $-CH_2CF_3$, CF_2CH_3, CF_2CH_2F, CF_2CHF_2, $-CF(CH_3)_2$, $-OCF_3$ and $-OCH(CH_3)_2$;

each R^2 is independently selected from the group consisting of halogen, unsubstituted or substituted C_{1-6} alkyl and C_{1-6} alkoxy, OH, CN, NRR', N(R)C(=O)RR', C(=O)R and C(=O)NRR';

each R^3 is independently selected from the group consisting of halogen, CN, CF_3, C_{1-5} alkyl, C_{3-7} cycloalkyl and heterocyclic;

each of R and R' is independently H, or C_{1-6} alkyl or cycloalkyl, optionally, R and R', together with the nitrogen or carbon atom to which they are attached, form a 3- to 6-membered ring, each optionally substituted with 0-3 substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, OH, OC_{1-3} alkyl and CN;

m is 0, 1, 2, 3 or 4;

n is 1, 2, 3, 4, 5, 6, 7 or 8; and

i is 0, 1 or 2.

[0014] In another aspect, the invention generally relates to a pharmaceutical composition comprising a compound disclosed herein.

[0015] In yet another aspect, the invention generally relates to a unit dosage form comprising a pharmaceutical composition that comprises a compound disclosed herein.

[0016] In yet another aspect, the invention generally relates to a method for treating or reducing a disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein.

[0017] In yet another aspect, the invention generally relates to a method for treating or reducing the effect of aging comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein.

[0018] In yet another aspect, the invention generally relates to a method for treating or reducing oxidative stress or ROS related diseases or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a TRPML1 agonist or a composition comprising of a TRPML1 agonist disclosed herein.

[0019] In yet another aspect, the invention generally relates to a method for treating or reducing oxidative stress or ROS related diseases or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein.

[0020] In yet another aspect, the invention generally relates to use of a compound disclosed herein, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a disease or disorder.

Definitions

[0021] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. General principles of organic chemistry, as well as specific functional moieties and reactivity, are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 2006.

[0022] The following terms, unless indicated otherwise according to the context wherein the terms are found, are intended to have the following meanings.

[0023] Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 16 is understood to include any number, combination of numbers, or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16.

[0024] Any compositions or methods disclosed herein can be combined with one or more of any of the other compositions and methods provided herein.

[0025] The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable or aspect herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[0026] Definitions of specific functional groups and chemical terms are described in more detail below. When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl. Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, *e.g.*, -C(=O)-O- is equivalent to -O-C(=O)-.

[0027] Structures of compounds of the invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds that are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions (*e.g.*, aqueous, neutral, and several known physiological conditions).

[0028] As used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference, unless the context clearly dictates otherwise.

[0029] As used herein, "at least" a specific value is understood to be that value and all values greater than that value.

[0030] As used herein, the terms "comprises," "comprising", or "having" when used to define compositions and methods, are intended to mean that the compositions and methods include the recited elements, but do not exclude other elements. The term "consisting essentially of", when used to define compositions and methods, shall mean that the compositions and methods include

the recited elements and exclude other elements of any essential significance to the compositions and methods. For example, "consisting essentially of" refers to administration of the pharmacologically active agents expressly recited and excludes pharmacologically active agents not expressly recited. The term consisting essentially of does not exclude pharmacologically inactive or inert agents, *e.g.*, pharmaceutically acceptable excipients, carriers or diluents. The term "consisting of", when used to define compositions and methods, shall mean excluding trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this invention.

[0031] As used herein, the terms "disease" and "disorder" are used interchangeably and refer to any condition that damages or interferes with the normal function of a cell, tissue, or organ.

[0032] As used herein, the term "hydrate" means a compound which further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

[0033] As used herein, the term "pharmaceutically acceptable" refers to being suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable form" of a disclosed compound includes, but is not limited to, pharmaceutically acceptable salts, esters, hydrates, solvates, polymorphs, isomers, prodrugs, and isotopically labeled derivatives thereof. In one embodiment, a "pharmaceutically acceptable form" includes, but is not limited to, pharmaceutically acceptable salts, esters, prodrugs and isotopically labeled derivatives thereof. In some embodiments, a "pharmaceutically acceptable form" includes, but is not limited to, pharmaceutically acceptable isomers and stereoisomers, prodrugs and isotopically labeled derivatives thereof.

[0034] In certain embodiments, the pharmaceutically acceptable form is a pharmaceutically acceptable salt. As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge et al. describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1-19. Pharmaceutically acceptable salts of the compounds provided herein include those derived from suitable inorganic and organic acids and

bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, besylate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. In some embodiments, organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, lactic acid, trifluoracetic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

[0035] The salts can be prepared *in situ* during the isolation and purification of the disclosed compounds, or separately, such as by reacting the free base or free acid of a parent compound with a suitable base or acid, respectively. Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines, including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine,

and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt can be chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0036] In certain embodiments, the pharmaceutically acceptable form is a "solvate" (*e.g.*, a hydrate). As used herein, the term "solvate" refers to compounds that further include a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. The solvate can be of a disclosed compound or a pharmaceutically acceptable salt thereof. Where the solvent is water, the solvate is a "hydrate". Pharmaceutically acceptable solvates and hydrates are complexes that, for example, can include 1 to about 100, or 1 to about 10, or 1 to about 2, about 3 or about 4, solvent or water molecules. It will be understood that the term "compound" as used herein encompasses the compound and solvates of the compound, as well as mixtures thereof.

[0037] In certain embodiments, the pharmaceutically acceptable form is a prodrug. As used herein, the term "prodrug" (or "pro-drug") refers to compounds that are transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable form of the compound. A prodrug can be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis (*e.g.*, hydrolysis in blood). In certain cases, a prodrug has improved physical and/or delivery properties over the parent compound. Prodrugs can increase the bioavailability of the compound when administered to a subject (*e.g.*, by permitting enhanced absorption into the blood following oral administration) or which enhance delivery to a biological compartment of interest (*e.g.*, the brain or lymphatic system) relative to the parent compound. Exemplary prodrugs include derivatives of a disclosed compound with enhanced aqueous solubility or active transport through the gut membrane, relative to the parent compound.

[0038] The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, *e.g.*, Bundgard, H., *Design of Prodrugs* (1985), pp. 7- 9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," *A.C.S. Symposium Series,* Vol. 14, and in *Bioreversible Carriers in Drug Design,* ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. Exemplary advantages of a prodrug can include, but are not limited to, its physical properties, such as enhanced water solubility for parenteral administration at physiological pH

compared to the parent compound, or it can enhance absorption from the digestive tract, or it can enhance drug stability for long-term storage.

[0039] Prodrugs commonly known in the art include well-known acid derivatives, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, amides prepared by reaction of the parent acid compound with an amine, basic groups reacted to form an acylated base derivative, *etc*. Of course, other prodrug derivatives may be combined with other features disclosed herein to enhance bioavailability. As such, those of skill in the art will appreciate that certain of the presently disclosed compounds having free amino, arnido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds having an amino acid residue, or a polypeptide chain of two or more (*e.g*., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of the presently disclosed compounds. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds having a carbonate, carbamate, amide or alkyl ester moiety covalently bonded to any of the above substituents disclosed herein.

[0040] Particularly favored prodrugs and prodrug salts are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (*e.g*., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (*e.g*., the brain or central nervous system) relative to the parent species. Examples of prodrugs include derivatives where a group that enhances aqueous solubility or active transport through the gut membrane is appended to the structure of formulae described herein. (See, *e.g*., Alexander, *et al.* **1988** *J Med Chem* 31, 318-322; Bundgaard, *et al.* **1985** *Elsevier: Amsterdam* 1-92; Bundgaard, *et al.* **1987** *J Med Chem* 30, 451-454; Bundgaard, H. A Textbook of Drug Design and Development; Harwood Academic Publ.: Switzerland, **1991**, 113-191; Digenis, *et al.* Handbook of Experimental Pharmacology **1975**, 28, 86-112; Friis, *et al.* Textbook of Drug Design and Development; 2 ed.; Overseas Publ.: Amsterdam, **1996**, 351-385; Pitman **1981** *Medicinal Research Reviews* 1, 189-214.)

[0041] As used herein, the term "pharmaceutically acceptable" excipient, carrier, or diluent refers to a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations. Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate, magnesium stearate, and polyethylene oxide-polypropylene oxide copolymer as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0042] As used herein, the term "polymorph" means solid crystalline forms of a compound or complex thereof which may be characterized by physical means such as, for instance, X-ray powder diffraction patterns or infrared spectroscopy. Different polymorphs of the same compound can exhibit different physical, chemical and/or spectroscopic properties. Different physical properties include, but are not limited to stability (*e.g.*, to heat, light or moisture), compressibility and density (important in formulation and product manufacturing), hygroscopicity, solubility, and dissolution rates (which can affect bioavailability). Differences in stability can result from changes in chemical reactivity (*e.g.*, differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical characteristics (*e.g.*, tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both (*e.g.*, tablets of one polymorph are more susceptible to breakdown at high humidity). Different

physical properties of polymorphs can affect their processing. For example, one polymorph might be more likely to form solvates or might be more difficult to filter or wash free of impurities than another due to, for example, the shape or size distribution of particles of it.
As used herein, the term "solvate" means a compound which further includes a stoichiometric or non-stoichiometric amount of solvent such as water, acetone, ethanol, methanol, dichloromethane, 2-propanol, or the like, bound by non-covalent intermolecular forces.
As used herein, the term "stable compounds" refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (*e.g.*, formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or disorder responsive to therapeutic agents).

[0043] As used herein, the term "stereoisomer" refers to both enantiomers and diastereomers. As used herein, the term "substantially free of other stereoisomers" means less than 25% of other stereoisomers, preferably less than 10% of other stereoisomers, more preferably less than 5% of other stereoisomers and most preferably less than 2% of other stereoisomers, or less than "X"% of other stereoisomers (wherein X is a number between 0 and 100, inclusive) are present. Methods of obtaining or synthesizing diastereomers are well known in the art and may be applied as practicable to final compounds or to starting material or intermediates. Other embodiments are those wherein the compound is an isolated compound. The term "at least X% enantiomerically enriched" as used herein means that at least X% of the compound is a single enantiomeric form, wherein X is a number between 0 and 100, inclusive.

[0044] As used herein, the terms "treatment" or "treating" a disease or disorder refers to a method of reducing, delaying or ameliorating such a condition before or after it has occurred. Treatment may be directed at one or more effects or symptoms of a disease and/or the underlying pathology. The treatment can be any reduction and can be, but is not limited to, the complete ablation of the disease or the symptoms of the disease. Treating or treatment thus refers to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving or stabilizing a patient's physical or mental well-being. The treatment or amelioration

of symptoms can be based on objective or subjective parameters, for example, the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. As compared with an equivalent untreated control, such reduction or degree of amelioration may be at least 5%, 10%, 20%, 40%, 50%, 60%, 80%, 90%, 95%, or 100% as measured by any standard technique.

[0045] As used herein, the terms "alk" or "alkyl" refer to straight, branched or cyclic hydrocarbon groups having 1 to 12 carbon atoms containing no unsaturation. Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; *e.g.*, "1 to 10 carbon atoms" means that the alkyl group can consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, "alkyl" can be a C_{1-6} alkyl group. In some embodiments, "alkyl" can be a C_{1-3} alkyl group.

[0046] As used herein, the term "alkenyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one double bond. Where an alkenyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a double bond.

[0047] As used herein, the term "alkoxy" refers to an -O-alkyl radical.

[0048] As used herein, the term "alkynyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one triple bond. Where an alkynyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a triple bond.

[0049] As used herein, the term "alkylene" refers to a divalent straight chain bridge of 1 to 5 carbon atoms connected by single bonds (*e.g.*, $-(CH_2)_x-$, wherein x is 1 to 5), which may be substituted with 1 to 3 lower alkyl groups.

[0050] As used herein, the term "alkenylene" refers to a straight chain bridge of 2 to 5 carbon atoms having one or two double bonds that is connected by single bonds and may be substituted with 1 to 3 lower alkyl groups. Exemplary alkenylene groups are -CH=CH-CH=CH-, $-CH_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-C(CH_3)_2CH=CH-$ and $-CH(C_2H_5)-CH=CH-$.

[0051] As used herein, the term "alkynylene" refers to a straight chain bridge of 2 to 5 carbon atoms that has a triple bond therein, is connected by single bonds, and may be substituted with 1

to 3 lower alkyl groups. Exemplary alkynylene groups are –C≡C-, -CH_2-C≡C-, -$CH(CH_3)$C≡C- and –C≡C-$CH(C_2H_5)CH_2$-.

[0052] As used herein, the term "arylalkyl" refers to a moiety in which an alkyl hydrogen atom is replaced by an aryl group.

[0053] As used herein, the terms "cycloalkyl" and "cycloalkenyl" as employed herein includes saturated and partially unsaturated cyclic, respectively, hydrocarbon groups having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbon.

[0054] As used herein, the terms "aromatic", "ar" or "aryl" refer to a radical with 6 to 14 ring atoms (*e.g.*, C_{6-14} aromatic or C_{6-14} aryl) that has at least one ring having a conjugated pi electron system which is carbocyclic (*e.g.*, phenyl, fluorenyl, naphthyl, and anthracene). An aryl group may be, for example, 6 membered monocyclic, 10 membered bicyclic or 14 membered tricyclic ring systems, each with 6 to 14 carbon atoms.

[0055] As used herein, the term "halo" or "halogen" refers to any radical of fluorine, chlorine, bromine or iodine.

[0056] As used herein, the terms "carbocycle", "carbocyclic" and "carbocyclyl" each refers to a monocyclic or polycyclic radical that contains only carbon as ring atoms, and can be saturated or partially unsaturated. Fully saturated carbocyclic is termed cycloalkyl. Partially unsaturated cycloalkyl groups can be termed "cycloalkenyl" if the carbocycle contains at least one double bond, or "cycloalkynyl" if the carbocycle contains at least one triple bond. Unless stated otherwise in the specification, the term is intended to include both substituted and unsubstituted carbocyclic groups. The term "carbocyclic" also includes bridged and spiro-fused cyclic structures containing no hetero ring atoms. The term also includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) groups. Polycyclic groups include bicycles, tricycles, tetracycles, and the like. Unless stated otherwise in the specification, a carbocyclic group can be optionally substituted by one or more substituents.

[0057] As used herein, the term "heteroaryl" or, alternatively, "heteroaromatic" refers to a refers to a radical of a 5-18 membered monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic, tetracyclic and the like) aromatic ring system (*e.g.*, having 6, 10 or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1-6 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous and sulfur ("5-18 membered heteroaryl"). Heteroaryl polycyclic ring systems can include one or

more heteroatoms in one or both rings. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range; *e.g.*, "5 to 18 ring atoms" means that the heteroaryl group can consist of 5 ring atoms, 6 ring atoms, *etc.*, up to and including 18 ring atoms. In some instances, a heteroaryl can have 5 to 14 ring atoms. In some embodiments, the heteroaryl has, for example, bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-ene" to the name of the corresponding univalent radical, *e.g.*, a pyridyl group with two points of attachment is a pyridylene. The term "heteroaryl", for example, may refer to a monocyclic or fused ring (*i.e.*, rings which share an adjacent pair of atoms) group of 5 to 12 ring atoms containing one, two, three or four ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, and, in addition, having a completely conjugated pi-electron system, wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent. Examples, without limitation, of heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, quinazoline, isoquinoline, purine and carbazole.

[0058] As used herein, the terms "heterocycle", "heterocyclic" or "heterocyclyl" refer to fully saturated or partially unsaturated cyclic groups, for example, 3 to 7 membered monocyclic, 7 to 12 membered bicyclic, or 10 to 15 membered tricyclic ring systems, which have at least one heteroatom in at least one ring, wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system.

[0059] As used herein, the term "oxo" refers to an oxygen atom, which forms a carbonyl when attached to carbon, an N-oxide when attached to nitrogen, and a sulfoxide or sulfone when attached to sulfur.

[0060] As used herein, the term "substituents" refers to a group "substituted" on any functional group delineated herein, *e.g.*, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, or heteroaryl group at any atom of that group. Suitable substituents include, without limitation halogen, CN, NO_2, OR^{15}, SR^{15}, $S(O)_2OR^{15}$, $NR^{15}R^{16}$, C_1-C_2 perfluoroalkyl, C_1-C_2

perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^{15}$, $C(O)NR^{15}R^{16}$, $OC(O)NR^{15}R^{16}$, $NR^{15}C(O)NR^{15}R^{16}$, $C(NR^{16})NR^{15}R^{16}$, $NR^{15}C(NR^{16})NR^{15}R^{16}$, $S(O)_2NR^{15}R^{16}$, R^{17}, $C(O)R^{17}$, $NR^{15}C(O)R^{17}$, $S(O)R^{17}$, $S(O)_2R^{17}$, R^{16}, oxo, $C(O)R^{16}$, $C(O)(CH_2)_mOH$, $(CH_2)_nOR^{15}$, $(CH_2)_mC(O)NR^{15}R^{16}$, $NR^{15}S(O)_2R^{17}$, where m is independently 0-6 inclusive. Each R^{15} is independently hydrogen, C_1-C_4 alkyl or C_3-C_6 cycloalkyl. Each R^{16} is independently hydrogen, alkenyl, alkynyl, C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl, C_1-C_4 alkyl or C_1-C_4 alkyl substituted with C_3-C_6 cycloalkyl, aryl, heterocyclyl or heteroaryl. Each R^{17} is independently C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl, C_1-C_4 alkyl or C_1-C_4 alkyl substituted with C_3-C_6 cycloalkyl, aryl, heterocyclyl or heteroaryl. Each C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl and C_1-C_4 alkyl in each R^{15}, R^{16} and R^{17} can optionally be substituted with halogen, CN, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, or 1,2-methylenedioxy.

[0061] The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

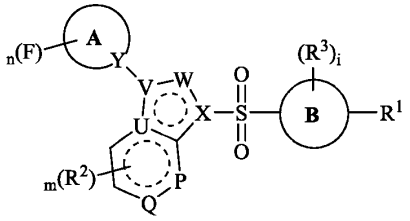
[0062] The compounds of this invention may contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of these compounds are expressly included in the present invention. The compounds of this invention may also be represented in multiple tautomeric forms, in such instances, the invention expressly includes all tautomeric forms of the compounds described herein. All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

Detailed Description of the Invention

[0063] The invention provides novel fluorinated cyclic derivatives of sulfonamides and sulfones, including salts, solvates, hydrates and polymorphs thereof, as TRPML modulators. The invention also provides pharmaceutical compositions comprising a compound of this invention and the use of such compositions in treating a range of diseases and conditions associated with TRPML or related to TRPML activities, such as neurodegenerative diseases, lysosome storage

diseases, muscular dystrophy, ROS or oxidative stress related diseases, and damages caused in skin or photoaging.

[0064] In one aspect, the invention generally relates to a compound having the structure of formula (**I**):



I

or a pharmaceutically acceptable form or an isotope derivative thereof,

wherein

Ring A is a 4- to 9-membered (*e.g.*, 4-, 5-, 6-, 7-, 8- or 9-membered) carbocycle or heterocycle substituted with 1-8 F's;

Ring B is a substituted or unsubstituted phenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, or thiophene, or a substituted or unsubstituted bi- or multi-cyclic carbocyclic or heterocyclic ring system;

P is CH, N or CR^2;

Q is CH, N or CR^2;

U is C or N;

V is C or N;

W is CH, N, C(=O), C(=S) or $CR^{W1}R^{W2}$, wherein each of R^{W1} and R^{W2} is independently H or C_{1-6} alkyl;

X is C or N;

Y is C, CR^Y or N, wherein R^Y is H, F or C_{1-6} alkyl;

R^1 is selected from the group consisting of F, CHF_2, $-CF_3$, $-CH_2CF_3$, CF_2CH_3, CF_2CH_2F, CF_2CHF_2, $-CF(CH_3)_2$, $-OCF_3$ and $-OCH(CH_3)_2$;

each R^2 is independently selected from the group consisting of halogen, unsubstituted or substituted C_{1-6} alkyl and C_{1-6} alkoxy, OH, CN, NRR', N(R)C(=O)RR', C(=O)R and C(=O)NRR';

each R^3 is independently selected from the group consisting of halogen, CN, CF_3, C_{1-5} alkyl, C_{3-7} cycloalkyl and heterocyclic;

each of R and R' is independently H, or C_{1-6} alkyl or cycloalkyl, optionally, R and R', together with the nitrogen or carbon atom to which they are attached, form a 3- to 6-membered ring, each optionally substituted with 0-3 substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, OH, OC_{1-3} alkyl and CN;

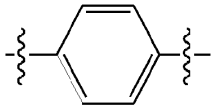
m is 0, 1, 2, 3 or 4;

n is 1, 2, 3, 4, 5, 6, 7 or 8; and

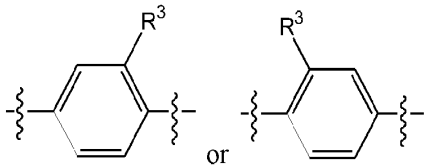
i is 0, 1 or 2.

[0065] In certain embodiments, Ring B is an unsubstituted phenyl or substituted phenyl.

[0066] In certain embodiments, *i* is 0 and Ring B is unsubstituted phenyl:

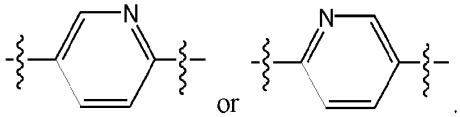


[0067] In certain embodiments, *i* is 0 and Ring B is a substituted phenyl:



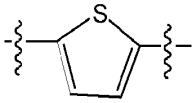
wherein R^3 is a halogen atom (*e.g.*, F).

[0068] In certain embodiments, Ring B is an unsubstituted pyridinyl:

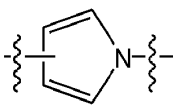


[0069] In certain embodiments, Ring B is a substituted or unsubstituted thiophene.

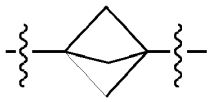
[0070] In certain embodiments, *i* is 0 and Ring B is a substituted or unsubstituted thiophene. In certain embodiments, Ring B is an unsubstituted thiophene:



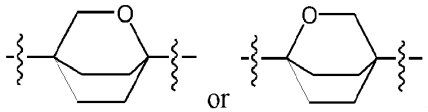
[0071] In certain embodiments, Ring B is a substituted or unsubstituted pyrrole. In certain embodiments, Ring B is an unsubstituted pyrrole:



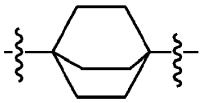
[0072] In certain embodiments, Ring B is bicyclo[1.1.1]pentane:



[0073] In certain embodiments, Ring B is 2-oxabicyclo[2.2.2]octane.

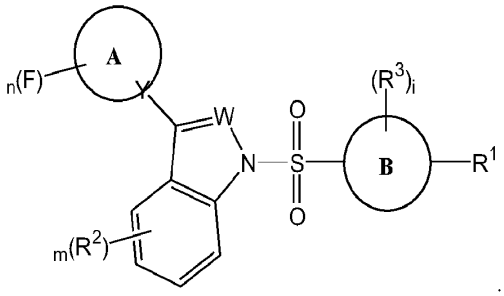


[0074] In certain embodiments, Ring B is:



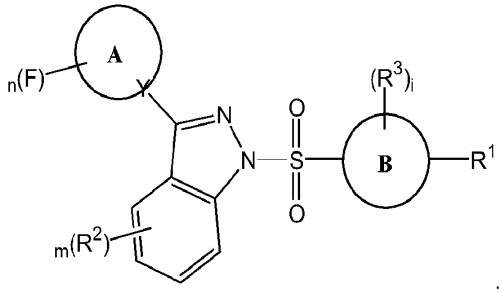
[0075] In certain embodiments of (**I**), X is N.

[0076] In certain embodiments of (**I**), X is N, P is CH, Q is CH, U is C and V is C:



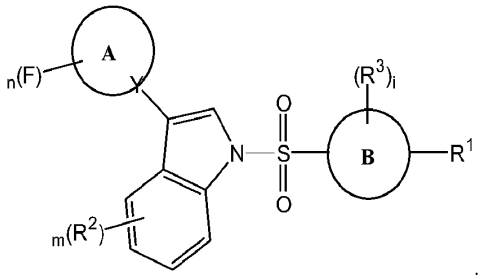
(**I$_a$**)

[0077] In certain embodiments of (**I$_a$**), W is N:



(**I$_b$**)

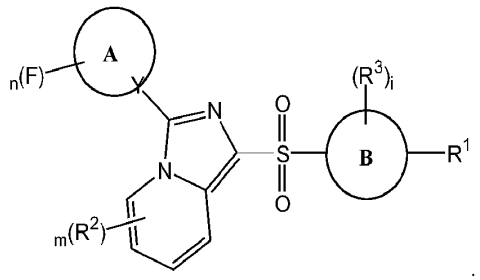
[0078] In certain embodiments of (**I$_a$**), W is CH:



(I_c)

[0079] In certain embodiments of (**I**), X is C.

[0080] In certain embodiments of (**I**), X is C, P is CH, Q is CH, U is N, V is C and W is N:



(I_d)

[0081] In certain embodiments of (**I**)-(I_d), Y is N.

[0082] In certain embodiments of (**I**)-(I_d), Y is C.

[0083] In certain embodiments of (**I**)-(I_d), Y is CH.

[0084] In certain embodiments of (**I**)-(I_d), Ring A is a 4-membered carbocyclic or heterocycle substituted with one or more F's.

[0085] In certain embodiments of (**I**)-(I_d), Ring A is a 5-membered carbocyclic or heterocycle substituted with one or more F's.

[0086] In certain embodiments of (**I**)-(I_d), Ring A is a 6-membered mono- or bicyclic carbocyclic or heterocycle substituted with one or more F's.

[0087] In certain embodiments of (**I**)-(I_d), Ring A is a 7-membered mono- or bicyclic carbocyclic or heterocycle substituted with one or more F's.

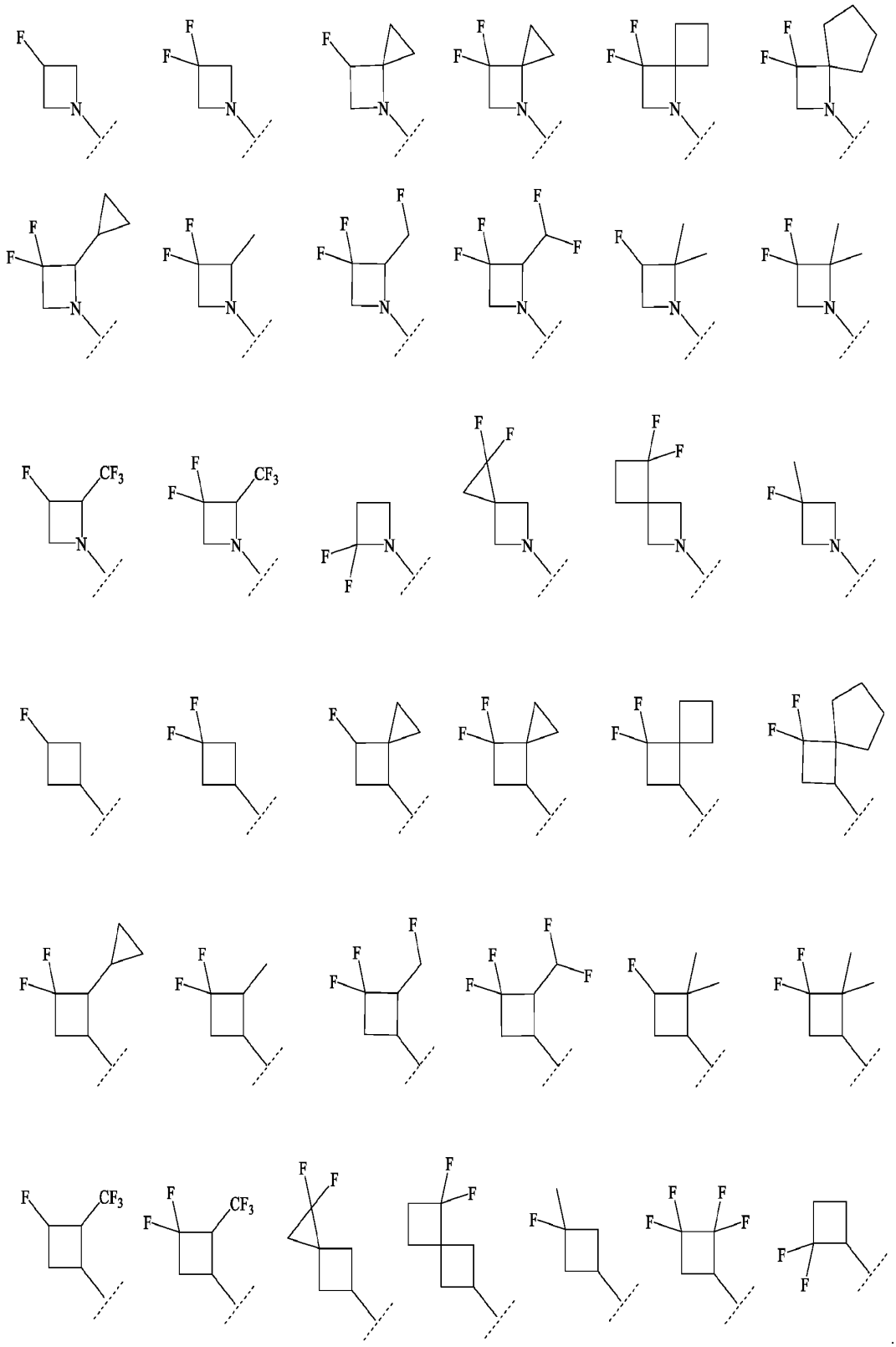
[0088] In certain embodiments of (**I**)-(I_d), Ring A is an 8-membered bicyclic carbocyclic or heterocycle substituted with one or more F's.

[0089] In certain embodiments of (**I**)-(I_d), Ring A is a 9-membered bicyclic carbocyclic or heterocycle substituted with one or more F's.

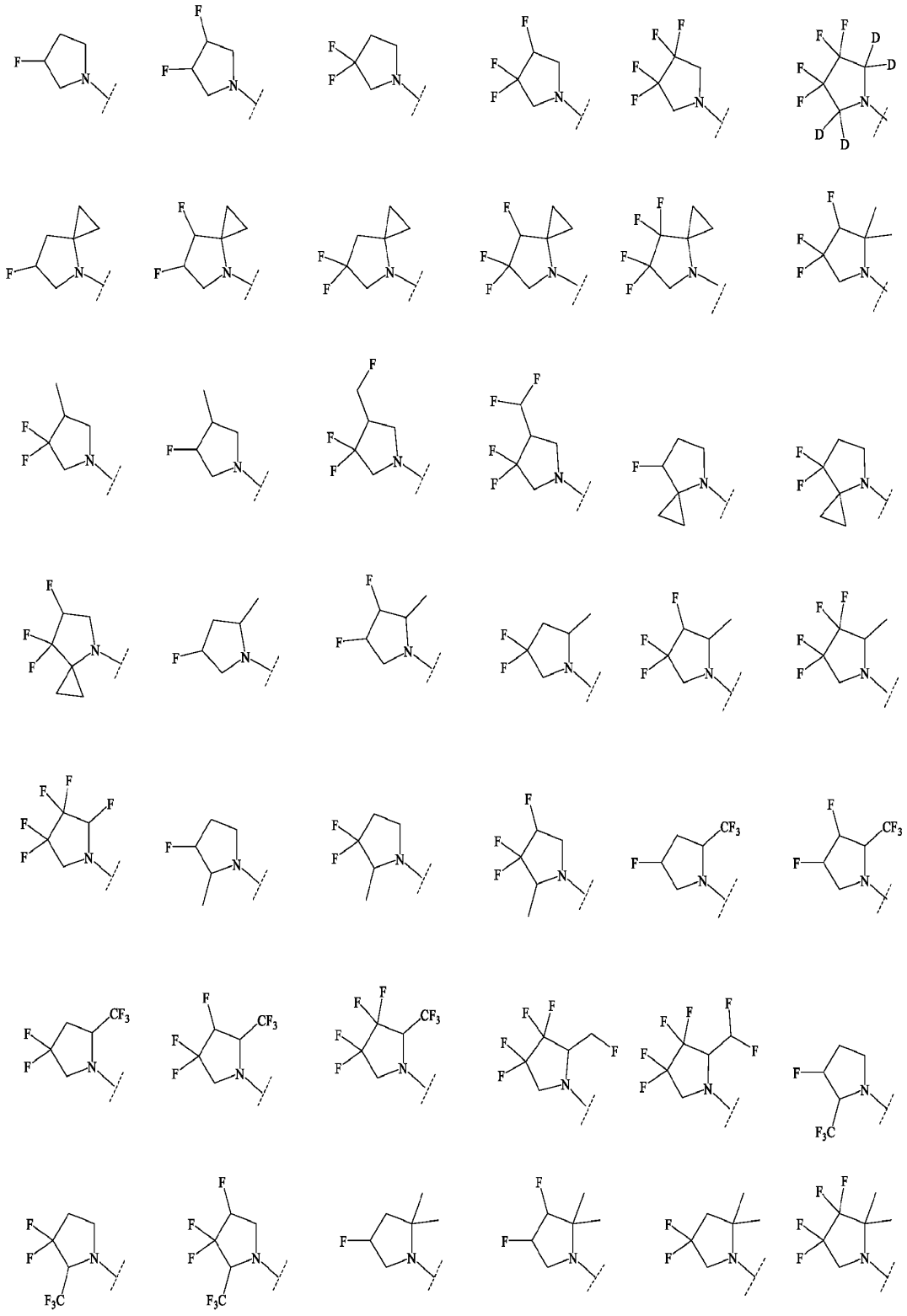
[0090] In certain embodiments of (**I**)-(**I_d**), Ring A is a heterobicycle substituted with one or more F's.

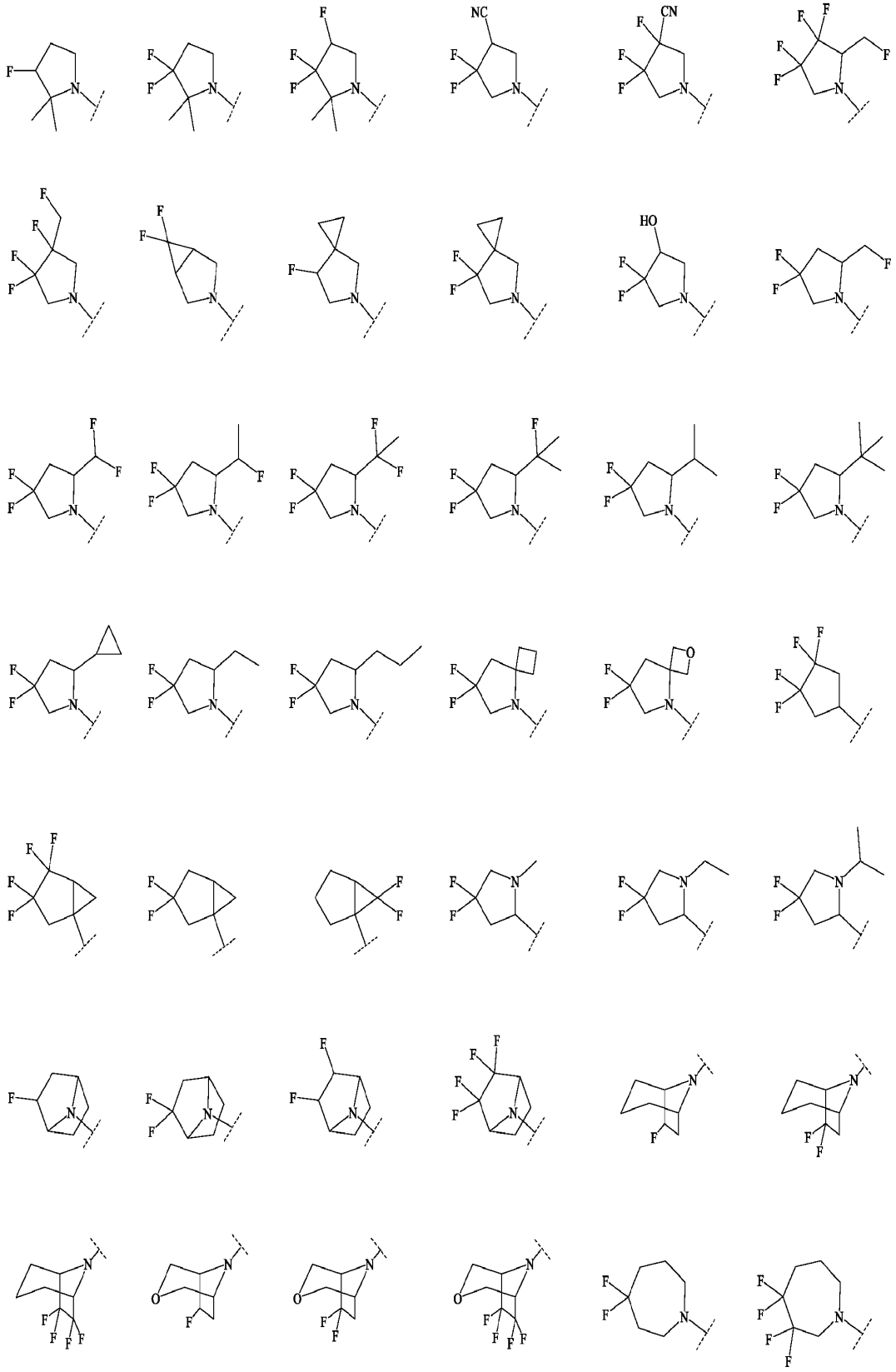
[0091] In certain embodiments of (**I**)-(**I_d**), Ring A is substituted with two or more F's (*e.g.*, 2, 3, 4, 5, 6, 7 or 8 F's).

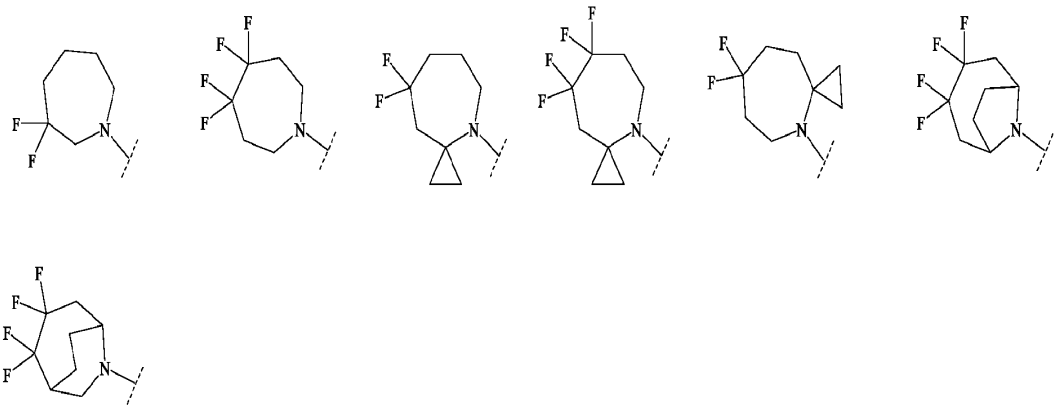
[0092] In certain embodiments of (**I**)-(**I_d**), Ring A has a structural formula selected from:



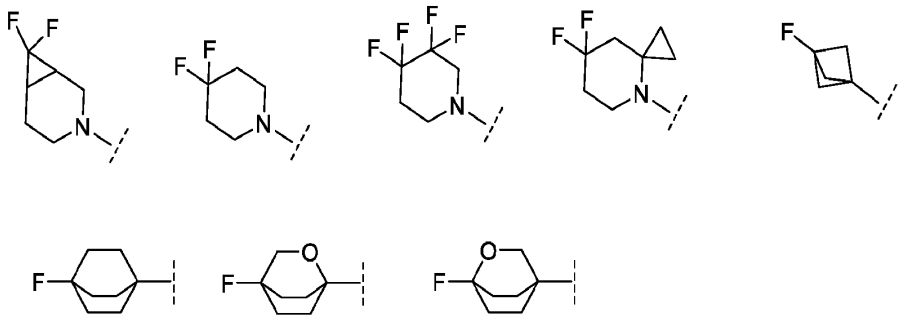
[0093] In certain embodiments of (I)-(I_d), Ring A has a structural formula selected from:



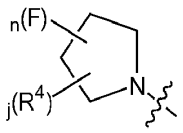




[0094] In certain embodiments of (**I**)-(**I$_d$**), Ring A has a structural formula selected from:



[0095] In certain embodiments of (**I**)-(**I$_d$**), Ring A is:



wherein

each R^4 is independently D, OH, CN, or C_{1-2} alkyl optionally substituted with 0-3 (*e.g.*, 0, 1, 2 or 3) F's, or two R^4's along with the carbon atom they are bound to form a 3- or 4-membered carbocyclic or heterocyclic ring, or two R^4's along with the carbon atoms they are bound to atom for a 3- to 7-membered (*e.g.*, 3-, 4-, 5-, 6- or 7-membered) carbocyclic or heterocyclic ring;

n is 1, 2, 3, 4, 5 or 6; and

j is 0, 1, 2, 3 or 4.

[0096] In certain embodiments, *j* is 0. In certain embodiments, *j* is 1. In certain embodiments, *j* is 2. In certain embodiments, *j* is 3. In certain embodiments, *j* is 4.

[0097] In certain embodiments of (**I**)-(**I$_d$**), R^1 is CHF_2.

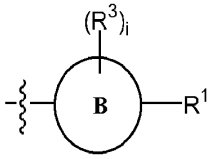
[0098] In certain embodiments of (**I**)-(**I$_d$**), R^1 is CF_2CH_3.

[0099] In certain embodiments of (**I**)-(**I$_d$**), R^1 is CF_2CHF.

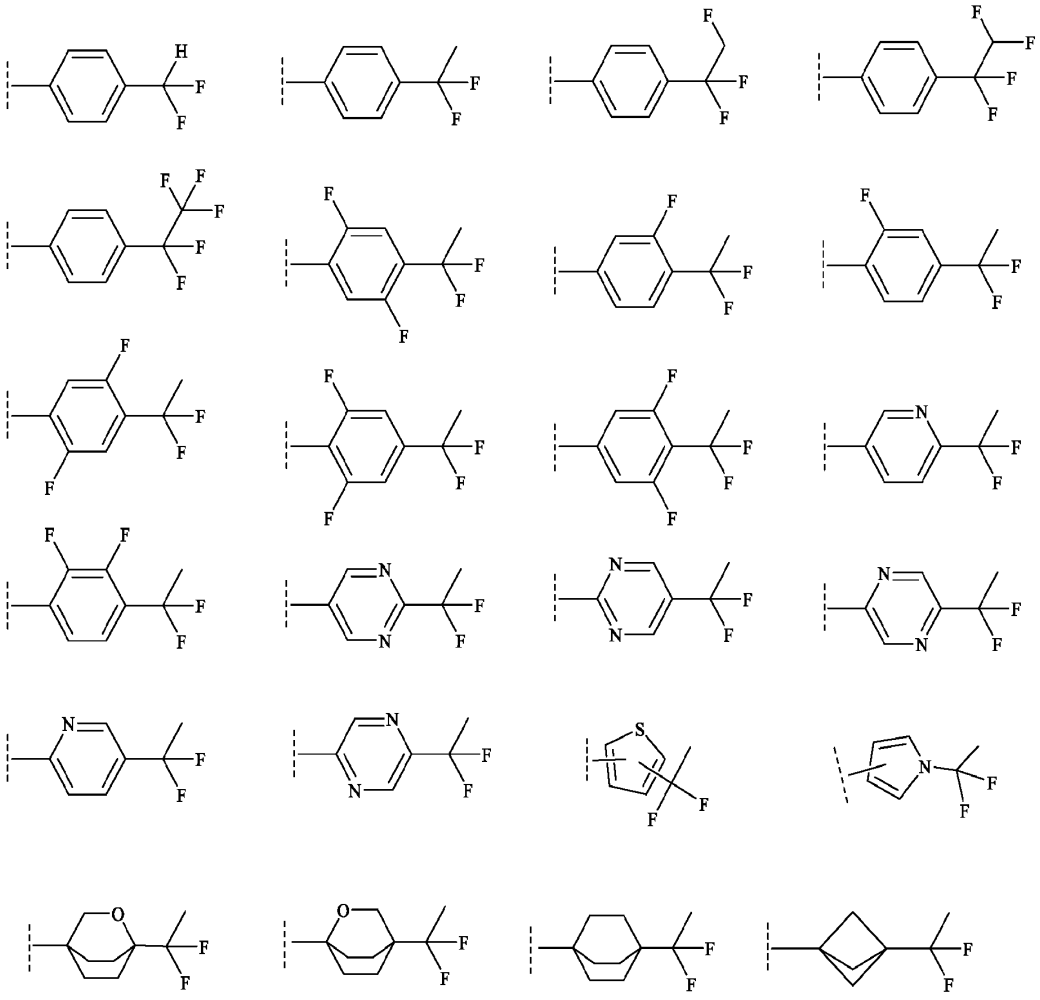
[00100] In certain embodiments of (**I**)-(**I$_d$**), R^1 is $CF_2CH_2F_2$.

[00101] In certain embodiments of (**I**)-(**I$_d$**), R^1 is F.

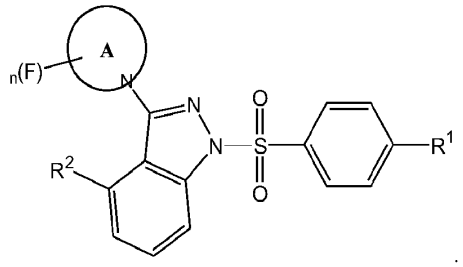
[00102] Non-limiting examples of



include:

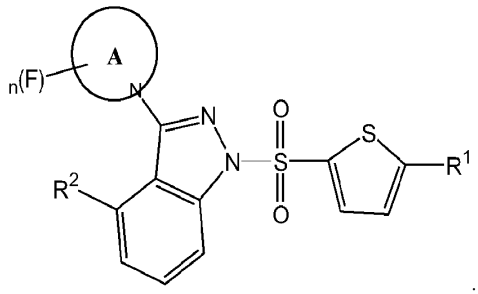


[00103] In certain embodiments, the compound has the structural formula:



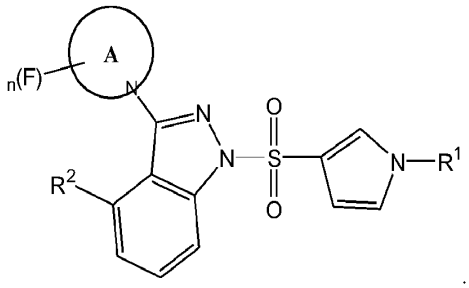
(I_e)

[00104] In certain embodiments, the compound has the structural formula:



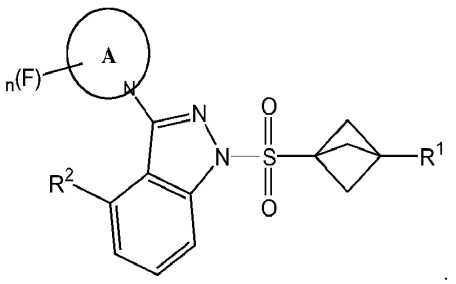
(I_f)

[00105] In certain embodiments, the compound has the structural formula:



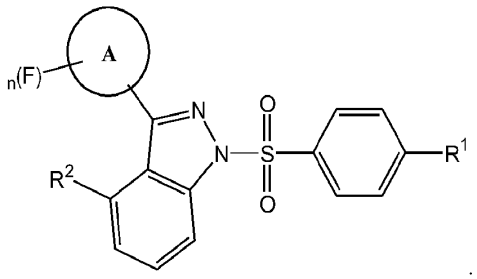
(I_g)

[00106] In certain embodiments, the compound has the structural formula:



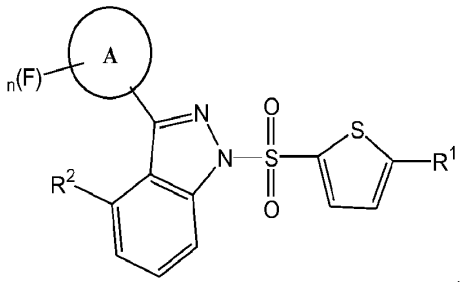
(I_h)

[00107] In certain embodiments, the compound has the structural formula:



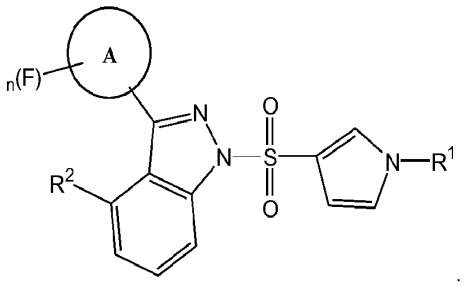
(I_i)

[00108] In certain embodiments, the compound has the structural formula:



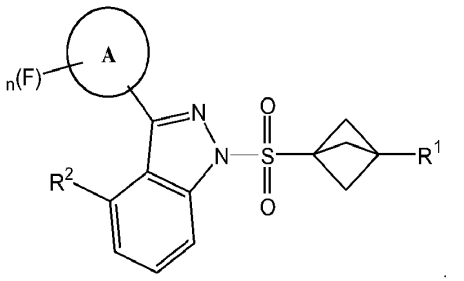
(I_j)

[00109] In certain embodiments, the compound has the structural formula:



(I_k)

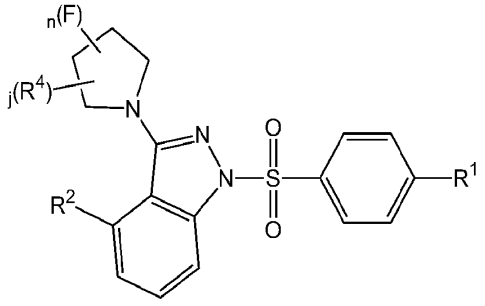
[00110] In certain embodiments, the compound has the structural formula:



(I_l)

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[00111] In certain embodiments, the compound has the structural formula:



(I_m)

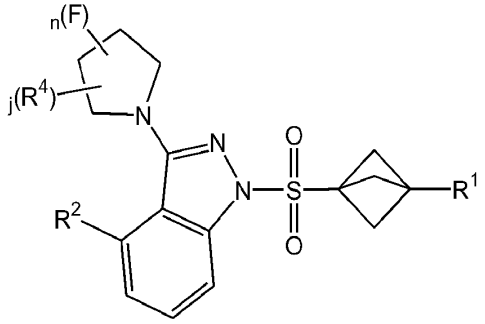
wherein

each R^4 is independently C_{1-2} alkyl optionally substituted with 0-3 (*e.g.*, 0, 1, 2 or 3) F's, or two R^4's along with the carbon atom they are bound to form a 3- or 4-membered carbocyclic or heterocyclic, or two R^4's along with the carbon atoms they are bound to atom for a 3- to 6-membered (*e.g.*, 3-, 4-, 5- or 6-membered) carbocyclic or heterocyclic ring;

n is 1, 2, 3, 4, 5 or 6; and

j is 0, 1, 2, 3 or 4.

[00112] In certain embodiments, the compound has the structural formula:



(I_n)

wherein

each R^4 is independently C_{1-2} alkyl optionally substituted with 0-3 (*e.g.*, 0, 1, 2 or 3) F's, or two R^4's along with the carbon atom they are bound to form a 3- or 4-membered carbocyclic or heterocyclic, or two R^4's along with the carbon atoms they are bound to atom for a 3- to 6-membered (*e.g.*, 3-, 4-, 5- or 6-membered) carbocyclic or heterocyclic ring;

n is 1, 2, 3, 4, 5 or 6; and

j is 0, 1, 2, 3 or 4.

[00113] In certain embodiments of (**I$_m$**)-(**I$_n$**), each R^4 is independently D, OH, CN, or C_{1-2} alkyl optionally substituted with 0-3 F's.

[00114] In certain embodiments of (**I$_m$**)-(**I$_n$**), two R^4's along with the carbon atom they are bound to form a 3-membered carbocyclic ring.

[00115] In certain embodiments of (**I$_m$**)-(**I$_n$**), two R^4's along with the carbon atom they are bound to form a 4-membered carbocyclic or heterocyclic ring.

[00116] In certain embodiments of (**I$_m$**)-(**I$_n$**), two R^4's along with the carbon atoms they are bound to atom for a 3- to 7-membered carbocyclic or heterocyclic ring.

[00117] In certain embodiments of (**I$_e$**)-(**I$_n$**), *j* is 0.

[00118] In certain embodiments of (**I$_e$**)-(**I$_n$**), *j* is 1 or 2.

[00119] In certain embodiments of (**I$_e$**)-(**I$_n$**), *j* is 3 or 4.

[00120] In certain embodiments of (**I$_e$**)-(**I$_n$**), *j* is 1 and R^4 is bound to a carbon atom adjacent to the N atom. In certain embodiments, R^4 is CF_3.

[00121] In certain embodiments of (**I$_e$**)-(**I$_n$**), *j* is 2 and both R^4's are bound to a carbon atom adjacent to the N atom of Ring A. In certain embodiments, one or both of the two R^4's is a C_{1-3} alkyl, optionally substituted with 1-5 F's.

[00122] In certain embodiments of (**I$_e$**)-(**I$_n$**), *j* is 2 and the two R^4's, along with the carbon atom they are bound to, form a cyclopropyl group.

[00123] In certain embodiments of (**I$_e$**)-(**I$_n$**), *j* is 2 and the two R^4's along with the carbon atoms they are bound to atom for a 5- to 7-membered carbocyclic or heterocyclic ring.

[00124] In certain embodiments of (**I**)-(**I$_n$**), *n* is an integer selected from 1, 2, 3, 4, 5 or 6.

[00125] In certain embodiments, *n* is 1. In certain embodiments, *n* is 2. In certain embodiments, *n* is 3. In certain embodiments, *n* is 4. In certain embodiments, *n* is 5. In certain embodiments, *n* is 6.

[00126] In certain embodiments of (**I$_e$**)-(**I$_n$**), R^1 is CF_2CH_3.

[00127] In certain embodiments of (**I$_e$**)-(**I$_n$**), R^1 is CF_2CH_2F.

[00128] In certain embodiments of (**I$_e$**)-(**I$_n$**), R^1 is CF_2CHF_2.

[00129] In certain embodiments of (**I$_e$**)-(**I$_n$**), R^1 is CHF_2.

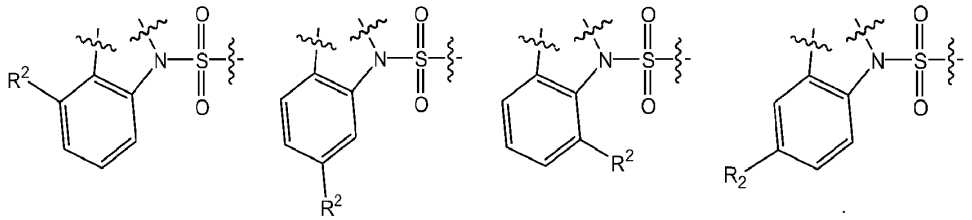
[00130] In certain embodiments of (**I$_e$**)-(**I$_n$**), R^1 is F.

[00131] In certain embodiments of (**I**)-(**I$_n$**), *m* is 0.

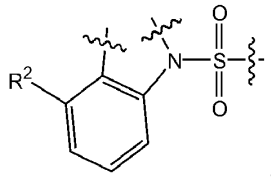
[00132] In certain embodiments of (**I**)-(**I$_n$**), *m* is 1.

[00133] In certain embodiments of (**I**)-(**I$_n$**), *m* is 2.

[00134] In certain embodiments of (**I**)-(**I$_n$**), *m* is 1 and R^2 has a positioning represented by:



[00135] In certain embodiments, R^2 has a positioning of:



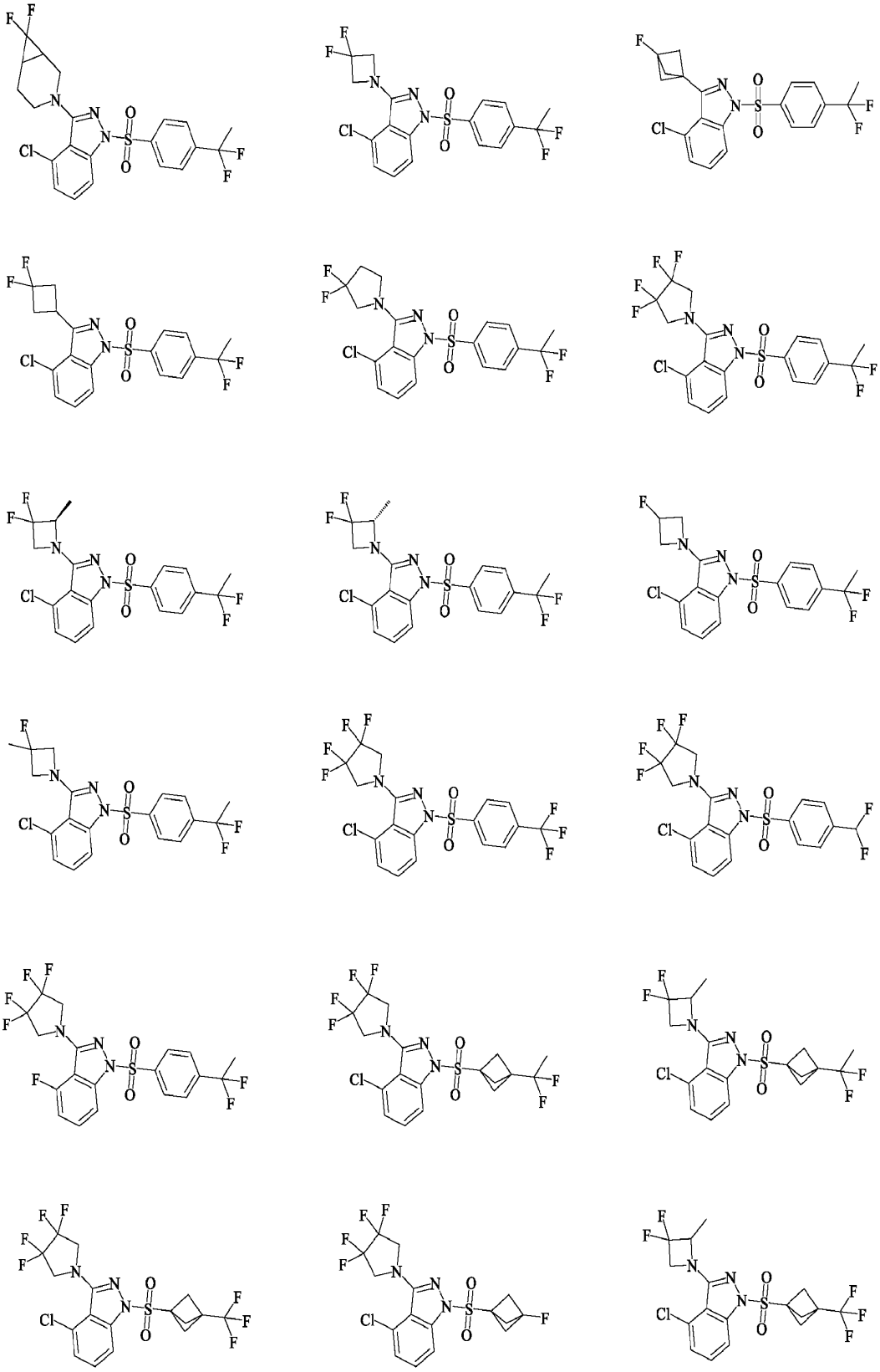
[00136] In certain embodiments, R^2 is a halogen.

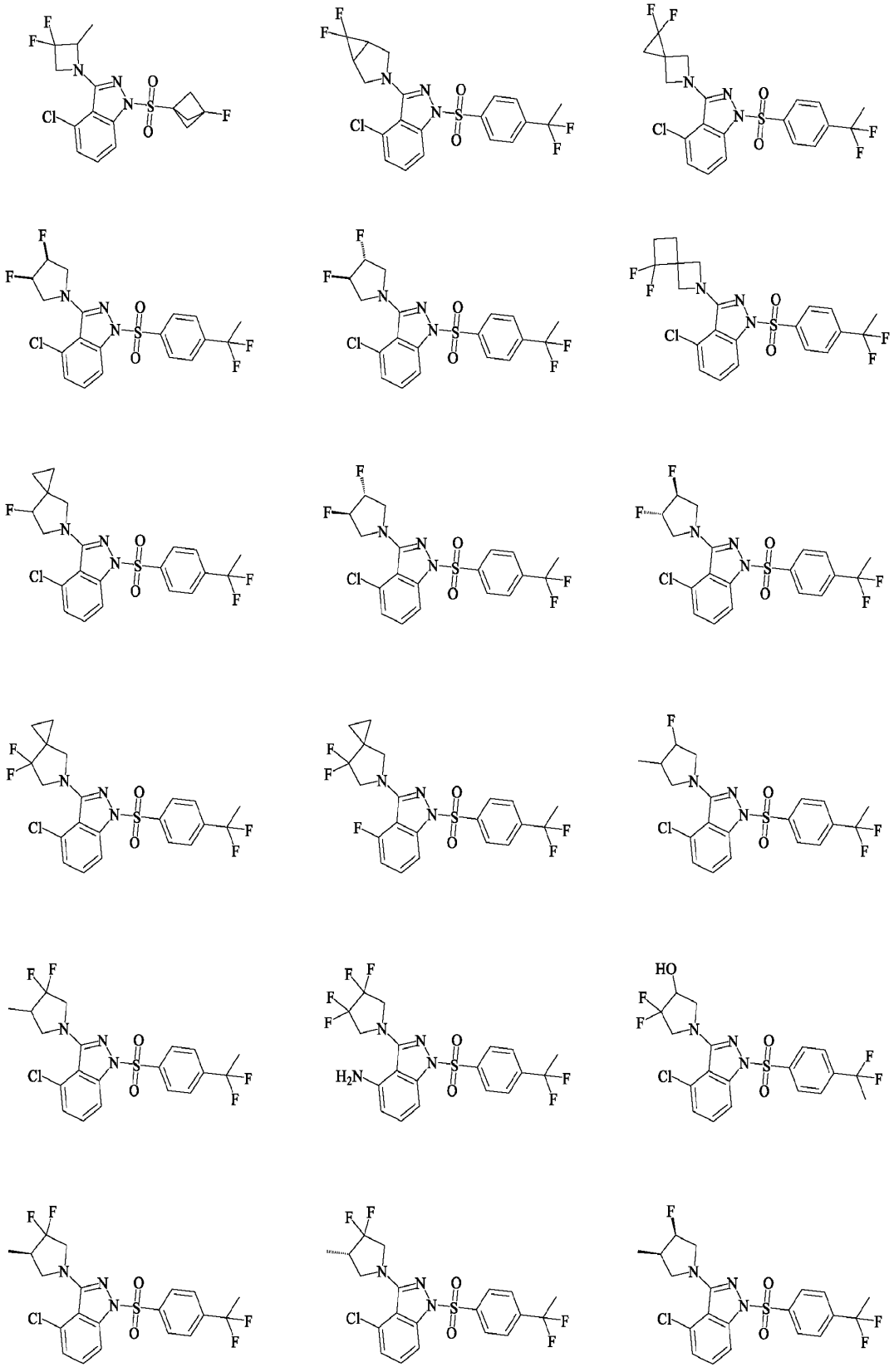
[00137] In certain embodiments, R^2 is Cl.

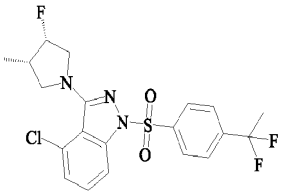
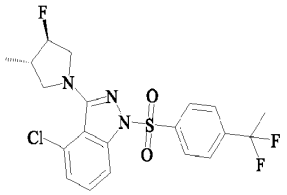
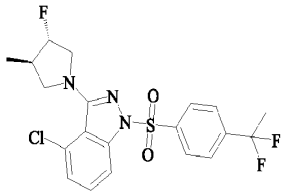
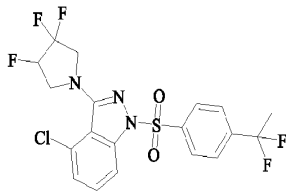
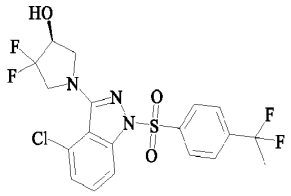
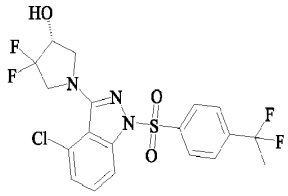
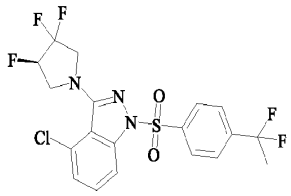
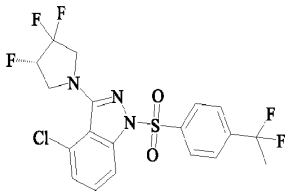
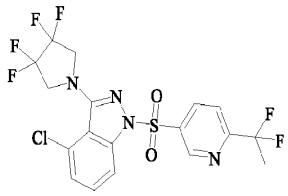
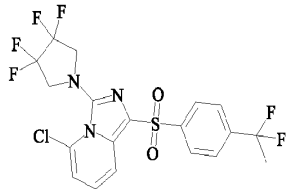
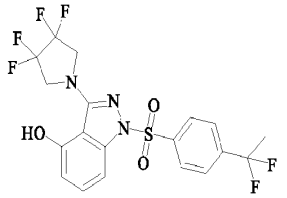
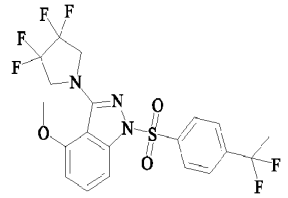
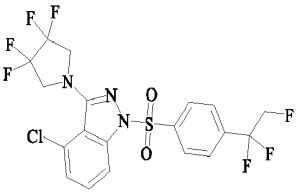
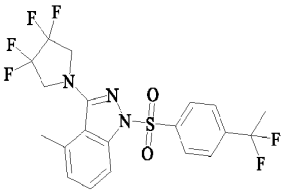
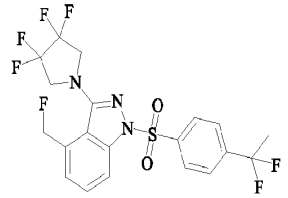
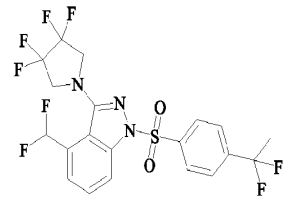
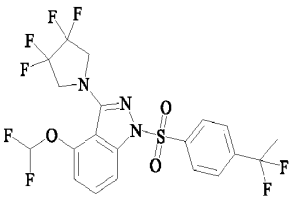
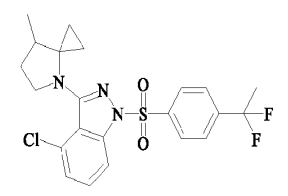
[00138] In certain embodiments, R^2 is amino, OH, C_1 alkyl or alkoxy, optionally substituted with 0-3 (*e.g.*, 0, 1, 2 or 3) F's.

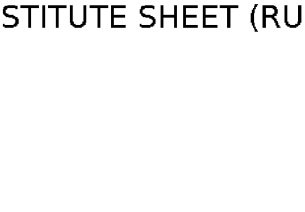
[00139] Exemplary compounds of the invention include those listed in **Table 1** below.

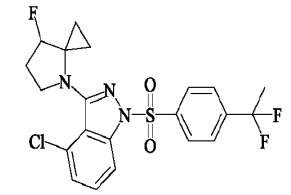
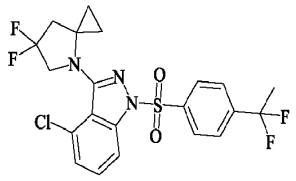
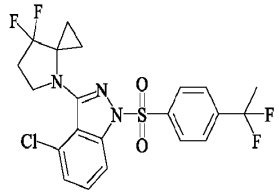
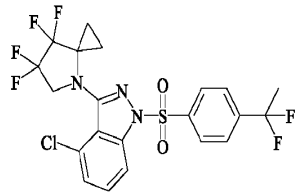
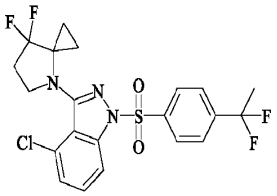
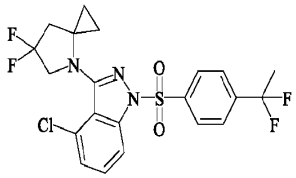
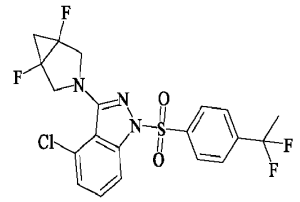
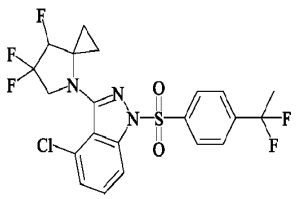
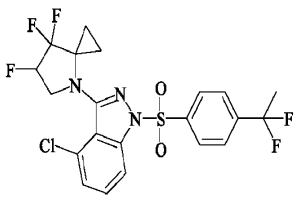
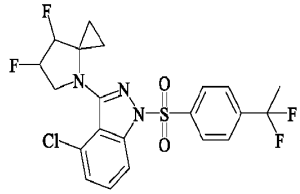
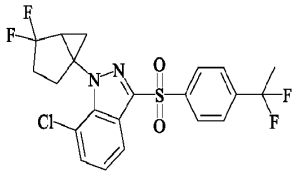
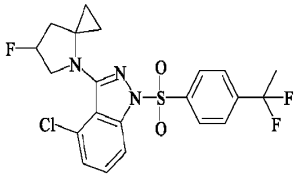
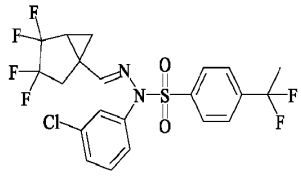
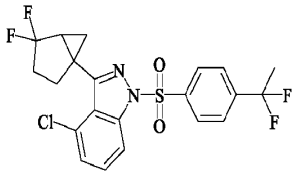
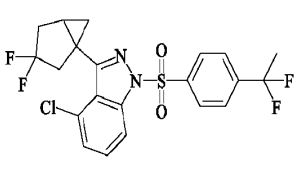
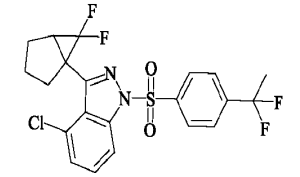
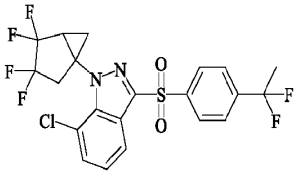
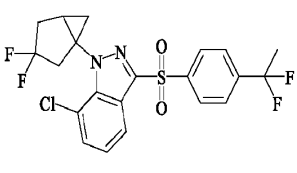
Table 1. Exemplary Compounds

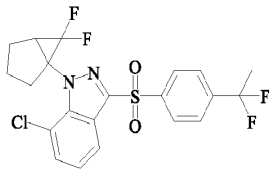
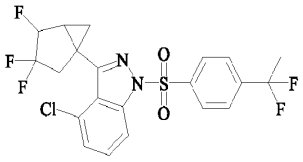
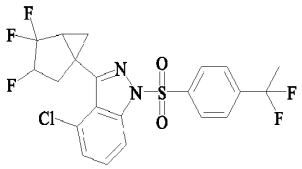
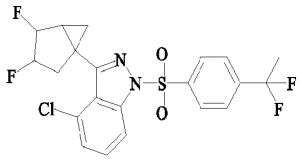
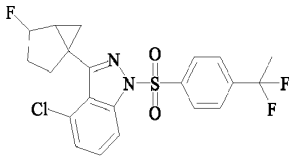
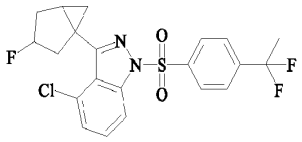
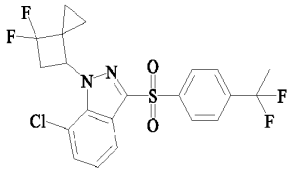
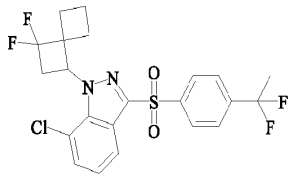
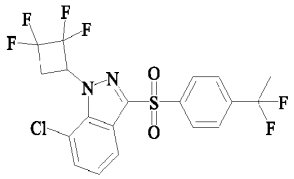
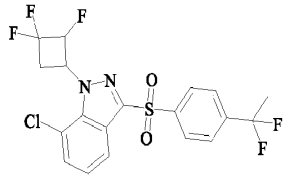
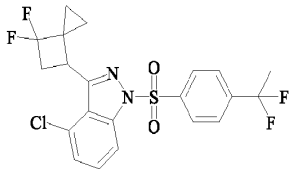
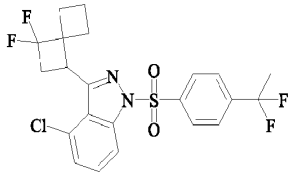
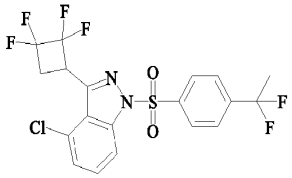
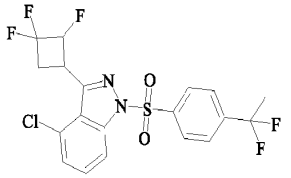
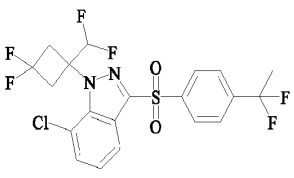
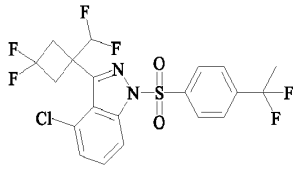
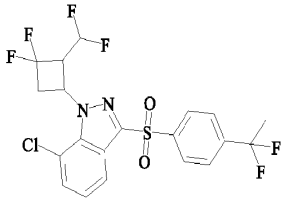
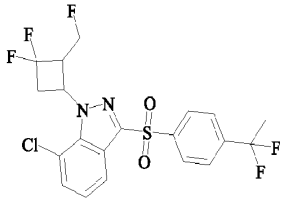


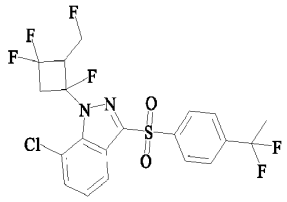
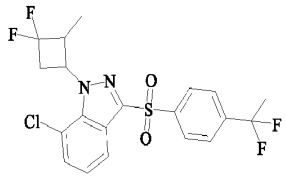
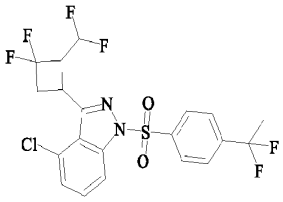
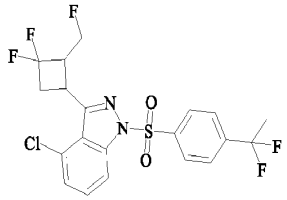
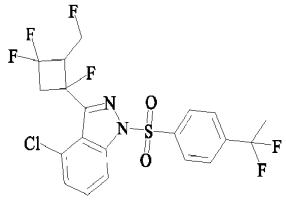
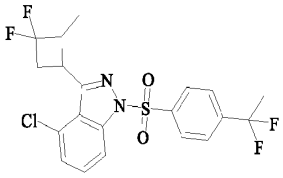
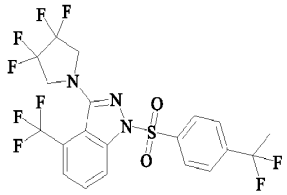
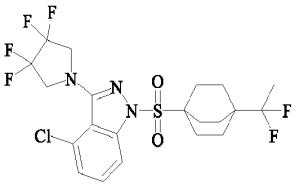
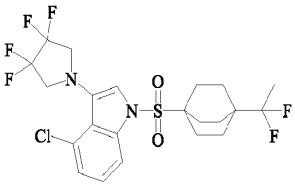
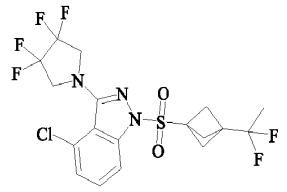
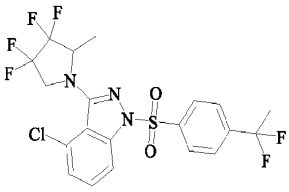
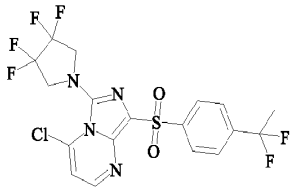
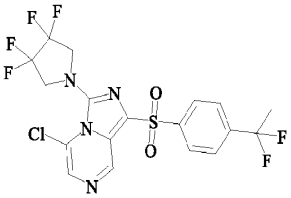
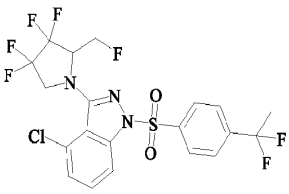
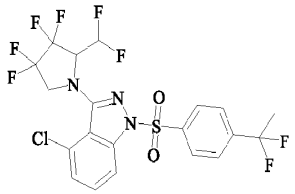
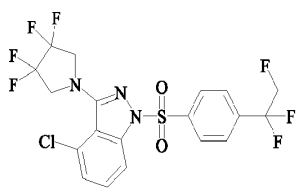
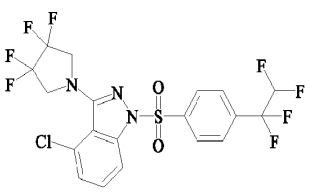
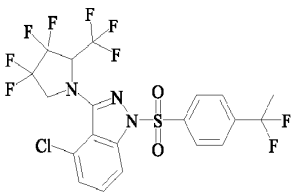


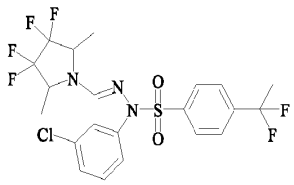
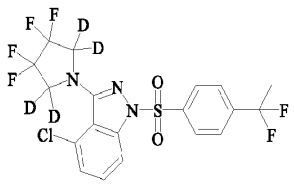
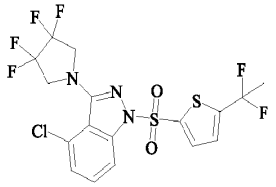
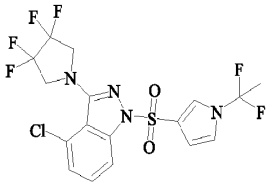
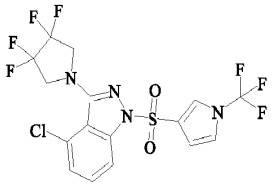
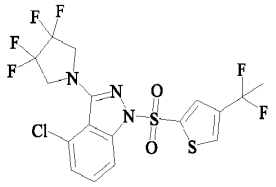
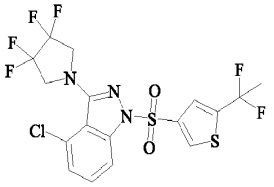
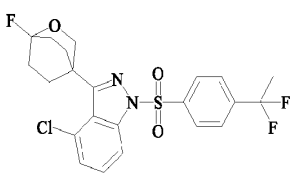
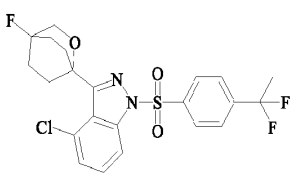
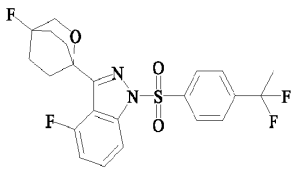
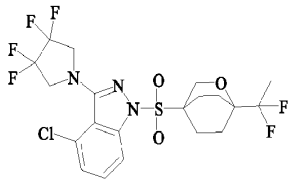
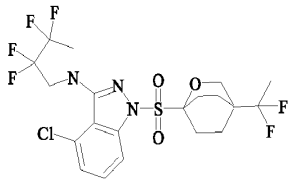
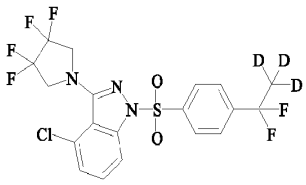
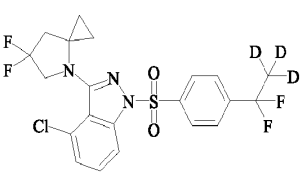
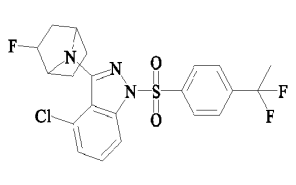
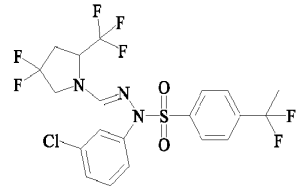
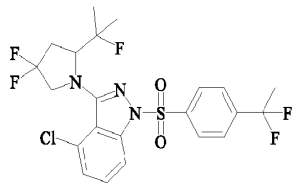
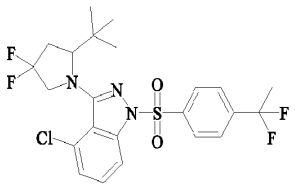



















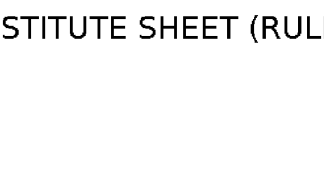


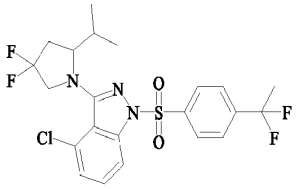
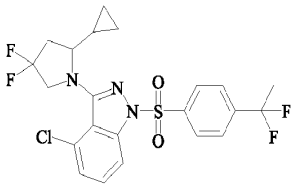
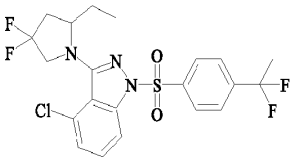
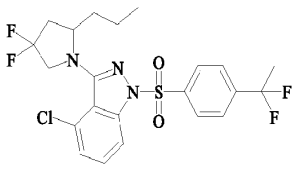
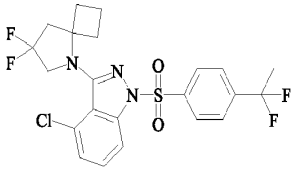
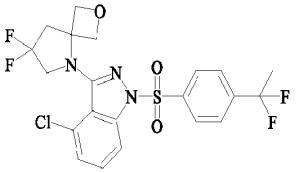
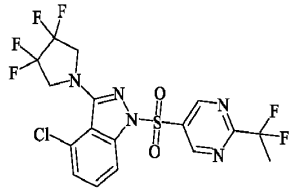
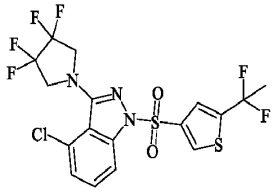
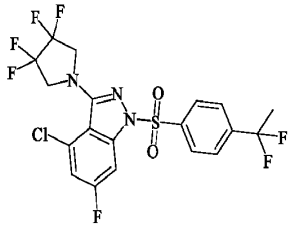
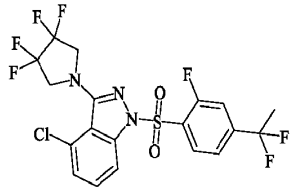
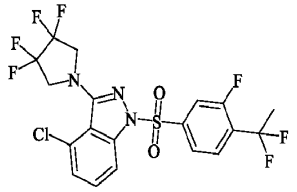
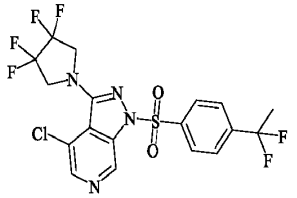
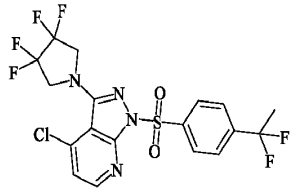
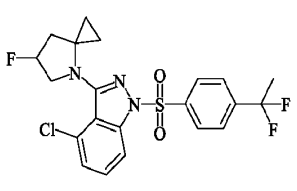
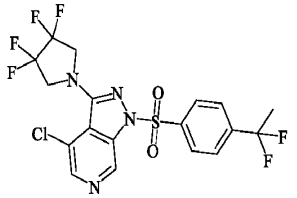
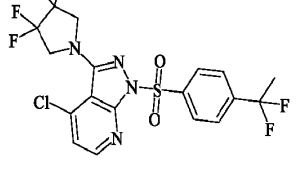
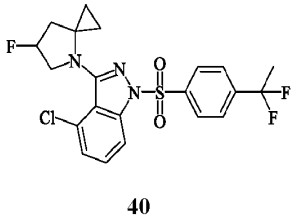
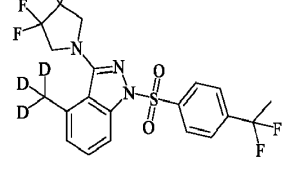



















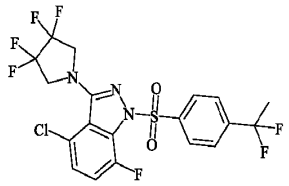
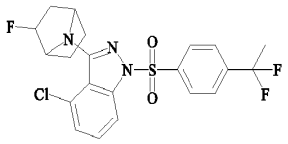
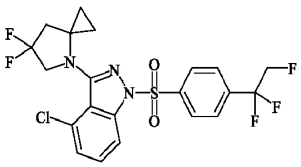
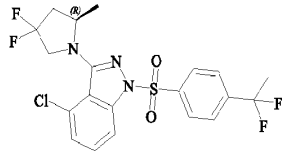
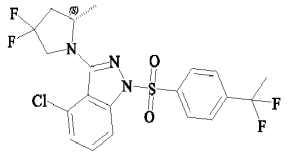
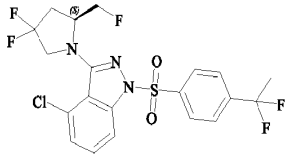
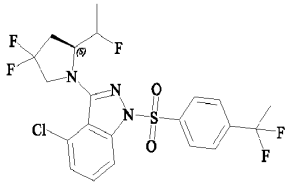
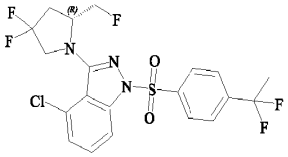
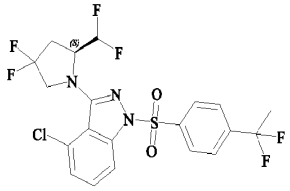
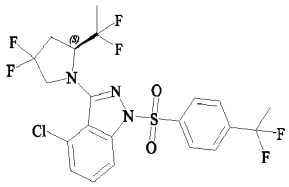
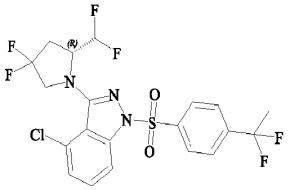
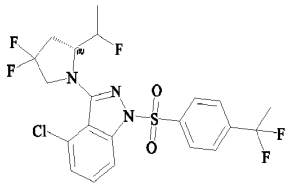
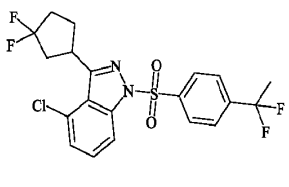
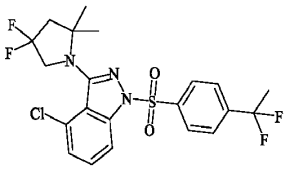
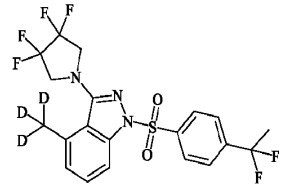
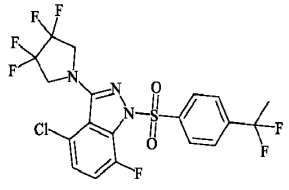
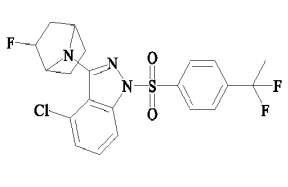
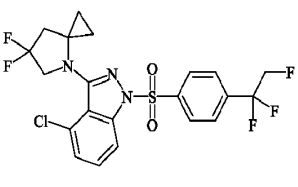



















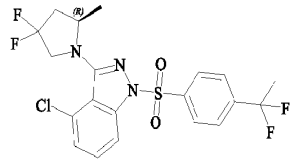
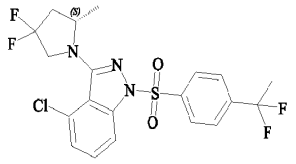
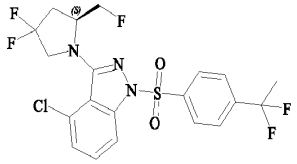
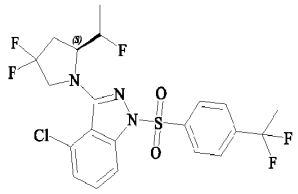
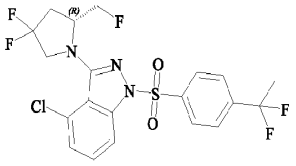
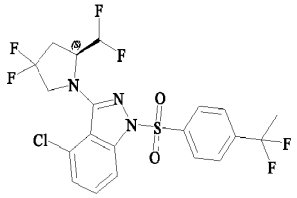
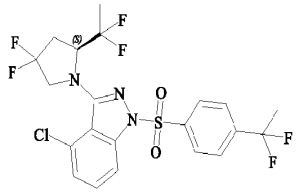
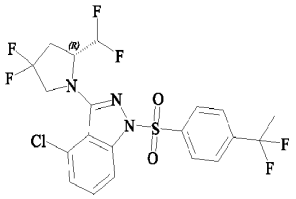
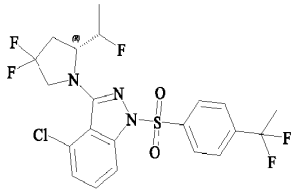
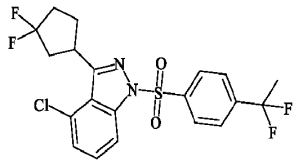
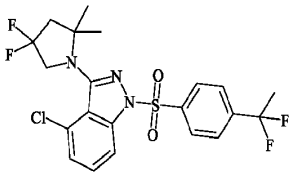
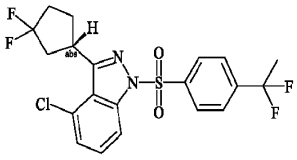
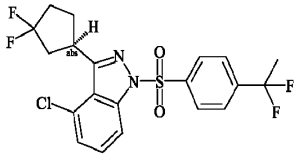
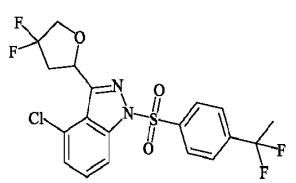
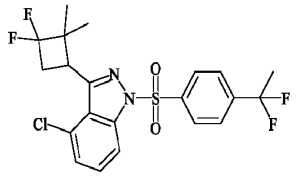
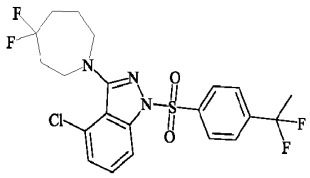
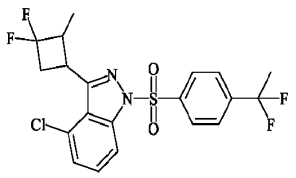
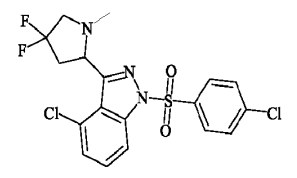



















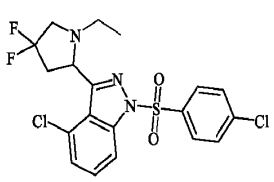
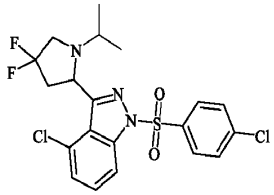
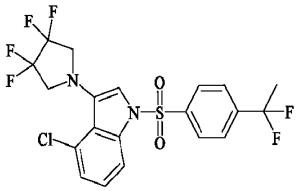
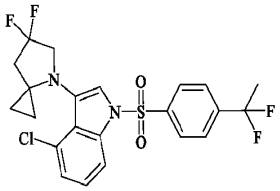
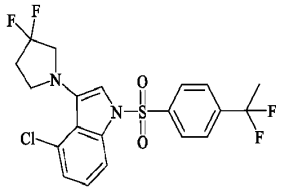
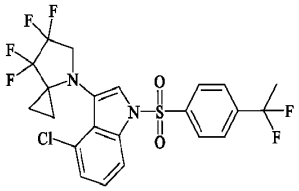
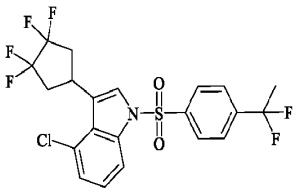
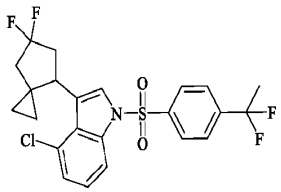
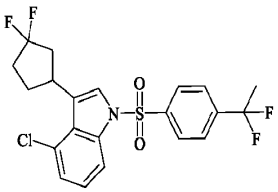
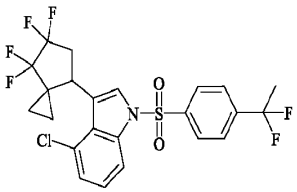
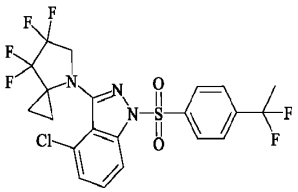
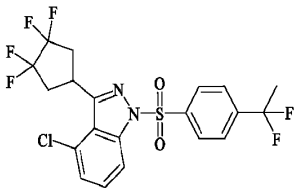
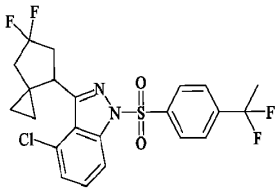
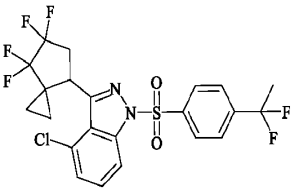
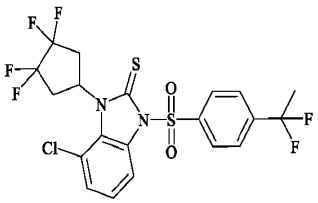
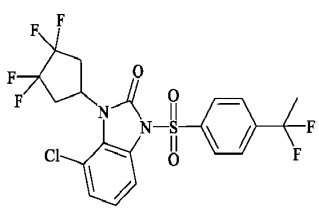
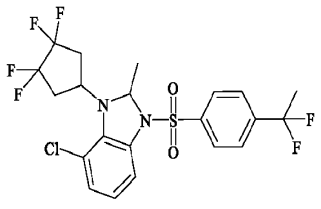
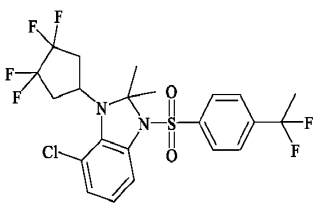



















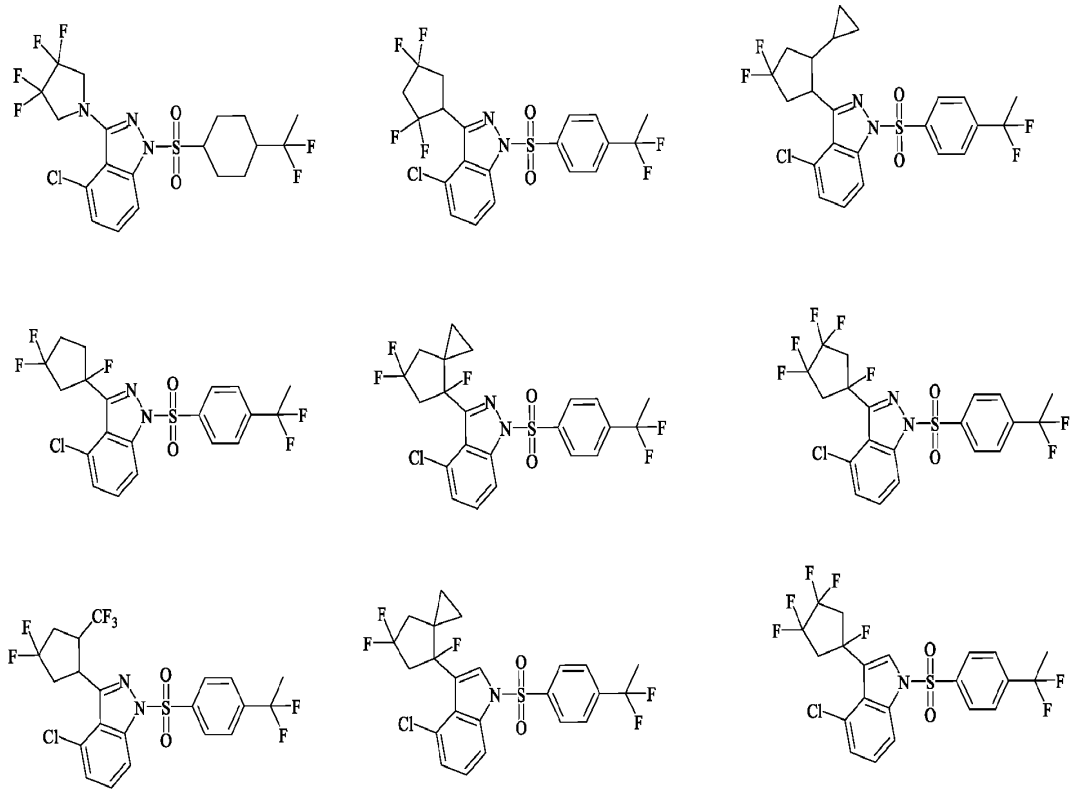




[00140] In certain embodiments, a compound disclosed herein has one or more deuterium atoms in place of one or more hydrogen atoms.

[00141] In certain embodiments, a compound disclosed herein has one deuterium atom in place of one hydrogen atom.

[00142] In another aspect, the invention generally relates to a pharmaceutical composition comprising a compound disclosed herein.

[00143] In yet another aspect, the invention generally relates to a unit dosage form comprising a pharmaceutical composition that comprises a compound disclosed herein.

[00144] In certain embodiments, the unit dosage is a tablet.

[00145] In certain embodiments, the unit dosage is a capsule.

[00146] In yet another aspect, the invention generally relates to a method for treating or reducing a disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein.

[00147] In certain embodiments, the methods disclosed herein are suitable for treating diseases or disorders that are mediated by the TRPMLs. In certain embodiments, the methods

disclosed herein are suitable for treating disease or disorders that are mediated by loss-of-function in TRPML1, *e.g.*, type IV Mucolipidosis (ML4) and Niemann–Pick type C (NPC).

[00148] In certain embodiments, the disease or disorder is a lysosome storage disease, or a related disease or disorder.

[00149] In certain embodiments, the disease or disorder is selected from the group consisting of age-related neurodegenerative disease, *e.g.*, Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease, Frontotemporal Dementia, or a related disease or disorder.

[00150] In certain embodiments, the disease or disorder is a neuronal ceroid lipofuscinoses (NCLs) or Batten diseases, or a related disease or disorder.

[00151] In certain embodiments, the disease or disorder is a NPC, or a related disease or disorder.

[00152] In certain embodiments, the disease or disorder is a Charcot-Marie-Tooth disease (CMT), or a related disease or disorder.

[00153] In certain embodiments, the disease or disorder is age-related macular degeneration (AMD), or a related disease or disorder.

[00154] In certain embodiments, the disease or disorder is cystic fibrosis (CF), or a related disease or disorder.

[00155] In certain embodiments, the disease or disorder is autosomal dominant polycystic kidney disease (ADPKD), or a related disease or disorder.

[00156] In certain embodiments, the disease or disorder is selected from cancers in which TRPML1 is overexpressed in cancer cells.

[00157] In certain embodiments, the disease or disorder is Batten's diseases.

[00158] In certain embodiments, the disease or disorder is muscular dystrophy, or a related disease or disorder.

[00159] In certain embodiments, the disease or disorder is oxidative stress or ROS, or a related disease or disorder.

[00160] In yet another aspect, the invention generally relates to a method for treating or reducing the effect of aging comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein.

[00161] In certain embodiments, the effect of aging comprises skin aging.

[00162] In certain embodiments, the effect of aging comprises photoaging.

[00163] In yet another aspect, the invention generally relates to a method for treating or reducing oxidative stress or ROS related diseases or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a TRPML1 agonist or a composition comprising of a TRPML1 agonist disclosed herein.

[00164] In yet another aspect, the invention generally relates to a method for treating or reducing oxidative stress or ROS related diseases or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein.

[00165] In certain embodiments of methods of the invention, administration to a subject is via oral administration.

[00166] In certain embodiments of methods of the invention, administration to a subject is via topical administration.

[00167] In yet another aspect, the invention generally relates to use of a compound disclosed herein, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a disease or disorder.

[00168] In certain embodiments of the use according to the invention, the disease or disorder is an neurodegenerative disease, *e.g.*, Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease, Frontotemporal Dementia, or a related disease or disorder.

[00169] In certain embodiments, the disease or disorder is selected from cancers in which TRPML1 is overexpressed in cancer cells.

[00170] In certain embodiments, the disease or disorder is Batten's disease.

[00171] In certain embodiments, the disease or disorder is muscular dystrophy, or a related disease or disorder.

[00172] In certain embodiments, the disease or disorder is oxidative stress or ROS, or a related disease or disorder.

[00173] In certain embodiments, the disease or disorder is skin aging.

[00174] In certain embodiments, the disease or disorder is photoaging.

[00175] The specific approaches and compounds disclosed herein are not intended to be limiting. The chemical structures in the schemes herein depict variables that are hereby defined commensurately with chemical group definitions (moieties, atoms, etc.) of the corresponding position in the compound formulae herein, whether identified by the same variable name (*e.g.*, R^1, R^2, R, R', X, *etc.*) or not. The suitability of a chemical group in a compound structure for use

in synthesis of another compound structure is within the knowledge of one of ordinary skill in the art. Additional methods of synthesizing compounds of the formulae herein and their synthetic precursors, including those within routes not explicitly shown in schemes herein, are within the means of chemists of ordinary skill in the art. Methods for optimizing reaction conditions, if necessary, minimizing competing by-products, are known in the art. The methods described herein may also additionally include steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compounds herein. In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

[00176] The methods delineated herein contemplate converting compounds of one formula to compounds of another formula. The process of converting refers to one or more chemical transformations, which can be performed *in situ*, or with isolation of intermediate compounds. The transformations can include reacting the starting compounds or intermediates with additional reagents using techniques and protocols known in the art, including those in the references cited herein. Intermediates can be used with or without purification (*e.g.*, filtration, distillation, sublimation, crystallization, trituration, solid phase extraction, and chromatography).

[00177] Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds.

[00178] Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, atropisomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl

group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[00179] Isomeric mixtures containing any of a variety of isomer ratios may be utilized in accordance with the present invention. For example, where only two isomers are combined, mixtures containing 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0 isomer ratios are contemplated by the present invention. Those of ordinary skill in the art will readily appreciate that analogous ratios are contemplated for more complex isomer mixtures.

[00180] If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic methods well known in the art, and subsequent recovery of the pure enantiomers.

[00181] Solvates and polymorphs of the compounds of the invention are also contemplated herein. Solvates of the compounds of the present invention include, for example, hydrates.

[00182] The invention also provides compositions comprising an effective amount of a compound of any of the formulae herein, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph or prodrug, if applicable, of said compound; and an acceptable carrier. Preferably, a composition of this invention is formulated for pharmaceutical use ("a pharmaceutical composition"), wherein the carrier is a pharmaceutically acceptable carrier. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in amounts typically used in medicaments.

[00183] Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica,

magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00184] The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (*e.g.*, using a transdermal patch). Other formulations may conveniently be presented in unit dosage form, *e.g.*, tablets and sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, PA (17^{th} ed. 1985).

[00185] Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers or both, and then if necessary, shaping the product.

[00186] In certain preferred embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, or packed in liposomes and as a bolus, *etc.* Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

[00187] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets optionally may be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. Methods of formulating such slow or controlled release compositions of

pharmaceutically active ingredients, such as those herein and other compounds known in the art, are known in the art and described in several issued US Patents, some of which include, but are not limited to, US Patent Nos. 4,369,172; and 4,842,866, and references cited therein. Coatings can be used for delivery of compounds to the intestine (see, *e.g.*, U.S. Patent Nos. 6,638,534, 5,217,720, and 6,569,457, 6,461,631, 6,528,080, 6,800,663, and references cited therein). A useful formulation for the compounds of this invention is the form of enteric pellets of which the enteric layer comprises hydroxypropyl methylcellulose acetate succinate.

[00188] In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[00189] Compositions suitable for topical administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

[00190] Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

[00191] Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are

mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

[00192] The pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[00193] The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

[00194] Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in

a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this invention.

[00195] Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (*e.g.*, by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (*e.g.*, the brain or central nervous system) relative to the parent species. Preferred prodrugs include derivatives where a group that enhances aqueous solubility or active transport through the gut membrane is appended to the structure of formulae described herein. (See, *e.g.*, Alexander, *et al.* **1988** *J Med Chem* 31, 318-322; Bundgaard **1985** *Elsevier: Amsterdam* 1-92; Bundgaard, *et al.* **1987** *J Med Chem* 30, 451-454; Bundgaard, H. *A Textbook of Drug Design and Development*; Harwood Academic Publ.: Switzerland, **1991**, 113-191; Digenis, *et al. Handbook of Experimental Pharmacology* **1975** 28, 86-112; Friis, **et al**. *A Textbook of Drug Design and Development*; 2 ed.; Overseas Publ.: Amsterdam, **1996**, 351-385; Pitman **1981** *Med Res Rev* 1, 189-214.)

[00196] Application of the subject therapeutics may be local, so as to be administered at the site of interest. Various techniques can be used for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access.

[00197] According to another embodiment, the invention provides a method of impregnating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this invention. Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, diffusible polymer capsules and biodegradable polymer wafers.

[00198] According to another embodiment, the invention provides an implantable medical device coated with a compound or a composition comprising a compound of this invention, such that said compound is therapeutically active.

[00199] In another embodiment, a composition of the present invention further comprises a second therapeutic agent. The second therapeutic agent includes any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered alone or with a compound of any of the formulae herein. Drugs that could be usefully combined with

these compounds include other kinase inhibitors and/or other chemotherapeutic agents for the treatment of the diseases and disorders discussed above.

[00200] Such agents are described in detail in the art. Preferably, the second therapeutic agent is an agent useful in the treatment or prevention of cancer.

[00201] Even more preferably the second therapeutic agent co-formulated with a compound of this invention is an agent useful in the treatment of TRPML mediated disease/disorders.

[00202] In another embodiment, the invention provides separate dosage forms of a compound of this invention and a second therapeutic agent that are associated with one another. The term "associated with one another" as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

[00203] In the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount. As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to reduce or ameliorate the severity, duration or progression of the disorder being treated, prevent the advancement of the disorder being treated, cause the regression of the disorder being treated, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy.

[00204] The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich, *et al.* **1966** *Cancer Chemother Rep* 50: 219. Body surface area may be approximately determined from height and weight of the patient. (See, *e.g.*, Scientific Tables, Geigy Pharmaceuticals, Ardley, N.Y., 1970, 537.) An effective amount of a compound of this invention can range from about 0.001 mg/kg to about 500 mg/kg, more preferably 0.01 mg/kg to about 50 mg/kg, more preferably 0.1 mg/kg to about 2.5 mg/kg. Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the patient, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician.

[00205] For pharmaceutical compositions that comprise a second therapeutic agent, an effective amount of the second therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount

is between about 70% and 100% of the normal monotherapeutic dose. The normal monotherapeutic dosages of these second therapeutic agents are well known in the art. (See, *e.g.*, Wells, *et al.*, eds. **2000** *Pharmacotherapy Handbook, 2nd Edition*, Appleton and Lange, Stamford, Conn.; PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia **2000**, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. **2000**, each of which references are entirely incorporated herein by reference.

[00206] It is expected that some of the second therapeutic agents referenced above will act synergistically with the compounds of this invention. When this occurs, it will allow the effective dosage of the second therapeutic agent and/or the compound of this invention to be reduced from that required in a monotherapy. This has the advantage of minimizing toxic side effects of either the second therapeutic agent of a compound of this invention, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

[00207] The term "co-administered" as used herein means that the second therapeutic agent may be administered together with a compound of this invention as part of a single dosage form (such as a composition of this invention comprising a compound of the invention and a second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the second therapeutic agent(s) are administered by conventional methods. The co-administration of a composition of this invention comprising both a compound of the invention and a second therapeutic agent to a subject does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said subject at another time during a course of treatment.

[00208] Effective amounts of these second therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells *et al.*, eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts. However, it is well within the skilled artisan's purview to determine the second therapeutic agent's optimal effective-amount range.

[00209] In one embodiment of the invention where a second therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount would be where the second therapeutic agent is not administered. In another embodiment, the effective amount of the second therapeutic agent is less than its effective amount would be where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

[00210] In yet another aspect, the invention provides the use of a compound of any of the formulae herein alone or together with one or more of the above-described second therapeutic agents in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment or prevention in a subject of a disease, disorder or symptom set forth above. Another aspect of the invention is a compound of the formulae herein for use in the treatment or prevention in a subject of a disease, disorder or symptom thereof delineated herein.

In other aspects, the methods herein include those further comprising monitoring subject response to the treatment administrations. Such monitoring may include periodic sampling of subject tissue, fluids, specimens, cells, proteins, chemical markers, genetic materials, etc. as markers or indicators of the treatment regimen. In other methods, the subject is prescreened or identified as in need of such treatment by assessment for a relevant marker or indicator of suitability for such treatment.

[00211] In one embodiment, the invention provides a method of monitoring treatment progress. The method includes the step of determining a level of diagnostic marker (Marker) (*e.g.*, any target or cell type delineated herein modulated by a compound herein) or diagnostic measurement (*e.g.*, screen, assay) in a subject suffering from or susceptible to a disorder or symptoms thereof delineated herein, in which the subject has been administered a therapeutic amount of a compound herein sufficient to treat the disease or symptoms thereof. The level of Marker determined in the method can be compared to known levels of Marker in either healthy normal controls or in other afflicted patients to establish the subject's disease status. In preferred embodiments, a second level of Marker in the subject is determined at a time point later than the determination of the first level, and the two levels are compared to monitor the course of disease or the efficacy of the therapy. In certain preferred embodiments, a pre-treatment level of Marker

in the subject is determined prior to beginning treatment according to this invention; this pre-treatment level of Marker can then be compared to the level of Marker in the subject after the treatment commences, to determine the efficacy of the treatment.

[00212] In certain method embodiments, a level of Marker or Marker activity in a subject is determined at least once. Comparison of Marker levels, *e.g.*, to another measurement of Marker level obtained previously or subsequently from the same patient, another patient, or a normal subject, may be useful in determining whether therapy according to the invention is having the desired effect, and thereby permitting adjustment of dosage levels as appropriate. Determination of Marker levels may be performed using any suitable sampling/expression assay method known in the art or described herein. Preferably, a tissue or fluid sample is first removed from a subject. Examples of suitable samples include blood, urine, tissue, mouth or cheek cells, and hair samples containing roots. Other suitable samples would be known to the person skilled in the art. Determination of protein levels and/or mRNA levels (*e.g.*, Marker levels) in the sample can be performed using any suitable technique known in the art, including, but not limited to, enzyme immunoassay, ELISA, radiolabeling/assay techniques, blotting/chemiluminescence methods, real-time PCR, and the like.

[00213] The present invention also provides kits for use to treat diseases, disorders, or symptoms thereof, including those delineated herein. These kits comprise: a) a pharmaceutical composition comprising a compound of any of the formula herein or a salt thereof; or a prodrug, or a salt of a prodrug thereof; or a hydrate, solvate, or polymorph thereof, wherein said pharmaceutical composition is in a container; and b) instructions describing a method of using the pharmaceutical composition to treat the disease, disorder, or symptoms thereof, including those delineated herein.

[00214] The container may be any vessel or other sealed or sealable apparatus that can hold said pharmaceutical composition. Examples include bottles, divided or multi-chambered holders or bottles, wherein each division or chamber comprises a single dose of said composition, a divided foil packet wherein each division comprises a single dose of said composition, or a dispenser that dispenses single doses of said composition. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister

pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle, which is in turn contained within a box. Preferably, the container is a blister pack.

[00215] The kit may additionally comprise information and/or instructions for the physician, pharmacist or subject. Such memory aids include numbers printed on each chamber or division containing a dosage that corresponds with the days of the regimen which the tablets or capsules so specified should be ingested, or days of the week printed on each chamber or division, or a card which contains the same type of information.

[00216] The following examples are meant to be illustrative of the practice of the invention and not limiting in any way.

Examples

Abbreviations

Abbreviation	Name
ACN	acetonitrile
DCM	dichloromethane
DHP	3,4-dihydro-2H-pyran
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
HPLC	high-performance liquid chromatography
LC-MS	liquid chromatography–mass spectrometry
NIS	N-iodosuccinimide
NBS	N-bromosuccinimide
TBS	tert-butyldimethylsilyl
TEA	triethyl amine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography

Compounds and Synthetic Methods

[00217] Compounds of the invention, including those specifically disclosed herein above and below, may be prepared as described in the following schemes.

Table 2

Compound #	EC_{50} of TFEB activation (nM)	Name
Compound 1	+++	4-chloro-3-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-3-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 2	+++	4-chloro-3-(3, 3-difluoroazetidin-1-yl)-1-((4-(1, 1-difluoroethyl) phenyl) sulfonyl)-1H-indazole
Compound 3	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3-fluorobicyclo[1.1.1]pentan-1-yl)-1H-indazole
Compound 4	+++	4-chloro-3-(3,3-difluorocyclobutyl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 5	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3,3-difluoropyrrolidin-1-yl)-1H-indazole
Compound 6	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole
Compound 7	+++	4-chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-[(2R)-3,3-difluoro-2-methyl-azetidin-1-yl]indazole
Compound 8	+++	4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2S)-3, 3-difluoro-2-methyl-azetidin-1-yl] indazole
Compound 9	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3-fluoroazetidin-1-yl)-1H-indazole
Compound 10	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3-fluoro-3-methylazetidin-1-yl)-1H-indazole
Compound 11	+++	4-chloro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1H-indazole
Compound 12	+++	4-chloro-1-((4-(difluoromethyl)phenyl)sulfonyl)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole
Compound 13	+++	1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-4-fluoro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole
Compound 14	+++	4-chloro-1-((3-(1,1-difluoroethyl)bicyclo[1.1.1]pentan-1-yl)sulfonyl)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole
Compound 15	+	4-chloro-3-(3,3-difluoro-2-methylazetidin-1-yl)-1-((3-(1,1-difluoroethyl)bicyclo[1.1.1]pentan-1-yl)sulfonyl)-1H-indazole
Compound 16	+	4-chloro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1-((3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)sulfonyl)-1H-indazole
Compound 17	+	4-chloro-1-((3-fluorobicyclo[1.1.1]pentan-1-yl)sulfonyl)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole
Compound 18	+	4-chloro-3-(3,3-difluoro-2-methylazetidin-1-yl)-1-((3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)sulfonyl)-1H-indazole
Compound 19	+	4-chloro-3-(3,3-difluoro-2-methylazetidin-1-yl)-1-((3-fluorobicyclo[1.1.1]pentan-1-yl)sulfonyl)-1H-indazole

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Compound 20	+++	4-chloro-3-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 21	+	4-chloro-3-(1,1-difluoro-5-azaspiro[2.3]hexan-5-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 22	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3,4-difluoropyrrolidin-1-yl)-1H-indazole
Compound 23	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-((3R,4R)-3,4-difluoropyrrolidin-1-yl)-1H-indazole
Compound 24	+	4-chloro-3-(5,5-difluoro-2-azaspiro[3.3]heptan-2-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 25	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(7-fluoro-5-azaspiro[2.4]heptan-5-yl)-1H-indazole
Compound 26	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-((3R,4R)-3,4-difluoropyrrolidin-1-yl)-1H-indazole
Compound 27	+	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-((3S,4S)-3,4-difluoropyrrolidin-1-yl)-1H-indazole
Compound 28	+++	4-chloro-3-(7,7-difluoro-5-azaspiro[2.4]heptan-5-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 29	+++	3-(7,7-difluoro-5-azaspiro[2.4]heptan-5-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-4-fluoro-1H-indazole
Compound 30	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3-fluoro-4-methylpyrrolidin-1-yl)-1H-indazole
Compound 31	+++	4-chloro-3-(3,3-difluoro-4-methylpyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 32	+	1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazol-4-amine
Compound 33	+	1-(4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazol-3-yl)-4,4-difluoropyrrolidin-3-ol
Compound 34	+++	(R)-4-chloro-3-(3,3-difluoro-4-methylpyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 35	+++	(S)-4-chloro-3-(3,3-difluoro-4-methylpyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 36	+	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-((3R,4R)-3-fluoro-4-methylpyrrolidin-1-yl)-1H-indazole
Compound 37	+	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-((3S,4S)-3-fluoro-4-methylpyrrolidin-1-yl)-1H-indazole
Compound 38	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-((3R,4S)-3-fluoro-4-methylpyrrolidin-1-yl)-1H-indazole
Compound 39	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-((3S,4R)-3-fluoro-4-methylpyrrolidin-1-yl)-1H-indazole
Compound 40	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3,3,4-trifluoropyrrolidin-1-yl)-1H-indazole
Compound 41	+	(S)-1-(4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazol-3-yl)-4,4-difluoropyrrolidin-3-ol

Compound 42	+++	(R)-1-(4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazol-3-yl)-4,4-difluoropyrrolidin-3-ol
Compound 43	+++	(R)-4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3,3,4-trifluoropyrrolidin-1-yl)-1H-indazole
Compound 44	+++	(S)-4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3,3,4-trifluoropyrrolidin-1-yl)-1H-indazole
Compound 45	+++	4-chloro-1-tanford1-difluoroethyl)-3-pyridyl] sulfonyl]-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole
Compound 46	+	5-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)imidazo[1,5-a]pyridine
Compound 47	+	1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazol-4-ol
Compound 48	+++	1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-4-methoxy-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole
Compound 49	+++	4-chloro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1-((4-(1,1,2-trifluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 50	+++	1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-4-methyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole
Compound 51	+++	1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-4-(fluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole
Compound 52	+++	1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-4-(difluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole
Compound 56	+++	4-chloro-3-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole
Compound 57	+++	4-chloro-3-(7,7-difluoro-4-azaspiro[2.4]heptan-4-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 58	+++	4-chloro-1-[4-(1, 1-difluoroethyl)-3-fluoro-phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole
Compound 59	+++	4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-[4-(2, 2, 2-trideuterio-1, 1-difluoro-ethyl) phenyl] sulfonyl-indazole
Compound 60	+++	4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(6R)-6-fluoro-4-azaspiro [2.4] heptan-4-yl] indazole
Compound 61	+++	4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(6S)-6-fluoro-4-azaspiro [2.4] heptan-4-yl] indazole
Compound 62	+++	4-chloro-3-(2, 2-difluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole
Compound 68	+	4-chloro-1-((2-(1,1-difluoroethyl)pyrimidin-5-yl)sulfonyl)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole
Compound 69	+++	4-chloro-1-((5-(1,1-difluoroethyl)thiophen-3-yl)sulfonyl)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole
Compound 70	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-6-fluoro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole
Compound 71	+++	4-chloro-1-((4-(1,1-difluoroethyl)-2-fluorophenyl)sulfonyl)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole

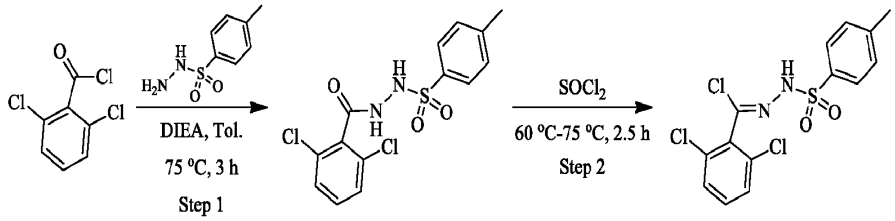
Compound 72	+++	4-chloro-1-((4-(1,1-difluoroethyl)-3-fluorophenyl)sulfonyl)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole
Compound 73	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-pyrazolo[3,4-c]pyridine
Compound 74	+	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-pyrazolo[3,4-b]pyridine
Compound 75	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(6-fluoro-4-azaspiro[2.4]heptan-4-yl)-1H-indazole
Compound 76	+++	1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-4-(methyl-d3)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole
Compound 77	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-7-fluoro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole
Compound 78	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(2-fluoro-7-azabicyclo[2.2.1]heptan-7-yl)-1H-indazole
Compound 79	+++	4-chloro-3-(6,6-difluoro-4-azaspiro[2.4]heptan-4-yl)-1-((4-(1,1,2-trifluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 80	+++	(R)-4-chloro-3-(4,4-difluoro-2-methylpyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 81	+++	(S)-4-chloro-3-(4,4-difluoro-2-methylpyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 82	+++	(S)-4-chloro-3-(4,4-difluoro-2-(fluoromethyl)pyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 83	+++	4-chloro-3-((S)-4,4-difluoro-2-((S)-1-fluoroethyl)pyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 84	+++	(R)-4-chloro-3-(4,4-difluoro-2-(fluoromethyl)pyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 85	+++	(S)-4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(2-(difluoromethyl)-4,4-difluoropyrrolidin-1-yl)-1H-indazole
Compound 86	+++	(S)-4-chloro-3-(2-(1,1-difluoroethyl)-4,4-difluoropyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 87	+++	(R)-4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(2-(difluoromethyl)-4,4-difluoropyrrolidin-1-yl)-1H-indazole
Compound 88	+++	4-chloro-3-((R)-4,4-difluoro-2-((R)-1-fluoroethyl)pyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 89	+++	4-chloro-3-(3,3-difluorocyclopentyl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 90	+++	4-chloro-3-(4,4-difluoro-2,2-dimethylpyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 91	+++	(S)-4-chloro-3-(3,3-difluorocyclopentyl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 92	+++	(R)-4-chloro-3-(3,3-difluorocyclopentyl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 93	+++	4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(4,4-difluorotetrahydrofuran-2-yl)-1H-indazole

Compound 94	+++	4-chloro-3-(3,3-difluoro-2,2-dimethylcyclobutyl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole
Compound 95	+++	4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3, 3-difluoro-2-methyl-cyclobutyl) indazole
Compound 96	+++	4-chloro-3-(4, 4-difluoroazepan-1-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole

*EC_{50} of TFEB activation (where data is provided): "+++" ≤ 1 uM; "++" 1 uM to 10 uM; "+" ≥ 10 uM

Synthetic Methods

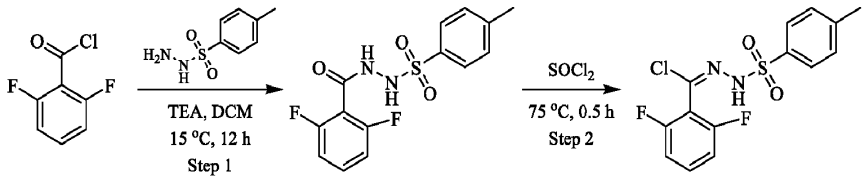
Intermediate-L1: (1Z)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride



[00218] ***Step 1***: To a solution of 2, 6-dichlorobenzoyl chloride (5 g, 23.9 mmol, 3.42 mL, 1 eq) in toluene (100 mL) were added 4-methylbenzenesulfonohydrazide (4.22 g, 22.7 mmol, 0.95 eq) and diisopropylethylamine (3.70 g, 28.7 mmol, 4.99 mL, 1.2 eq). The mixture was stirred at 75 °C for 3 hours. LC-MS showed 2, 6-dichlorobenzoyl chloride was consumed completely and one main peak with the desired mass was detected. The reaction mixture was filtered, and the filter cake was dried in vacuum to give the desired 2, 6-dichloro-N'-(p-tolylsulfonyl) benzohydrazide (5.5 g, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{14}H_{12}Cl_2N_2O_3S$ 357.99, m/z found 359.1 $[M+H]^+$.

[00219] ***Step 2***: A solution of 2, 6-dichloro-N'-(p-tolylsulfonyl) benzohydrazide (1.6 g, 4.45 mmol, 1 eq) in thionyl chloride (6.09 g, 51.2 mmol, 3.72 mL, 11.5 eq) was stirred at 75 °C for 1.5 hours. The reaction was cooled to 60 °C and an additional portion of 2, 6-dichloro-N'-(p-tolylsulfonyl) benzohydrazide (1.60 g, 4.45 mmol, 1 eq) was added and the reaction was heated back to 75 °C for 1 hour. LC-MS (the sample quenched with piperidine) showed 2, 6-dichloro-N'-(p-tolylsulfonyl) benzohydrazide was consumed completely and the desired mass was detected. The reaction mixture was concentrated to give the desired (1Z)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (1.7 g, crude) as a yellow gum. MS (ESI): mass calcd. For $C_{14}H_{11}Cl_3N_2O_2S$ 375.96, m/z found 426.1 $[M+H+49]^+$.

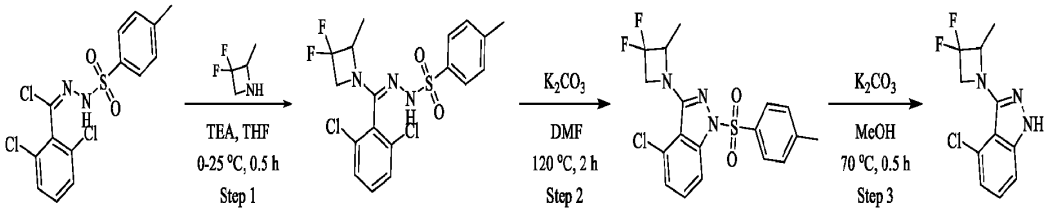
Intermediate-L2: (E)-2, 6-difluoro-N'-tosylbenzohydrazonoyl chloride



[00220] ***Step 1:*** To a solution of 2, 6-difluorobenzoyl chloride (5 g, 28.3 mmol, 3.57 mL, 1 eq) in DCM (50 mL) were added TEA (7.16 g, 70.8 mmol, 9.85 mL, 2.5 eq) and 4-methylbenzenesulfonohydrazide (5.80 g, 31.2 mmol, 1.1 eq). The mixture was stirred at 15 °C for 12 hours. LC-MS showed 2, 6-difluorobenzoyl chloride was consumed completely and one main peak with the desired mass was detected. The crude was added HCl (1M, 100 mL), the reaction mixture was concentrated under reduced pressure to give the desired N'-(2, 6-difluorobenzoyl)-4-methylbenzenesulfonohydrazide (5.0 g, crude) as a white solid. MS (ESI): mass calcd. For $C_{14}H_{12}F_2N_2O_3S$ 326.05, m/z found 327.2 $[M+H]^+$.

[00221] ***Step 2:*** A solution of 2, 6-difluoro-N'-(p-tolylsulfonyl) benzohydrazide (700 mg, 2.15 mmol, 1 eq) in $SOCl_2$ (10 mL) was stirred at 75 °C for 0.5 hour. TLC indicated 2, 6-difluoro-N'-(p-tolylsulfonyl) benzohydrazide was consumed completely and one new spot was formed. The reaction mixture was concentrated under reduced pressure to give the desired (E)-2, 6-difluoro-N'-tosylbenzohydrazonoyl chloride (700 mg, crude) as a light yellow solid.

Intermediate-L3: 4-Chloro-3-(3, 3-difluoro-2-methyl-azetidin-1-yl)-1H-indazole



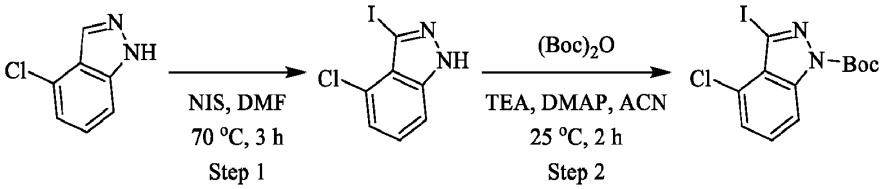
[00222] ***Step 1:*** To a solution of 3, 3-difluoro-2-methyl-azetidine (150 mg, 1.04 mmol, 1 eq, HCl) in THF (2 mL) was added TEA (106 mg, 1.04 mmol, 145 μL, 1 eq) dropwise at 25 °C. After addition, the mixture was stirred at this temperature for 10 minutes, the solution of (1Z)-2,6-dichloro-N-(p-tolylsulfonyl)benzohydrazonoyl chloride (434 mg, 1.15 mmol, 1.1 eq) in THF (2 mL) was added dropwise to the mixture at 0 °C. The resulting mixture was stirred at 25 °C for 20 minutes. LC-MS showed 3, 3-difluoro-2-methyl-azetidine was consumed completely and one main peak with the desired mass was detected. Then it was separated between 20 mL of water

and 40 mL of ethyl acetate. The organic phase was separated, washed with 30 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2,6-dichlorophenyl)-(3, 3-difluoro-2-methyl-azetidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (500 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{18}H_{17}Cl_2F_2N_3O_2S$ 447.04, m/z found 448.2 $[M+H]^+$.

[00223] ***Step 2:*** To a solution of N-[(E)-[(2, 6-dichlorophenyl)-(3, 3-difluoro-2-methyl-azetidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (500 mg, 1.12 mmol, 1 eq) in DMF (10 mL) was added K_2CO_3 (771 mg, 5.58 mmol, 5 eq). The mixture was stirred at 120 °C for 2 hours. LC-MS showed N-[(E)-[(2, 6-dichlorophenyl)-(3, 3-difluoro-2-methyl-azetidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. The reaction mixture was added to water (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(3,3-difluoro-2-methyl-azetidin-1-yl)-1-(p-tolylsulfonyl)indazole (450 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{18}H_{16}ClF_2N_3O_2S$ 411.06, m/z found 412.1 $[M+H]^+$.

[00224] ***Step 3:*** To a solution of 4-chloro-3-(3, 3-difluoro-2-methyl-azetidin-1-yl)-1-(p-tolylsulfonyl) indazole (450 mg, 1.09 mmol, 1 eq) in MeOH (5 mL) was added K_2CO_3 (3.02 g, 21.9 mmol, 20 eq). The mixture was stirred at 70 °C for 0.5 hour. LC-MS showed 4-chloro-3-(3, 3-difluoro-2-methyl-azetidin-1-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ ethyl acetate = 2/1) to give the desired 4-chloro-3-(3,3-difluoro-2-methyl-azetidin-1-yl)-1H-indazole (110 mg, crude) as a white solid. MS (ESI): mass calcd. For $C_{11}H_{10}ClF_2N_3$ 257.05, m/z found 258.0 $[M+H]^+$.

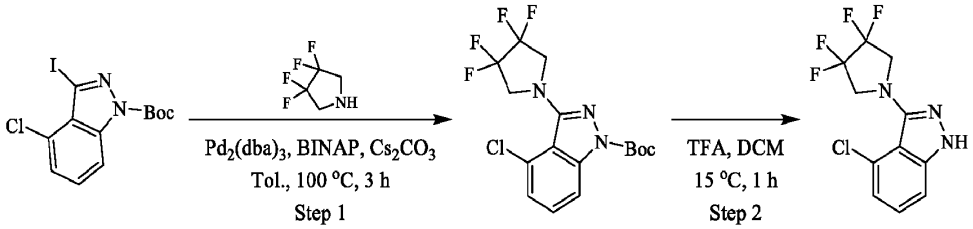
Intermediate-L4: Tert-butyl 4-chloro-3-iodo-1H-indazole-1-carboxylate



[00225] ***Step 1***: To a solution of 4-chloro-1H-indazole (5 g, 32.8 mmol, 1 eq) in DMF (20 mL) was added NIS (8.11 g, 36.1 mmol, 1.1 eq). The mixture was stirred at 70 °C for 3 hours. LC-MS showed 4-chloro-1H-indazole was consumed completely and the desired mass was detected. The crude was added H_2O (50 mL) and extracted with MTBE (50 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-iodo-1H-indazole (8 g, crude) as a yellow solid. MS (ESI): mass calcd. For $C_7H_4ClIN_2$ 277.91 m/z found 278.8 $[M+H]^+$.

[00226] ***Step 2***: To a solution of 4-chloro-3-iodo-1H-indazole (8 g, 28.7 mmol, 1 eq) in ACN (80 mL) were added tertbutoxycarbonyl tert-butyl carbonate (9.40 g, 43.1 mmol, 9.90 mL, 1.5 eq) and TEA (5.81 g, 57.5 mmol, 8.00 mL, 2 eq) and DMAP (3.51 g, 28.7 mmol, 1 eq). The mixture was stirred at 25 °C for 2 hours. LC-MS showed 4-chloro-3-iodo-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was concentrated to give the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~20% EtOAc/petroleum ether gradient @ 80 mL/min) to give the desired tert-butyl 4-chloro-3-iodo-indazole-1-carboxylate (9.5 g, 25.1 mmol, 87.4% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{12}H_{12}ClIN_2O_2$ 377.96 m/z found 322.8 $[M+H-56]^+$.

Intermediate-L5: 4-Chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole

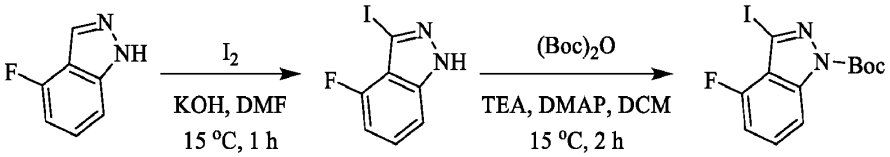


[00227] ***Step 1***: A mixture of tert-butyl 4-chloro-3-iodo-indazole-1-carboxylate (300 mg, 792 μmol, 1 eq), 3, 3, 4, 4-tetrafluoropyrrolidine (142 mg, 792 μmol, 1 eq, HCl), $Pd_2(dba)_3$ (72.6 mg, 79.2 μmol, 0.1 eq), Cs_2CO_3 (775 mg, 2.38 mmol, 3 eq) and BINAP (49.3 mg, 79.2 μmol, 0.1 eq) in toluene (2 mL) was degassed and purged with N_2 for 3 times. The mixture was stirred at 100 °C for 3 hours under N_2 atmosphere. LC-MS showed tert-butyl 4-chloro-3-iodo-indazole-1-carboxylate was consumed completely and the desired mass was detected. To the crude was added H_2O (20 mL), and the resulting solution was extracted with EtOAc (15 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and

concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ethyl acetate = 3/1) give the desired tert-butyl 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole-1-carboxylate (200 mg, 508 μmol, 64.1% yield) as a yellow oil. MS (ESI): mass calcd. For $C_{16}H_{16}ClF_4N_3O_2$ 393.09 m/z found 338.1 $[M+H-56]^+$.

[00228] ***Step 2***: To a solution of tert-butyl 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole-1-carboxylate (200 mg, 508 μmol, 1 eq) in DCM (2 mL) was added TFA (1.45 g, 12.7 mmol, 943 μL, 25 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed tert-butyl 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole-1-carboxylate was consumed completely and the desired mass was detected. The reaction mixture was concentrated in vacuum to give the desired 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (200 mg, crude, TFA) as a brown oil. MS (ESI): mass calcd. For $C_{11}H_8ClF_4N_3$ 293.03 m/z found 294.0 $[M+H]^+$.

Intermediate-L6: Tert-butyl 4-fluoro-3-iodo-indazole-1-carboxylate



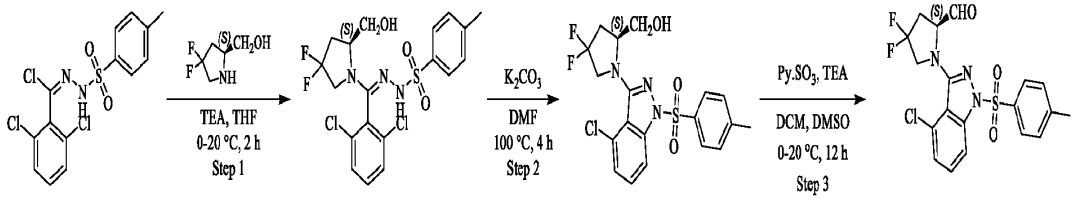
[00229] ***Step 1***: To a solution of I_2 (3.73 g, 14.7 mmol, 2.96 mL, 1 eq) in DMF (15 mL) were added 4-fluoro-1H-indazole (2 g, 14.7 mmol, 1 eq) and KOH (824 mg, 14.7 mmol, 1 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-fluoro-1H-indazole was remained and the desired compound was detected. The reaction mixture was quenched by addition sat. aq. $NaHCO_3$ (30 mL) at 15 °C, and then diluted with EtOAc (50 mL) and extracted with H_2O (30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-fluoro-3-iodo-1H-indazole (5.16 g, crude) as a red solid. MS (ESI): mass calcd. For $C_7H_4FIN_2$ 261.94, m/z found 262.9 $[M+H]^+$.

[00230] ***Step 2***: To a solution of 4-fluoro-3-iodo-1H-indazole (500 mg, 1.91 mmol, 1 eq) and tert-butoxycarbonyl tert-butyl carbonate (541 mg, 2.48 mmol, 570 μL, 1.3 eq) in DCM (5 mL) were added TEA (1.93 g, 19.1 mmol, 2.66 mL, 10 eq) and DMAP (23.3 mg, 191 μmol, 0.1 eq). The mixture was stirred at 15 °C for 2 hours. LC-MS showed 4-fluoro-3-iodo-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 30 mL of EtOAc. The organic phase was separated, washed with 10 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the

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crude product. The residue was purified by column chromatography (silica gel, petroleum ether/ ethyl acetate =5/1 to 4/1) to give the desired tert-butyl 4-fluoro-3-iodo-indazole-1-carboxylate (300 mg, 828 μmol, 43.4% yield) as an orange solid. MS (ESI): mass calcd. For $C_{12}H_{12}FIN_2O_2$ 361.99, m/z found 306.9 $[M+H-56]^+$.

Intermediate-L7: (2S)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidine-2-carbaldehyde



[00231] ***Step 1***: To a solution of [(2S)-4, 4-difluoropyrrolidin-2-yl] methanol (0.7 g, 4.03 mmol, 1 eq, HCl) in THF (10 mL) was added TEA (1.22 g, 12.1 mmol, 1.68 mL, 3 eq), and then the solution of (E)-2,6-dichloro-N-tosylbenzohydrazonoyl chloride (1.68 g, 4.44 mmol, 1.1 eq) in THF (10 mL) was added dropwise at 0 °C. The mixture was stirred at 20 °C for 2 hours. LC-MS showed [(2S)-4, 4-difluoropyrrolidin-2-yl] methanol was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added H_2O (100 mL) and extracted with EtOAc (50 mL X 3). The combined organic phase was washed with brine (30 mL X 2), dried over Na_2SO_4, filtered, and concentrated in vacuum to give the desired N-[(E)-[(2, 6-dichlorophenyl)-[(2S)-4, 4-difluoro-2-(hydroxymethyl) pyrrolidin-1-yl] methylene] amino] - 4-methyl-benzenesulfonamide (2 g, crude) as an orange solid. MS (ESI): mass calcd. For $C_{19}H_{19}Cl_2F_2N_3O_3S$ 477.05, m/z found 478.1 $[M+H]^+$.

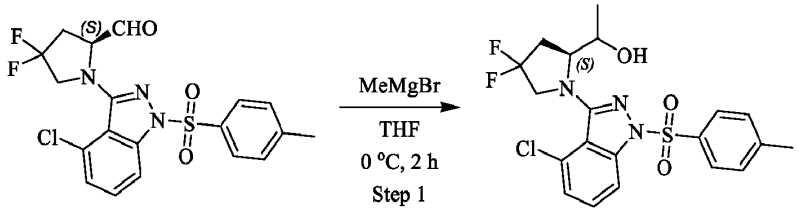
[00232] ***Step 2***: To a solution of N-[(E)- [(2, 6-dichlorophenyl)-[(2S)-4, 4-difluoro-2-(hydroxymethyl) pyrrolidin-1- yl] methylene] amino]-4-methyl-benzenesulfonamide (2 g, 4.18 mmol, 1 eq) in DMF (20 mL) was added K_2CO_3 (1.73 g, 12.5 mmol, 3 eq). The mixture was stirred at 100 °C for 4 hours. LC-MS showed N-[(E)- [(2, 6-dichlorophenyl)-[(2S)-4, 4-difluoro-2-(hydroxymethyl) pyrrolidin-1-yl] methylene] amino] - 4-methyl-benzenesulfonamide remained and the desired compound was detected. The reaction mixture was added H_2O (200 mL) and extracted with EtOAc (100 mL X 3). The combined organic phase was washed with brine (100 mL X 2), dried over Na_2SO_4, filtered, and concentrated in vacuum to give the desired [(2S)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol (1.5 g, crude) as

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a yellow solid. MS (ESI): mass calcd. For $C_{19}H_{18}ClF_2N_3O_3S$ 441.07, m/z found 460.2 $[M+H+18]^+$.

[00233] ***Step 3***: To a solution of pyridine; sulfur trioxide (630 mg, 3.96 mmol, 3.5 eq) in DCM (10 mL) and DMSO (2 mL) was added TEA (687 mg, 6.79 mmol, 945 μL, 6 eq). The mixture was stirred at 0 °C for 1 hour. Then [(2S)-1- [4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol (500 mg, 1.13 mmol, 1 eq) was added into the reaction mixture. The reaction mixture was stirred at 20 °C for 11 hours. LC-MS showed [(2S)-1- [4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added H_2O (100 mL) and extracted with MTBE (50 mL X 3). The combined organic phase was washed with brine (50 mL X 2), dried over Na_2SO_4, filtered, and concentrated in vacuum to give the desired (2S)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidine-2-carbaldehyde (500 mg, crude) as a purple solid. MS (ESI): mass calcd. For $C_{19}H_{16}ClF_2N_3O_3S$ 439.06, m/z found 440.1 $[M+H]^+$.

Intermediate-L8: 1-((S)-1-(4-chloro-1-tosyl-1H-indazol-3-yl)-4,4-difluoropyrrolidin-2-yl)ethan-1-ol

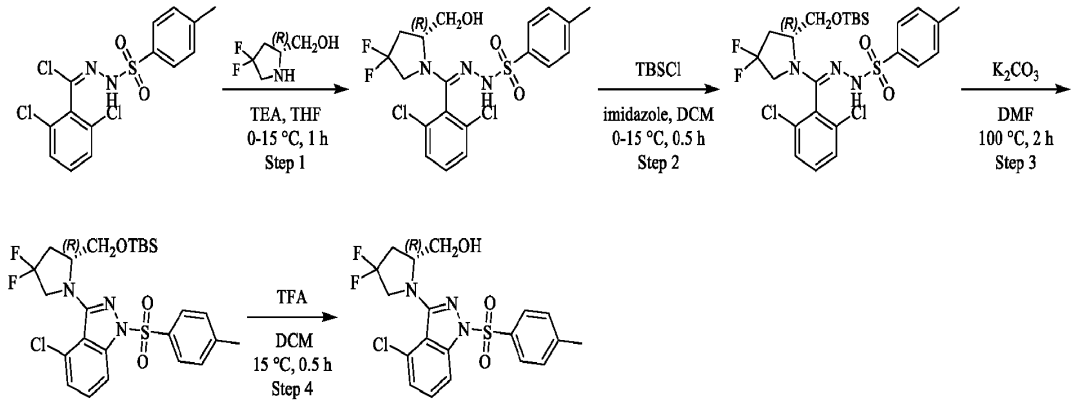


[00234] ***Step 1***: To a solution of (2S)-1-[4-chloro-1-(p-tolylsulfonyl)indazol-3-yl]-4,4-difluoro-pyrrolidine-2-carbaldehyde (500 mg, 1.14 mmol, 1 eq) in THF (10 mL) was added MeMgBr (3 M, 757 μL, 2 eq) under N_2 atmosphere. The mixture was stirred at 0 °C for 2 hours. LC-MS showed (S)-1-(4-chloro-1-tosyl-1H-indazol-3-yl)-4, 4-difluoropyrrolidine-2-carbaldehyde was consumed completely and one main peak with the desired mass was detected. The reaction mixture was quenched by HCl (1M, 20 ml), then added H_2O (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic phase was washed with brine (10 mL X 2), dried over Na_2SO_4, filtered, and concentrated in vacuum to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 45%-75% B over 8.0 min) to give the desired

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1-((S)-1-(4-chloro-1-tosyl-1H-indazol-3-yl)-4,4-difluoropyrrolidin-2-yl)ethan-1-ol (80 mg, 157.9 µmol, 13.9% yield, 90% purity) as a white solid. MS (ESI): mass calcd. For $C_{20}H_{20}ClF_2N_3O_3S$ 455.09, m/z found 456.2 $[M+H]^+$.

Intermediate-L9: [(2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol



[00235] ***Step 1***: To a solution of [(2R)-4, 4-difluoropyrrolidin-2-yl]methanol (500 mg, 2.88 mmol, 1 eq, HCl) in THF (10 mL) were added TEA (1.17 g, 11.5 mmol, 1.60 mL, 4 eq) and (1E)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (1.20 g, 3.17 mmol, 1.1 eq) at 0 °C. The mixture was stirred at 15 °C for 1 hour. LC-MS showed [(2R)-4, 4-difluoropyrrolidin-2-yl] methanol was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 30 mL of H_2O and 50 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2,6-dichlorophenyl)-[(2R)-4, 4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl] methylene] amino]-4-methyl-benzenesulfonamide (1.38 g, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{19}H_{19}Cl_2F_2N_3O_3S$ 477.0, m/z found 478.0 $[M+H]^+$.

[00236] ***Step 2***: To a solution of N-[(E)-[(2, 6-dichlorophenyl)-[(2R)-4, 4-difluoro-2-(hydroxymethyl) pyrrolidin-1-yl] methylene] amino]-4-methyl-benzenesulfonamide (400 mg, 836 µmol, 1 eq) in DCM (5 mL) were added imidazole (114 mg, 1.67 mmol, 2 eq) and tert-butyl-chloro-dimethyl-silane (151 mg, 1.00 mmol, 124 µL, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed N-[(E)-[(2, 6-dichlorophenyl)-[(2R)-4, 4-difluoro-2- (hydroxymethyl) pyrrolidin-1-yl] methylene] amino]-4-methyl-benzenesulfonamide

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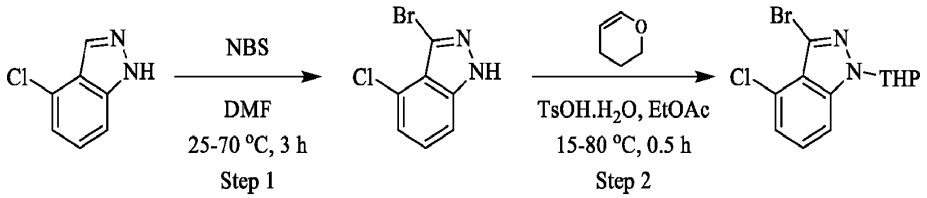
was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 20 mL of H_2O and 30 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by flash silica gel chromatography (ISCO®;20 g SepaFlash® Silica Flash Column, Eluent of 0~5% Ethyl acetate/petroleum ether gradient @ 60 mL/min) to give the desired (R,E)-N'-((2-(((tert-butyldimethylsilyl)oxy)methyl)-4,4-difluoropyrrolidin-1-yl)(2,6-dichlorophenyl)methylene)-4-methylbenzenesulfonohydrazide (320 mg, 540 μmol, 64.6% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{25}H_{33}Cl_2F_2N_3O_3SSi$ 591.1, m/z found 592.1 $[M+H]^+$.

[00237] ***Step 3***: To a solution of (R,E)-N'-((2-(((tert-butyldimethylsilyl)oxy)methyl)-4,4-difluoropyrrolidin-1-yl)(2,6-dichlorophenyl)methylene)-4-methylbenzenesulfonohydrazide (320 mg, 540 μmol, 1 eq) in DMF (6 mL) was added K_2CO_3 (746 mg, 5.40 mmol, 10 eq). The mixture was stirred at 100 °C for 2 hours. LC-MS showed (R,E)-N'-((2-(((tert-butyldimethylsilyl)oxy)methyl)-4,4-difluoropyrrolidin-1-yl)(2,6-dichlorophenyl)methylene)-4-methylbenzenesulfonohydrazide was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 40 mL of H_2O and 50 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired tert-butyl-dimethyl-[[(2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methoxy] silane (210 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{25}H_{32}ClF_2N_3O_3SSi$ 555.2, m/z found 556.1 $[M+H]^+$.

[00238] ***Step 4***: To a solution of tert-butyl-dimethyl-[[(2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methoxy] silane (200 mg, 360 μmol, 1 eq) in DCM (4 mL) was added TFA (3.07 g, 26.9 mmol, 2 mL, 74.9 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed tert-butyl-dimethyl-[[(2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methoxy] silane was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 30 mL of H_2O and 40 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether/Ethyl acetate = 1/1) to give the desired [(2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol (70 mg, 158

μmol, 44.1% yield) as a white solid. MS (ESI): mass calcd. For $C_{19}H_{18}ClF_2N_3O_3S$ 444.1, m/z found 445.0 $[M+H]^+$.

Intermediate-L10: 3-Bromo-4-chloro-1-tetrahydropyran-3-yl-indazole

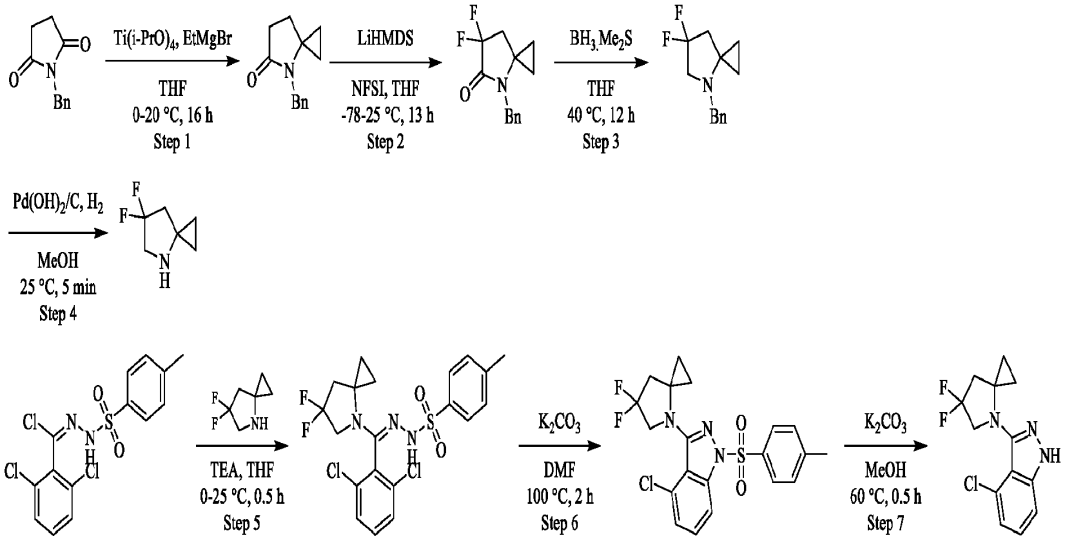


[00239] ***Step 1***: To a solution of 4-chloro-1H-indazole (5 g, 32.8 mmol, 1 eq) in DMF (50 mL) was added NBS (6.42 g, 36.1 mmol, 1.1 eq) at 25 °C. The mixture was stirred at 70 °C for 3 hours. LC-MS showed 4-chloro-1H-indazole was consumed completely and the desired mass was detected. Pour the reaction to H_2O (150 mL) at 25 °C and stir the mixture at 25 °C for 0.5 hour. Filter and washed the filter cake with H_2O (100 mL X 2). Collect the solid and dry under reduced pressure to give the desired 3-bromo-4-chloro-1H-indazole (7.5 g, 32.40 mmol, 98.9% yield) as a yellow solid. MS (ESI): mass calcd. For $C_7H_4BrClN_2$ 229.92, m/z found 230.9 $[M+H]^+$.

[00240] ***Step 2***: To a solution of 3-bromo-4-chloro-1H-indazole (6.5 g, 28.1 mmol, 1 eq) in EtOAc (60 mL) were added $TsOH.H_2O$ (534 mg, 2.81 mmol, 0.1 eq) and DHP (3.54 g, 42.1 mmol, 3.85 mL, 1.5 eq) at 15 °C. The mixture was stirred at 80 °C for 0.5 hour. LC-MS showed a little 3-bromo-4-chloro-1H-indazole remained. Several new peaks were shown on LC-MS and the desired compound was detected. The reaction mixture was added to water (200 mL) and extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/petroleum ether gradient @ 100 mL/min) to give the desired 3-bromo-4-chloro-1-tetrahydropyran-3-yl-indazole (6.1 g, 19.3 mmol, 68.8% yield) as a white solid. MS (ESI): mass calcd. For $C_{12}H_{12}BrClN_2O$ 313.98, m/z found 315.0 $[M+H]^+$.

Intermediate-L11: 4-Chloro-3-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl)-1H-indazole

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[00241] ***Step 1***: To a solution of 1-benzylpyrrolidine-2, 5-dione (3 g, 15.9 mmol, 1 eq) in THF (30 mL) were added Ti(i-PrO)$_4$ (22.5 g, 79.3 mmol, 23.4 mL, 5 eq) and EtMgBr (3 M, 18.5 mL, 3.5 eq) at 0 °C. The mixture was stirred at 20 °C for 12 hours. LC-MS showed 1-benzylpyrrolidine-2, 5-dione was consumed completely. $BF_3.Et_2O$ (11.3 g, 79.3 mmol, 9.75 mL, 5 eq) was added to the mixture. The mixture was stirred at 20 °C for 4 hours. LC-MS showed 1-benzylpyrrolidine-2, 5-dione was consumed completely and one main peak with the desired mass was detected. The reaction mixture was quenched by 3N hydrochloric acid (30 mL) and extracted with EtOAc (60 mL X 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (0.1% TFA condition) to give the desired 4-benzyl-4-azaspiro [2.4] heptan-5-one (2 g, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{15}NO$ 201.0, m/z found 202.2 $[M+H]^+$.

[00242] ***Step 2***: To a solution of 4-benzyl-4-azaspiro [2.4] heptan-5-one (450 mg, 2.24 mmol, 1 eq) in THF (20 mL) was added LiHMDS (1 M, 8.94 mL, 4 eq) at -78 °C under N_2. The mixture was stirred at -78 °C for 1 hour. NFSI (2.82 g, 8.94 mmol, 4 eq) in THF (10 mL) was added to the mixture at -78 °C. The mixture was stirred at 25 °C for 12 hours. LC-MS showed 4-benzyl-4-azaspiro [2.4] heptan-5-one remained. Several new peaks were shown on LC-MS and the desired compound was detected. The reaction mixture was quenched by addition saturated aqueous NH_4Cl (200 mL) at 0 °C, and extracted with EtOAc (300 mL X 3). The combined organic phase was washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuum*. The

residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75*30mm*3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 30%-55% B over 8.0 min) to give the desired 4-benzyl-6, 6-difluoro-4-azaspiro [2.4] heptan-5-one (100 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{13}F_2NO$ 237.10, m/z found 238.2 $[M+H]^+$.

[00243] ***Step 3***: To a solution of 4-benzyl-6, 6-difluoro-4-azaspiro [2.4] heptan-5-one (110 mg, 464 μmol, 1 eq) in THF (3 mL) was added BH_3-Me_2S (10 M, 92.7 μL, 2 eq). The mixture was stirred at 40 °C for 12 hours. LC-MS showed 4-benzyl-6, 6-difluoro-4-azaspiro [2.4] heptan-5-one was consumed completely and the desired compound was detected. MeOH (1 mL) was added dropwise to the mixture at 0 °C, then the mixture was stirred at 80 °C for 0.5 hour. The reaction mixture was quenched by addition HCl (1M, 1 mL) and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75*30mm*3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 20%-45% B over 8.0 min) to give the desired 4-benzyl-6, 6-difluoro-4-azaspiro [2.4] heptane (85 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{15}F_2N$ 223.12, m/z found 224.2 $[M+H]^-$.

[00244] ***Step 4***: Two reactions were carried out in parallel. A mixture of 4-benzyl-6, 6-difluoro-4-azaspiro [2.4] heptane (30 mg, 134 μmol, 1 eq), $Pd(OH)_2/C$ (40 mg, 28.5 μmol, 10% purity, 2.12 e^{-1} eq) in MeOH (5 mL) was degassed and purged with H_2(15 psi) for 3 times, and then the mixture was stirred at 25 °C for 5 min under H_2 atmosphere. LC-MS showed 4-benzyl-6, 6-difluoro-4-azaspiro [2.4] heptane was consumed completely, and the desired mass was detected. Two reactions were combined for workup. The reaction mixture was filtered, and concentrated under reduced pressure to give the desired 6, 6-difluoro-4-azaspiro [2.4] heptane (40 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_6H_9F_2N$ 133.07, m/z found 134.2 $[M+H]^+$.

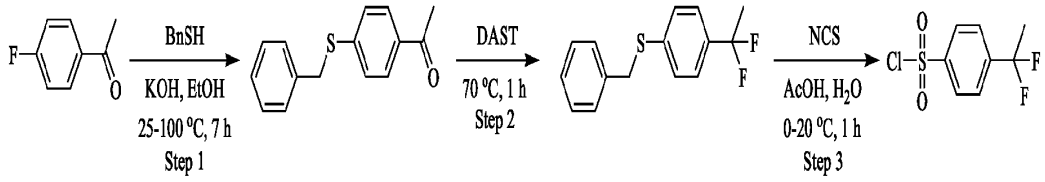
[00245] ***Step 5***: To a solution of 6, 6-difluoro-4-azaspiro [2.4] heptane (35 mg, 263 μmol, 1 eq) in THF (1 mL) was added dropwise TEA (266 mg, 2.63 mmol, 366 μL, 10 eq) at 25 °C. After addition, the mixture was stirred at this temperature for 10 min, and then (1Z)-2,6-dichloro-N-(p-tolylsulfonyl)benzohydrazonoyl chloride (99.3 mg, 263 μmol, 1 eq) in THF (1 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 20 min. LC-MS showed 6, 6-difluoro-4-azaspiro [2.4] heptane was consumed completely and one main peak with the desired mass was detected. Then it was separated between 20 mL of water and 40 mL of ethyl acetate. The organic phase was separated, washed with 30 mL of brine, dried over Na_2SO_4,

filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2,6-dichlorophenyl)-(6,6-difluoro-4-azaspiro[2.4]heptan-4-yl)methylene]amino]-4-methyl-benzenesulfonamide (140 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{20}H_{19}Cl_2F_2N_3O_2S$ 473.05, m/z found 474.0 $[M+H]^+$.

[00246] ***Step 6***: Two reactions were carried out in parallel. To a solution of N-[(E)-[(2, 6-dichlorophenyl)-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl) methylene] amino]-4-methyl-benzenesulfonamide (70 mg, 148 μmol, 1 eq) in DMF (3 mL) was added K_2CO_3 (102 mg, 738 μmol, 5 eq). The mixture was stirred at 100 °C for 2 hours. LC-MS showed N-[(E)-[(2, 6-dichlorophenyl)-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. Two reactions were combined for workup. The reaction mixture was added to water (5 mL) and extracted with EtOAc (3 mL X 3). The combined organic layers were washed with brine (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(6,6-difluoro-4-azaspiro[2.4]heptan-4-yl)-1-(p-tolylsulfonyl)indazole (120 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{18}ClF_2N_3O_2S$ 437.08, m/z found 438.1 $[M+H]^+$.

[00247] ***Step 7***: To a solution of 4-chloro-3-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl)-1-(p-tolylsulfonyl) indazole (120 mg, 274 μmol, 1 eq) in MeOH (3 mL) was added K_2CO_3 (189 mg, 1.37 mmol, 5 eq). The mixture was stirred at 60 °C for 0.5 hour. LC-MS showed 4-chloro-3-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (5 mL) and extracted with EtOAc (3 mL X 3). The combined organic layers were washed with brine (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl)-1H-indazole (25 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{12}ClF_2N_3$ 283.07, m/z found 284.0 $[M+H]^+$.

Intermediate-R1: 4-(1, 1-Difluoroethyl) benzenesulfonyl chloride

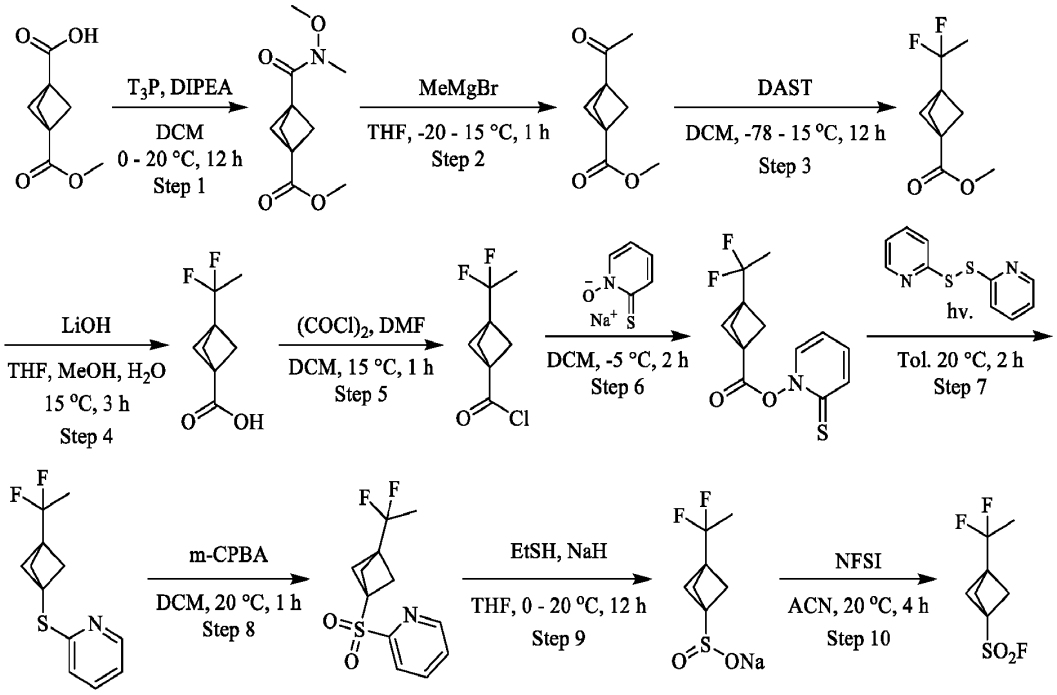


[00248] ***Step 1***: KOH (3.25 g, 57.9 mmol, 1 eq) was added to a solution of phenylmethanethiol (7.91 g, 63.7 mmol, 7.46 mL, 1.1 eq) in EtOH (100 mL). The mixture was heated to reflux until the KOH was completely dissolved and then cooled to 25 °C. A solution of 1-(4-fluorophenyl) ethanone (8 g, 57.9 mmol, 7.02 mL, 1 eq) in EtOH (20 mL) was added dropwise to the mixture and the mixture was heated to 100 °C for 7 hours. TLC (petroleum ether/ ethyl acetate = 5/1) indicated 1-(4-fluorophenyl) ethanone was consumed completely and one new spot was formed. The crude was added H_2O (100 mL) and extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ ethyl acetate = 5/1) to give the desired 1-(4-benzylsulfanylphenyl) ethanone (14 g, crude) as a brown oil.

[00249] ***Step 2***: A solution of 1-(4-benzylsulfanylphenyl) ethanone (12 g, 49.5 mmol, 1 eq) in DAST (120 mL) was stirred at 70 °C for 1 hour. TLC (petroleum ether/ ethyl acetate = 5/1) indicated 1-(4-benzylsulfanylphenyl) ethanone was consumed completely and two new spots were formed. The reaction mixture was partitioned between water (200 mL) and EtOAc (150 mL X 3). The organic phase was separated, washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 SepaFlash® Silica Flash Column, Eluent of 0~5% EtOAc/petroleum ether gradient @ 80 mL/min) to give the desired 1-benzylsulfanyl-4-(1, 1-difluoroethyl) benzene (2.5 g, 9.46 mmol, 19.1% yield) as a white solid.

[00250] ***Step 3***: To a solution of 1-benzylsulfanyl-4-(1, 1-difluoroethyl) benzene (2.5 g, 9.46 mmol, 1 eq) in AcOH (20 mL) and H_2O (5 mL) was added NCS (5.05 g, 37.8 mmol, 4 eq) at 0 °C. The mixture was stirred at 20 °C for 1 hour. LC-MS showed 1-benzylsulfanyl-4-(1, 1-difluoroethyl) benzene was consumed completely and the desired mass was detected (the sample quenched with piperidine). The reaction mixture was filtered, and the filter liquor was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~5% EtOAc/petroleum ether gradient @ 60 mL/min) to give the desired 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (1.33 g, 5.53 mmol, 58.4% yield) as a yellow oil. MS (ESI): mass calcd. For $C_8H_7F_2SO_2Cl$ 239.98, mass found 290.1$[M+H+49]^+$.

Intermediate-R2: 3-(1, 1-Difluoroethyl) bicycle [1.1.1] pentane-1-sulfonyl fluoride



[00251] ***Step 1:*** To the mixture of 3-methoxycarbonylbicyclo[1.1.1]pentane-1-carboxylic acid (2 g, 11.8 mmol, 1 eq), N-methoxymethanamine (1.15 g, 11.8 mmol, 1 eq, HCl) and DIPEA (9.11 g, 70.5 mmol, 12.3 mL, 6 eq) in DCM (50 mL) was added T_3P (12.7 g, 20.0 mmol, 11.9 mL, 50% purity, 1.70 eq) at 0 °C under the atmosphere of nitrogen. The mixture was stirred at 20 °C for 12 hours. TLC showed 3-methoxycarbonylbicyclo [1.1.1] pentane-1-carboxylic acid was consumed completely and a new spot was formed. The reaction was added DCM (50 mL). The mixture was washed with water (50 mL) and HCl (50 mL, 1M). The organic phase was separated, washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate/petroleum ether gradient @ 60 mL/min) to give the desired methyl 3-[methoxy (methyl) carbamoyl] bicycle [1.1.1] pentane-1-carboxylate (2.3 g, 10.8 mmol, 91.8% yield) as a white solid. ^1H NMR (Chloroform-*d*) δ 3.69 (s, 3H), 3.67 (s, 3H), 3.18 (s, 3H), 2.38 (s, 6H).

[00252] ***Step 2:*** To a solution of methyl 3-[methoxy (methyl) carbamoyl] bicycle [1.1.1] pentane-1-carboxylate (1.8 g, 8.44 mmol, 1 eq) in THF (18 mL) was added MeMgBr (3 M, 2.81 mL, 1 eq) at -20 °C under the atmosphere of nitrogen. The mixture was stirred at 15 °C for 1

hour. TLC indicated methyl 3-[methoxy (methyl) carbamoyl] bicycle [1.1.1] pentane-1-carboxylate was consumed completely and one new spot was formed. The reaction mixture was quenched by addition saturated aqueous NH_4Cl (50 mL) at 0°C slowly under N_2 and stirred at 25 °C for 15 minutes. THF was removed in vacuum. The resulting solution was diluted with water (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic phase was washed with brine (30 mL X 2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate/petroleum ethergradient @ 80 mL/min) to give the desired methyl 3-acetylbicyclo[1.1.1]pentane-1-carboxylate (700 mg, 4.16 mmol, 49.3% yield) as a light yellow solid.

[00253] ***Step 3:*** To a solution of methyl 3-acetylbicyclo [1.1.1] pentane-1-carboxylate (700 mg, 4.16 mmol, 1 eq) in DCM (10 mL) was added DAST (6.71 g, 41.6 mmol, 5.50 mL, 10 eq) at -78 °C. The mixture was stirred at 15 °C for 12 hours. TLC indicated methyl 3-acetylbicyclo [1.1.1] pentane-1-carboxylate was consumed completely and one new spot was formed. The reaction was quenched by saturated sodium bicarbonate solution (50 ml) and extracted with EtOAc (50 mL X 3). The organic phase was separated, washed with brine (30 mL X 2), dried over Na_2SO_4, filtered, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate / petroleum ether gradient @ 80 mL/min) to give the desired methyl 3-(1, 1-difluoroethyl) bicycle [1.1.1] pentane-1-carboxylate (450 mg, 2.37 mmol, 56.9% yield) as a light-yellow solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 3.71 - 3.68 (m, 3H), 2.14 - 2.09 (m, 6H), 1.63 - 1.47 (m, 3H).

[00254] ***Step 4:*** To a solution of methyl 3-(1, 1-difluoroethyl) bicycle [1.1.1] pentane-1-carboxylate (450 mg, 2.37 mmol, 1 eq) in H_2O (1 mL), MeOH (1 mL) and THF (3 mL) was added LiOH (113 mg, 4.73 mmol, 2 eq). The mixture was stirred at 15 °C for 3 hours. TLC indicated methyl 3-(1, 1-difluoroethyl) bicycle [1.1.1] pentane-1-carboxylate was consumed completely and one new spot was formed. The pH value of the reaction mixture was adjusted to 3~4 with 1N HCl, then the reaction mixture was partitioned between H_2O (30 mL) and EtOAc (20 mL X 3). The organic phase was separated, washed with brine (15 mL X 2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 3-(1,1-difluoroethyl) bicycle [1.1.1] pentane-1-carboxylic acid (300 mg, crude) as a white solid.

[00255] ***Step 5:*** To the mixture of 3-(1, 1-difluoroethyl) bicycle [1.1.1] pentane-1-carboxylic acid (280 mg, 1.59 mmol, 1 eq) and DMF (11.6 mg, 159 μmol, 12.2 μL, 0.1 eq) in DCM (3 mL) was added $(COCl)_2$ (242 mg, 1.91 mmol, 167 μL, 1.2 eq) at 15 °C and the mixture was stirred at 15 °C for 1 hour. TLC indicated 3-(1, 1-difluoroethyl) bicycle [1.1.1] pentane-1-carboxylic acid was consumed completely and a new spot was detected. The reaction was concentrated under reduced pressure to give the desired 3-(1, 1-difluoroethyl) bicycle [1.1.1] pentane-1-carbonyl chloride (300 mg, crude) as a yellow oil.

[00256] ***Step 6:*** To the mixture of 3-(1, 1-difluoroethyl) bicycle [1.1.1] pentane-1-carbonyl chloride (300 mg, 1.54 mmol, 1 eq) in DCM (2 mL) was added sodium;1-oxidopyridin-1-ium-2-thiolate (252 mg, 1.70 mmol, 207 μL, 1.1 eq) at -5 °C and the mixture was stirred at -5 °C for 2 hours. TLC indicated 3-(1, 1-difluoroethyl) bicycle [1.1.1] pentane-1-carbonyl chloride was consumed completely and a new spot was detected. The reaction was concentrated under reduced pressure to give the desired (2-thioxo-1-pyridyl) 3-(1, 1-difluoroethyl) bicycle [1.1.1] pentane-1-carboxylate (430 mg, crude) as a yellow solid.

[00257] ***Step 7:*** The mixture of (2-thioxo-1-pyridyl) 3-(1, 1-difluoroethyl) bicycle [1.1.1] pentane-1-carboxylate (430 mg, 1.51 mmol, 1 eq) and 2-(2-pyridyldisulfanyl) pyridine (996 mg, 4.52 mmol, 3 eq) in toluene (20 mL) was degassed with Ar for 3 times and irradiated with a 2000 W halogen lamp under argon atmosphere at 20 °C for 2 hours. LCMS showed (2-thioxo-1-pyridyl) 3-(1, 1-difluoroethyl) bicycle [1.1.1] pentane-1-carboxylate was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate/petroleum ether gradient @ 80 mL/min) to give the desired 2-[[3-(1, 1-difluoroethyl)-1-bicyclo [1.1.1] pentanyl] sulfanyl] pyridine (162 mg, crude) as a colorless oil. MS (ESI): mass calcd. For $C_{12}H_{13}F_2SN$ 241.07 m/z found 242.0 $[M+H]^+$.

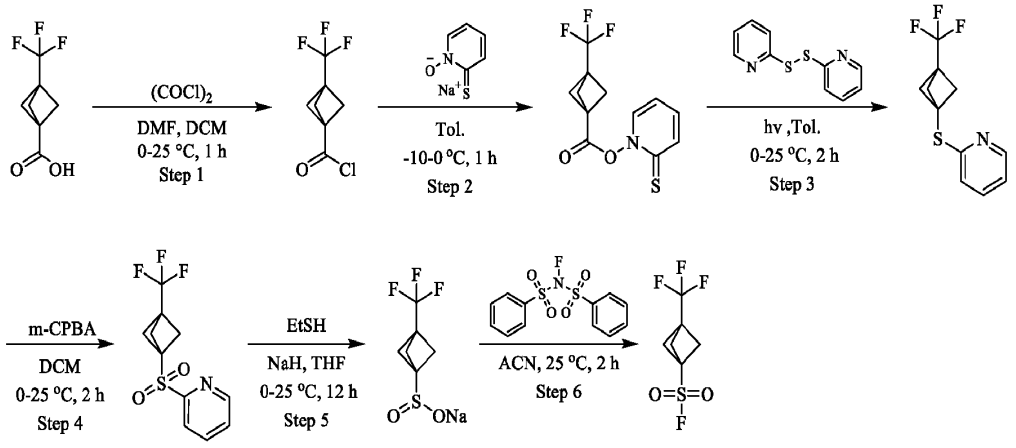
[00258] ***Step 8:*** To the mixture of 2-[[3-(1, 1-difluoroethyl)-1-bicyclo [1.1.1] pentanyl] sulfanyl] pyridine (160 mg, 663 μmol, 1 eq) in DCM (10 mL) was added *m*-CPBA (404 mg, 1.99 mmol, 85% purity, 3 eq) at 20 °C and the mixture was stirred at 20 °C for 1 hour. LCMS showed 2-[[3-(1, 1-difluoroethyl)-1-bicyclo [1.1.1] pentanyl] sulfanyl] pyridine was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®;

40 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate/petroleum ether gradient @ 80 mL/min) to give the desired 2-[[3-(1, 1-difluoroethyl)-1-bicyclo [1.1.1] pentanyl] sulfanyl] pyridine (162 mg, crude) as a colorless oil. MS (ESI): mass calcd. For $C_{12}H_{13}F_2SNO_2$ 273.06 m/z found 274.0 $[M+H]^+$.

[00259] ***Step 9:*** To the mixture of NaH (22.0 mg, 549 μmol, 60% purity, 1.5 eq) in THF (2 mL) was added EtSH (0.3 g, 4.83 mmol, 357 μL, 13.2 eq) at 0 °C and the mixture was stirred at 0 °C for 1 hour. To the mixture was added 2-[[3-(1, 1-difluoroethyl)-1-bicyclo [1.1.1] pentanyl] sulfonyl] pyridine (100 mg, 366 μmol, 1 eq) and the mixture was stirred at 20 °C for 11 hours. TLC showed 2-[[3-(1, 1-difluoroethyl)-1-bicyclo [1.1.1] pentanyl] sulfonyl] pyridine was consumed completely and a new spot was detected. The mixture was diluted with MTBE (10 mL), the precipitate was filtered, washed with MTBE (10 mL), and dried in vacuo to give the desired [3-(1, 1-difluoroethyl)-1-bicyclo [1.1.1] pentanyl] sulfinyloxysodium (40 mg, crude) as a white solid which was used into next directly.

[00260] ***Step 10:*** To the mixture of [3-(1, 1-difluoroethyl)-1-bicyclo [1.1.1] pentanyl] sulfinyloxysodium (40 mg, 183 μmol, 1 eq) in ACN (2 mL) was added NFSI (86.7 mg, 275 μmol, 1.5 eq) at 20 °C and the mixture was stirred at 20 °C for 4 hours. TLC showed [3-(1, 1-difluoroethyl)-1-bicyclo [1.1.1] pentanyl] sulfinyloxysodium was consumed completely and a new spot was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate / petroleum ether gradient @ 40 mL/min) to give the desired 3-(1, 1-difluoroethyl) bicycle [1.1.1] pentane-1-sulfonyl fluoride (27.9 mg, 130 μmol, 71.1% yield) as a white solid. ^{1}H NMR (Chloroform-d) δ: 2.47 (s, 6H), 1.62 (m, 3H).

Intermediate-R3: 3-(Trifluoromethyl) bicycle [1.1.1] pentane-1-sulfonyl fluoride



[00261] ***Step 1:*** To a solution of 3-(trifluoromethyl) bicycle [1.1.1] pentane-1-carboxylic acid (2 g, 11.1 mmol, 1 eq) in DCM (30 mL) was added DMF (81.2 mg, 1.11 mmol, 85.4 µL, 0.1 eq) was degassed and purged with N_2 for 3 times. To the mixture was added $(COCl)_2$ (1.83 g, 14.4 mmol, 1.26 mL, 1.3 eq) at 0 °C. The mixture was stirred at 25 °C for 1 hour under N_2 atmosphere. TLC (petroleum ether/ ethyl acetate = 3/1) indicated 3-(trifluoromethyl) bicycle [1.1.1] pentane-1-carboxylic acid was consumed completely and one new spot was formed (quenched with MeOH 0.5 mL). The reaction mixture was concentrated to give the desired 3-(trifluoromethyl) bicycle [1.1.1] pentane-1-carbonyl chloride (2 g, crude) as a yellow oil.

[00262] ***Step 2:*** The mixture of sodium; 1-oxidopyridin-1-ium-2-thiolate (2.55 g, 17.1 mmol, 2.09 mL, 1.7 eq) in toluene (5 mL) was degassed and purged with Ar for 3 times. To the mixture was added 3-(trifluoromethyl) bicycle [1.1.1] pentane-1-carbonyl chloride (2 g, 10.1 mmol, 1 eq) at -10 °C. The mixture was stirred at 0 °C for 1 hour under Ar atmosphere in dark**.** LCMS showed 3-(trifluoromethyl) bicycle [1.1.1] pentane-1-carbonyl chloride was consumed completely and the desired mass was detected. The reaction mixture was concentrated to give the desired (2-thioxo-1-pyridyl) 3-(trifluoromethyl) bicycle [1.1.1] pentane-1-carboxylate (2 g, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{12}H_{10}F_3NO_2S$ 289.04 m/z found 290.2 $[M+H]^+$.

[00263] ***Step 3:*** The mixture of (2-thioxo-1-pyridyl) 3-(trifluoromethyl) bicycle [1.1.1] pentane-1-carboxylate (2 g, 6.91 mmol, 1 eq) in toluene (50 mL) was degassed and purged with Ar for 3 times. To the mixture was added 2-(2-pyridyldisulfanyl) pyridine (3.81 g, 17.3 mmol, 2.5 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hours under argon atmosphere under 1000 w lamp. LCMS showed (2-thioxo-1-pyridyl) 3-(trifluoromethyl) bicycle [1.1.1] pentane-1-

carboxylate was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was added water (30 mL) and extracted with EtOAc (3 X 50 mL). The residue was purified by column chromatography (silica gel, petroleum ether/ ethyl acetate = 97/3 to 90/10) to give the desired 2-[[3-(trifluoromethyl)-1-bicyclo [1.1.1] pentanyl] sulfanyl] pyridine (1.4 g, 5.71 mmol, 82.6% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{11}H_{10}F_3NS$ 245.05 m/z found 246.2 $[M+H]^+$.

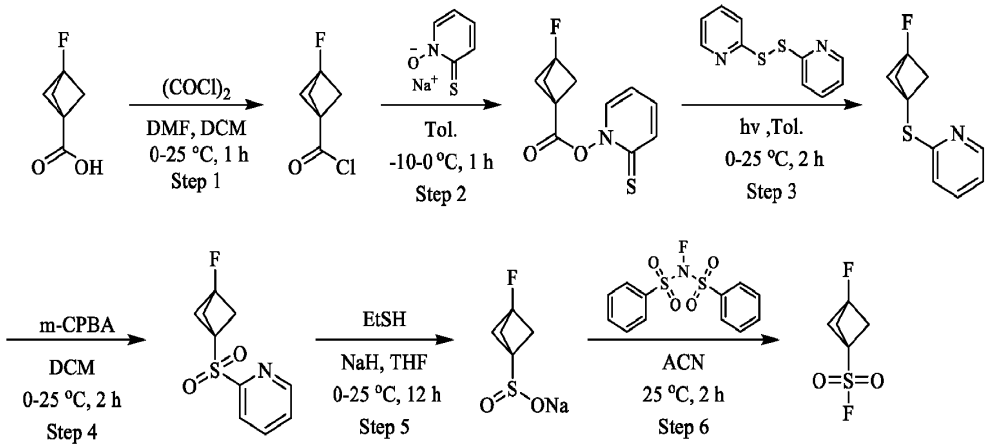
[00264] ***Step 4:*** The mixture of 2-[[3-(trifluoromethyl)-1-bicyclo [1.1.1] pentanyl] sulfanyl] pyridine (1.3 g, 5.30 mmol, 1 eq) in DCM (50 mL) was added *m*-CPBA (3.23 g, 15.9 mmol, 85% purity, 3 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hours. LCMS showed 2-[[3-(trifluoromethyl)-1-bicyclo [1.1.1] pentanyl] sulfanyl] pyridine was consumed completely and the desired mass was detected. The reaction mixture was quenched by addition sat. aq. Na_2SO_3 (30 mL) at 0 °C and extracted with DCM (3 X 50 mL), then the combined organic layers were washed with sat. aq. Na_2CO_3 (20 mL). The residue was purified by column chromatography (silica gel, petroleum ether/ ethyl acetate =10/1 to 5/1). The reaction mixture was concentrated to give the desired 2-[[3-(trifluoromethyl)-1-bicyclo [1.1.1] pentanyl] sulfonyl] pyridine (1.1 g, 3.97 mmol, 74.9% yield) as a white solid. MS (ESI): mass calcd. For $C_{11}H_{10}F_3NO_2S$ 277.04 m/z found 278.2 $[M+H]^+$.

[00265] ***Step 5:*** The mixture of NaH (238 mg, 5.95 mmol, 60% purity, 1.5 eq) in THF (15 mL) was degassed and purged with Ar for 3 times. EtSH (986 mg, 15.9 mmol, 1.17 mL, 4 eq) was added dropwise to the mixture. The mixture was stirred at 0 °C for 1 hour. To the mixture was added 2-[[3-(trifluoromethyl)-1-bicyclo [1.1.1] pentanyl] sulfonyl] pyridine (1.1 g, 3.97 mmol, 1 eq) at 0 °C. The mixture was stirred at 25 °C for 11 hours under Ar atmosphere. TLC (petroleum ether/ ethyl acetate = 3/1) indicated 2-[[3-(trifluoromethyl)-1-bicyclo [1.1.1] pentanyl] sulfonyl] pyridine was consumed completely and one new spot was formed. The reaction mixture was concentrated under reduced pressure to give a residue. The reaction mixture was washed with MTBE (10 mL) and the filter cake was concentrated under reduced pressure to give a residue. The reaction mixture was concentrated to give the desired [3-(trifluoromethyl)-1-bicyclo [1.1.1] pentanyl] sulfinyloxysodium (500 mg, 2.25 mmol, 56.7% yield) as a white solid which was used in the next step.

[00266] ***Step 6:*** To a solution of [3-(trifluoromethyl)-1-bicyclo [1.1.1] pentanyl] sulfinyloxysodium (500 mg, 2.25 mmol, 1 eq) in ACN (20 mL) was added N-(benzenesulfonyl)-

N-fluoro-benzenesulfonamide (1.06 g, 3.38 mmol, 1.5 eq). The mixture was stirred at 25 °C for 2 hours. TLC (petroleum ether/ ethyl acetate = 1/1) indicated [3-(trifluoromethyl)-1-bicyclo [1.1.1] pentanyl] sulfinyloxysodium was consumed completely and one new spot was formed. The residue was added water (30 mL) and extracted with EtOAc (3 X 50 mL). The residue was purified by column chromatography (silica gel, petroleum ether/ ethyl acetate =20/1 to 10:1) to give the desired 3-(trifluoromethyl) bicycle [1.1.1] pentane-1-sulfonyl fluoride (130 mg, 596 µmol, 26.5% yield) as a white solid which was used in the next step.

Intermediate-R4: 3-Fluorobicyclo [1.1.1] pentane-1-sulfonyl fluoride



[00267] ***Step 1:*** To a solution of 3-fluorobicyclo [1.1.1] pentane-1-carboxylic acid (3.6 g, 27.7 mmol, 1 eq) in DCM (100 mL) were added DMF (202 mg, 2.77 mmol, 213 µL, 0.1 eq) and $(COCl)_2$ (5.27 g, 41.5 mmol, 3.63 mL, 1.5 eq) at 0 °C. The mixture was stirred at 25 °C for 1 hour under N_2 atmosphere. TLC (petroleum ether/ ethyl acetate = 3/1) indicated 3-fluorobicyclo [1.1.1] pentane-1-carboxylic acid was consumed completely and one new spot was formed (quenched with MeOH 0.5 mL). The reaction mixture was concentrated to give the desired 3-fluorobicyclo [1.1.1] pentane-1-carbonyl chloride (3.6 g, crude) as a yellow oil.

[00268] ***Step 2:*** The mixture of sodium; 1-oxidopyridin-1-ium-2-thiolate (4.34 g, 29.1 mmol, 3.55 mL, 1.2 eq) in toluene (50 mL) was degassed and purged with Ar for 3 times. To the mixture was added 3-fluorobicyclo [1.1.1] pentane-1-carbonyl chloride (3.6 g, 24.2 mmol, 1 eq) at -10 °C. The mixture was stirred at 0 °C for 1 hour under Ar atmosphere in dark**.** LCMS showed sodium; 1-oxidopyridin-1-ium-2-thiolate was consumed completely and the desired mass was detected. The reaction mixture was concentrated to give the desired (2-thioxo-1-

pyridyl) 3-fluorobicyclo [1.1.1] pentane-1-carboxylate (3.6 g, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{11}H_{10}FNO_2S$ 239.04 m/z found 240.2 $[M+H]^+$.

[00269] ***Step 3:*** The mixture of (2-thioxo-1-pyridyl) 3-fluorobicyclo [1.1.1] pentane-1-carboxylate (3.6 g, 15.1 mmol, 1 eq) in toluene (100 mL) was degassed and purged with Ar for 3 times. To the mixture was added 2-(2-pyridyldisulfanyl) pyridine (8.29 g, 37.6 mmol, 2.5 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hours under argon atmosphere under 1000 w lamp. LCMS showed (2-thioxo-1-pyridyl) 3-fluorobicyclo [1.1.1] pentane-1-carboxylate was consumed completely and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove toluene. The residue was added water (30 mL) and extracted with EtOAc (3 X 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether/ ethyl acetate = 93/7 to 90/10) to give the desired 2-[(3-fluoro-1-bicyclo [1.1.1] pentanyl) sulfanyl] pyridine (600 mg, 3.07 mmol, 20.4% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{10}H_{10}FNS$ 195.05 m/z found 196.2 $[M+H]^+$.

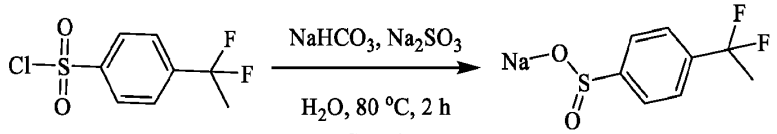
[00270] ***Step 4:*** To a solution of 2-[(3-fluoro-1-bicyclo [1.1.1] pentanyl) sulfanyl] pyridine (600 mg, 3.07 mmol, 1 eq) in DCM (20 mL) was added *m*-CPBA (1.87 g, 9.22 mmol, 85% purity, 3 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hours. LCMS showed 2-[(3-fluoro-1-bicyclo [1.1.1] pentanyl) sulfonyl] pyridine was consumed completely and the desired mass was detected. The reaction mixture was quenched by addition sat. aq. Na_2SO_3 (30 mL) at 0 °C and extracted with DCM (3 X 50 mL). The combined organic layers were washed with sat. aq. Na_2CO_3 (20 mL). The residue was purified by column chromatography (silica gel, petroleum ether/ ethyl acetate = 10/1 to 5/1) to give the desired 2-[(3-fluoro-1-bicyclo [1.1.1] pentanyl) sulfonyl] pyridine (500 mg, 2.20 mmol, 71.6% yield) as a white solid. MS (ESI): mass calcd. For $C_{10}H_{10}FNO_2S$ 227.04 m/z found 228.2 $[M+H]^+$.

[00271] ***Step 5:*** The mixture of NaH (132 mg, 3.30 mmol, 60% purity, 1.5 eq) in THF (20 mL) was degassed and purged with Ar for 3 times. EtSH (2.05 g, 33.0 mmol, 2.44 mL, 15 eq) was added dropwise to the mixture at 0 °C. The mixture was stirred at 0 °C for 1 hour. To the mixture was added 2-[(3-fluoro-1-bicyclo [1.1.1] pentanyl) sulfonyl] pyridine (500 mg, 2.20 mmol, 1 eq) at 0 °C. The mixture was stirred at 25 °C for 11 hours under Ar atmosphere. TLC (petroleum ether/ ethyl acetate = 3/1) indicated 2-[(3-fluoro-1-bicyclo [1.1.1] pentanyl) sulfonyl]

pyridine was consumed completely and one new spot was formed. The reaction mixture concentrated under reduced pressure to give a residue. The reaction mixture was washed with MTBE (10 mL) and the filter cake was concentrated under reduced pressure to give the desired (3-fluoro-1-bicyclo [1.1.1] pentanyl) sulfinyloxysodium (340 mg, 1.97 mmol, 89.8% yield) as a white solid which was used in the next step.

[00272] ***Step 6:*** To a solution of (3-fluoro-1-bicyclo [1.1.1] pentanyl) sulfinyloxysodium (340 mg, 1.97 mmol, 1 eq) in ACN (15 mL) was added N-(benzenesulfonyl)-N-fluoro-benzenesulfonamide (934 mg, 2.96 mmol, 1.5 eq). The mixture was stirred at 25 °C for 2 hours. TLC (petroleum ether/ ethyl acetate = 1/1) indicated (3-fluoro-1-bicyclo [1.1.1] pentanyl) sulfinyloxysodium was consumed completely and one new spot was formed. The residue was added water (30 mL) and extracted with EtOAc (3 X 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether/ ethyl acetate = 20/1 to 10/1) to give the desired 3-fluorobicyclo [1.1.1] pentane-1-sulfonyl fluoride (100 mg, 595 μmol, 30.1% yield) as a white solid which was used in the next step.

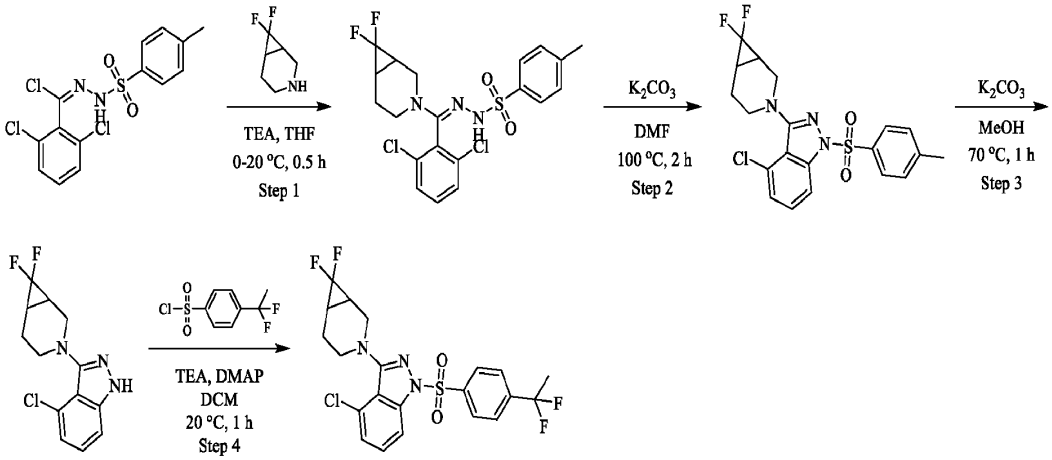
Intermediate-R5: [4-(1, 1-Difluoroethyl) phenyl] sulfinyloxysodium



[00273] ***Step 1:*** To a solution of 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (1 g, 4.16 mmol, 1 eq) in H_2O (10 mL) were added $NaHCO_3$ (698 mg, 8.31 mmol, 323 μL, 2 eq) and Na_2SO_3 (1.05 g, 8.31 mmol, 2 eq). The mixture was stirred at 80 °C for 2 hours. TLC (petroleum ether/ ethyl acetate = 3/1) indicated 4-(1, 1-difluoroethyl) benzenesulfonyl chloride was consumed completely and one new spot was formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was added MeOH (20 mL). The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give the desired [4-(1, 1-difluoroethyl) phenyl] sulfinyloxysodium (1 g, crude) as a white solid.

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Compound 1: 4-Chloro-3-(7, 7-difluoro-3-azabicyclo [4.1.0] heptan-3-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole



[00274] ***Step 1:*** To the solution of 7, 7-difluoro-3-azabicyclo [4.1.0] heptane (100 mg, 590 μmol, 1 eq, HCl) and TEA (597 mg, 5.90 mmol, 821 μL, 10 eq) in THF (1 mL) was added (1E)-2,6-dichloro-N-(p-tolylsulfonyl)benzohydrazonoyl chloride (334 mg, 884 μmol, 1.5 eq) at 0 °C and the solution was stirred at 20 °C for 0.5 hour. LCMS showed (1E)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride was consumed completely and the desired mass was detected. The reaction was concentrated to give the desired N-[(E)-[(2, 6-dichlorophenyl)-(7, 7-difluoro-3-azabicyclo [4.1.0] heptan-3-yl) methylene] amino]-4-methyl-benzenesulfonamide (260 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{19}Cl_2F_2N_3O_2S$ 473.05, m/z found 474.1 $[M+H]^+$.

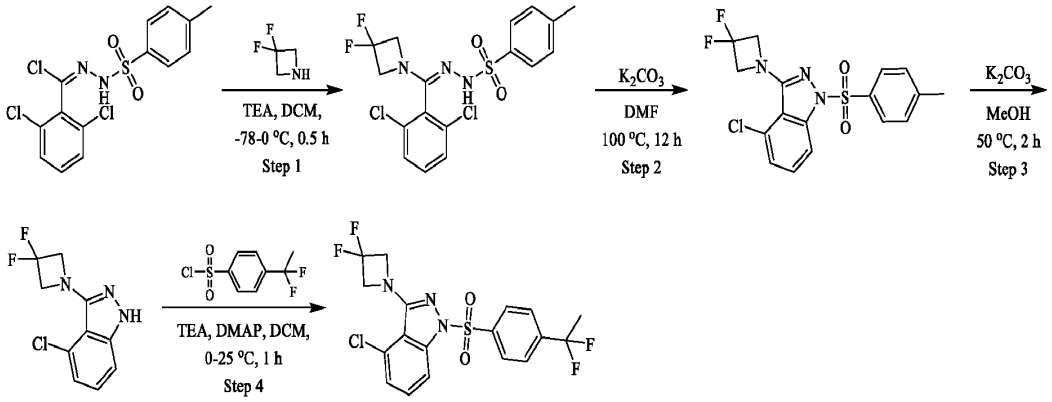
[00275] ***Step 2:*** To a solution of N-[(E)-[(2, 6-dichlorophenyl)-(7, 7-difluoro-3-azabicyclo [4.1.0] heptan-3-yl) methylene] amino]-4-methyl-benzenesulfonamide (260 mg, 548 μmol, 1 eq) in DMF (5 mL) was added K_2CO_3 (1.52 g, 11.0 mmol, 20 eq). The mixture was stirred at 100 °C for 2 hours. LC-MS showed N-[(E)-[(2, 6-dichlorophenyl)-(7, 7-difluoro-3-azabicyclo [4.1.0] heptan-3-yl) methylene] amino]-4-methyl-benzenesulfonamide remained and the desired mass was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(7, 7-difluoro-3-azabicyclo [4.1.0] heptan-3-yl)-1-(p-tolylsulfonyl) indazole (240 mg, crude) as an orange oil. MS (ESI): mass calcd. For $C_{20}H_{18}ClF_2N_3O_2S$ 437.08, m/z found 438.0 $[M+H]^+$.

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[00276] ***Step 3:*** To a solution of 4-chloro-3-(7, 7-difluoro-3-azabicyclo [4.1.0] heptan-3-yl)-1-(p-tolylsulfonyl) indazole (240 mg, 548 μmol, 1 eq) in MeOH (5 mL) was added K_2CO_3 (1.52 g, 11.0 mmol, 20 eq). The mixture was stirred at 70 °C for 1 hour. LC-MS showed 4-chloro-3-(7, 7-difluoro-3-azabicyclo [4.1.0] heptan-3-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-(7, 7-difluoro-3-azabicyclo [4.1.0] heptan-3-yl)-1H-indazole (110 mg, crude) as an orange oil. MS (ESI): mass calcd. For $C_{13}H_{12}ClF_2N_3$ 283.07, m/z found 284.0 $[M+H]^+$.

[00277] ***Step 4:*** To a solution of 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (67.9 mg, 282 μmol, 2 eq) and 4-chloro-3-(7, 7-difluoro-3-azabicyclo [4.1.0] heptan-3-yl)-1H-indazole (40 mg, 141 μmol, 1 eq) in DCM (2 mL) was added dropwise TEA (71.3 mg, 705 μmol, 98.1 μL, 5 eq) and DMAP (1.72 mg, 14.1 μmol, 0.1 eq). The mixture was stirred at 20 °C for 1 hour. LC-MS showed 4-chloro-3-(7, 7-difluoro-3-azabicyclo [4.1.0] heptan-3-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was concentrated to give the crude product. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [water (TFA)-ACN]; B%: 45%-75%,8min) to give the desired 4-chloro-3-(7, 7-difluoro-3-azabicyclo [4.1.0] heptan-3-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole (13.9 mg, 28.5 μmol, 20.2% yield, 100.00% purity) as a white solid. ^1H NMR (DMSO-d_6) δ 8.07 (d, 1H), 7.96 (d, 2H), 7.77 (d, 2H), 7.63 (m, 1H), 7.47 (d, 1H), 3.65 (br m, 1H), 3.28 (br m, 1H), 3.04-3.14 (m, 1H), 2.86-2.97 (m, 1H), 2.00-2.12 (m, 2H), 1.92 (m, 5H). HPLC: 100.00% (220 nm), 92.48% (210 nm), 100.00% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{18}ClF_4N_3O_2S$ 487.07, m/z found 488.1 $[M+H]^+$.

Compound 2: 4-Chloro-3-(3, 3-difluoroazetidin-1-yl)-1-((4-(1, 1-difluoroethyl) phenyl) sulfonyl)-1H-indazole



[00278] ***Step 1:*** To a solution of 3, 3-difluoroazetidine (137 mg, 1.06 mmol, 1 eq, HCl) in DCM (5 mL) were added TEA (1.07 g, 10.6 mmol, 1.47 mL, 10 eq) and (1E)-2,6-dichloro-N-(p-tolylsulfonyl)benzohydrazonoyl chloride (0.4 g, 1.06 mmol, 1 eq) at -78 °C. The mixture was stirred at 0 °C for 0.5 hour. LCMS showed (1E)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride was complete and the desired MS was detected. The reaction mixture was added H_2O (5 mL) at 0 °C, and extracted with EtOAc (3 X 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2,6-dichlorophenyl)-(3,3-difluoroazetidin-1-yl)methylene]amino]-4-methyl-benzenesulfonamide (0.45 g, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{17}H_{15}Cl_2F_2N_3O_2S$ 433.02 m/z found 434.0 $[M+H]^+$.

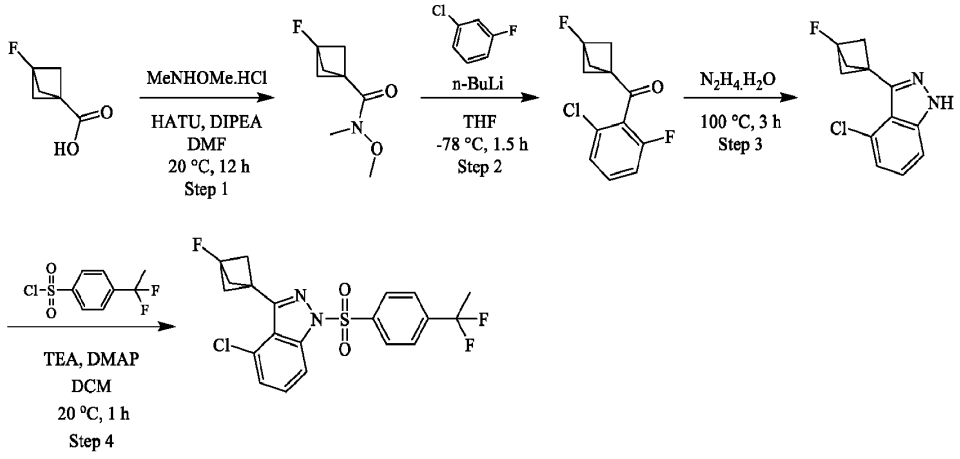
[00279] ***Step 2:*** To a solution of N-[(E)-[(2, 6-dichlorophenyl)-(3, 3-difluoroazetidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (0.4 g, 921 μmol, 1 eq) in DMF (5 mL) was added K_2CO_3 (382 mg, 2.76 mmol, 3 eq). The mixture was stirred at 100 °C for 12 hours. LCMS showed N-[(E)-[(2, 6-dichlorophenyl)-(3, 3-difluoroazetidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide was complete and the desired mass was detected. The reaction mixture was added H_2O (5 mL) at 0°C, and extracted with EtOAc (3 X 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(3, 3-difluoroazetidin-1-yl)-1-(p-tolylsulfonyl) indazole (0.4 g, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{17}H_{14}ClF_2N_3O_2S$ 397.05 m/z found 398.0 $[M+H]^+$.

[00280] ***Step 3:*** To a solution of 4-chloro-3-(3, 3-difluoroazetidin-1-yl)-1-(p-tolylsulfonyl) indazole (0.3 g, 754 μmol, 1 eq) in MeOH (4 mL) was added K_2CO_3 (208 mg, 1.51 mmol, 2 eq). The mixture was stirred at 50 °C for 2 hours. LCMS showed 4-chloro-3-(3, 3-difluoroazetidin-1-yl)-1-(p-tolylsulfonyl) indazole was complete and the desired mass was detected. The reaction

mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 3/1) to give the desired 4-chloro-3-(3, 3-difluoroazetidin-1-yl)-1H-indazole (0.1 g, 410 μmol, 54.4% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{10}H_8ClF_2N_3$ 243.04 m/z found 244.0 $[M+H]^+$.

[00281] ***Step 4:*** To a solution of 4-chloro-3-(3,3-difluoroazetidin-1-yl)-1H-indazole (80 mg, 328 μmol, 1 eq) and TEA (332 mg, 3.28 mmol, 457 μL, 10 eq) in DCM (1 mL) was added 4-(1,1-difluoroethyl)benzenesulfonyl chloride (237 mg, 985 μmol, 3 eq) and DMAP (4.01 mg, 32.8 μmol, 0.1 eq) at 0 °C. The mixture was stirred at 25 °C for 1 hour. LCMS showed 4-chloro-3-(3, 3-difluoroazetidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was quenched with saturated NH_4Cl (5 mL) at 0 °C, and extracted with EtOAc (3 X 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O(0.1%TFA)-ACN]; gradient: 50% - 80% B over 8.0 min) to give the desired 4-chloro-3-(3,3-difluoroazetidin-1-yl)-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-indazole (56.6 mg, 126 μmol, 38.3% yield, 99.87% purity) as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.08 (d, J = 8.5 Hz, 1H), 7.99 (br d, J = 8.1 Hz, 2H), 7.78 (br d, J = 8.4 Hz, 2H), 7.66 (t, J = 8.1 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 4.64 (br t, J = 12.9 Hz, 4H), 1.94 (br t, J = 19.1 Hz, 3H). HPLC: 99.87% (220 nm), 99.68% (215 nm), 100.00% (254 nm). MS (ESI): mass calcd. For $C_{18}H_{14}ClF_4N_3O_2S$ 447.04 m/z found 448.0 $[M+H]^+$.

Compound 3: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3-fluoro-1-bicyclo [1.1.1] pentanyl) indazole



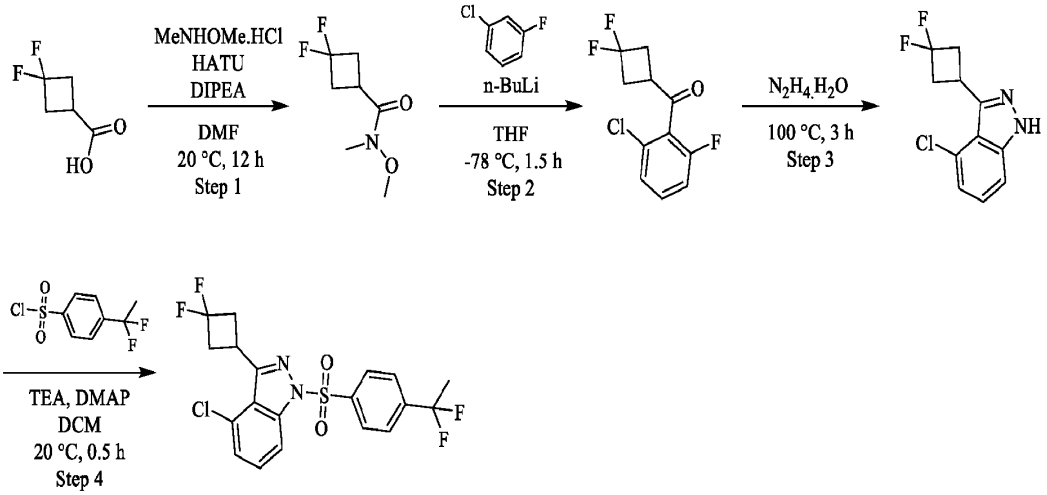
[00282] ***Step 1:*** To a solution of 3-fluorobicyclo [1.1.1] pentane-1-carboxylic acid (5 g, 38.4 mmol, 1 eq) in DMF (50 mL) were added DIPEA (19.9 g, 154 mmol, 26.8 mL, 4 eq), HATU (21.9 g, 57.6 mmol, 1.5 eq) at 20 °C under the atmosphere of N_2. The mixture was stirred at 20 °C for 1 hour. To a solution was added N-methoxymethanamine hydrochloride (5.62 g, 57.6 mmol, 1.5 eq) at 20 °C and the mixture was stirred at 20 °C for 11 hours. TLC indicated 3-fluorobicyclo [1.1.1] pentane-1-carboxylic acid was consumed completely and one new spot was formed. The residue was diluted with H_2O (50 mL) and extracted with EtOAc (100 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/petroleum ether gradient @ 80 mL/min) to give the desired 3-fluoro-N-methoxy-N-methyl-bicyclo [1.1.1] pentane-1-carboxamide (5 g, 28.9 mmol, 75.1% yield) as a yellow oil.

[00283] ***Step 2:*** To the solution of 1-chloro-3-fluoro-benzene (603 mg, 4.62 mmol, 495 µL, 1.6 eq) in THF (6 mL) was added *n*-BuLi (2.5 M, 1.85 mL, 1.6 eq) at -78 °C and the solution was stirred at -78 °C for 0.5 hour under the atmosphere of nitrogen. To the solution was added 3-fluoro-N-methoxy-N-methyl-bicyclo [1.1.1] pentane-1-carboxamide (500 mg, 2.89 mmol, 1 eq) at -78 °C and the solution was stirred at -78 °C for 1 hour. TLC showed 3-fluoro-N-methoxy-N-methyl-bicyclo [1.1.1] pentane-1-carboxamide a new spot was detected. To the solution was added NH_4Cl solution (0.5 mL) and extracted with EtOAc (2 X 5 mL). The combined organics were concentrated to get a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired (2-chloro-6-fluoro-phenyl)-(3-fluoro-1-bicyclo [1.1.1] pentanyl) methanone (450 mg, crude) as a yellow oil.

[00284] ***Step 3:*** A mixture of (2-chloro-6-fluoro-phenyl)-(3-fluoro-1-bicyclo [1.1.1] pentanyl) methanone (300 mg, 1.24 mmol, 1 eq) in $NH_2NH_2.H_2O$ (6 mL) was stirred at 100 °C for 3 hours. LC-MS showed (2-chloro-6-fluoro-phenyl)-(3-fluoro-1-bicyclo [1.1.1] pentanyl) methanone was consumed completely and one main peak with the desired mass was detected. The reaction mixture was diluted with H_2O (30 ml) and extracted with EtOAc (20 mL X 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-(3-fluoro-1-bicyclo [1.1.1] pentanyl)-1H-indazole (40 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{12}H_{10}ClFN_2$ 236.05, m/z found 237.0 $[M+H]^+$.

[00285] ***Step 4:*** To a solution of 4-chloro-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-1H-indazole (30 mg, 127 μmol, 1 eq) and 4-(1,1-difluoroethyl)benzenesulfonyl chloride (45.8 mg, 190 μmol, 1.5 eq) in DCM (2 mL) was added TEA (38.5 mg, 380 μmol, 52.9 μL, 3 eq) and DMAP (1.55 mg, 12.7 μmol, 0.1 eq). The mixture was stirred at 20 °C for 1 hour. LC-MS showed 4-chloro-3-(3-fluoro-1-bicyclo [1.1.1] pentanyl)-1H-indazole was consumed completely and one main peak with the desired mass was detected. The reaction mixture was concentrated to give the crude product. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm *3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 55% - 90% B over 8.0 min) to give the desired 4-chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)indazole (11.3 mg, 25.6 μmol, 20.2% yield, 99.11% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, J = 8.4 Hz, 1H), 8.10 (br d, J = 8.3 Hz, 2H), 7.83 (br d, J = 8.3 Hz, 2H), 7.69 (t, J = 8.1 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 2.63 (d, J = 2.1 Hz, 6H), 1.95 (t, J = 19.1 Hz, 3H). HPLC: 99.11% (220 nm), 99.21% (210 nm), 99.09% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{16}ClF_3N_2O_2S$ 440.06, m/z found 441.1 $[M+H]^+$.

Compound 4: 4-Chloro-3-(3, 3-difluorocyclobutyl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole



[00286] ***Step 1:*** To a solution of 3, 3-difluorocyclobutanecarboxylic acid (300 mg, 2.20 mmol, 1 eq) in DCM (5 mL) were added N-methoxymethanamine hydrochloride (886 mg, 6.61 mmol, 3 eq, HCl), HATU (2.51 g, 6.61 mmol, 3 eq) and DIEA (2.28 g, 17.6 mmol, 3.07 mL, 8 eq). The mixture was stirred at 20 °C for 12 hours. LC-MS showed 3, 3-difluorocyclobutanecarboxylic

acid was consumed completely and the desired mass was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate=1/0 to 0/1) to give the desired 3, 3-difluoro-N-methoxy-N-methyl-cyclobutanecarboxamide (300 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_7H_{11}F_2NO_2$ 179.08, m/z found 180.0 $[M+H]^+$.

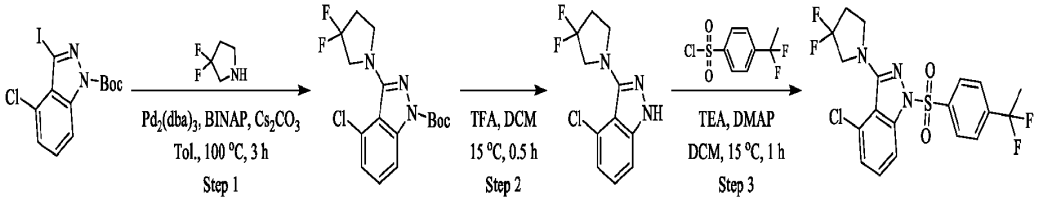
[00287] ***Step 2:*** To the solution of 1-chloro-3-fluoro-benzene (175 mg, 1.34 mmol, 143 µL, 1.2 eq) in THF (6 mL) was added *n*-BuLi (2.5 M, 536 µL, 1.2 eq) at -78 °C and the solution was stirred at -78 °C for 0.5 hour under the atmosphere of nitrogen. To the solution was added 3,3-difluoro-N-methoxy-N-methyl-cyclobutanecarboxamide (200 mg, 1.12 mmol, 1 eq) at -78 °C and the solution was stirred at -78 °C for 1 hour. TLC (petroleum ether / ethyl acetate = 3/1) showed 3, 3-difluoro-N-methoxy-N-methyl-cyclobutanecarboxamide remained and a new spot was detected. To the solution was added NH_4Cl solution (0.5 mL) and extracted with EtOAc (2 X 5 mL). The combined organics were concentrated to get a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ethyl acetate = 3/1) to give the desired (2-chloro-6-fluoro-phenyl)-(3, 3-difluorocyclobutyl) methanone (100 mg, crude) as a yellow oil.

[00288] ***Step 3:*** A mixture of (2-chloro-6-fluoro-phenyl)-(3, 3-difluorocyclobutyl) methanone (100 mg, 402 µmol, 1 eq) in $NH_2NH_2.H_2O$ (2 mL) was stirred at 100 °C for 3 hours. TLC indicated (2-chloro-6-fluoro-phenyl)-(3, 3-difluorocyclobutyl) methanone was consumed completely and one new spot was formed. The reaction was clean according to TLC. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (10 mL X 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ ethyl acetate = 2/1) to give the desired 4-chloro-3-(3, 3-difluorocyclobutyl)-1H-indazole (40 mg, crude) as a white solid. .

[00289] ***Step 4:*** To a solution of 4-chloro-3-(3, 3-difluorocyclobutyl)-1H-indazole (35 mg, 144 µmol, 1 eq) and 4-(1,1-difluoroethyl)benzenesulfonyl chloride (52.1 mg, 216 µmol, 1.5 eq) in DCM (1 mL) were added TEA (43.8 mg, 433 µmol, 60.2 µL, 3 eq) and DMAP (1.76 mg, 14.4 µmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hours. LC-MS showed 4-chloro-3-(3, 3-difluorocyclobutyl)-1H-indazole was consumed completely and one main peak with the desired mass was detected. The reaction mixture was concentrated to give the crude product. The residue

was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 55% - 80% B over 8.0 min) to give the desired 4-chloro-3-(3, 3-difluorocyclobutyl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole (4.3 mg, 9.41 μmol, 6.52% yield, 97.76% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (dd, J = 8.4, 17.1 Hz, 3H), 7.82 (d, J = 8.4 Hz, 2H), 7.70 (t, J = 8.1 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 4.03 (br dd, J = 7.5, 9.0 Hz, 1H), 3.21 - 3.07 (m, 2H), 3.07 - 2.94 (m, 2H), 1.96 (t, J = 19.1 Hz, 3H). HPLC: 97.76% (220 nm), 98.82% (210 nm), 98.60% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{15}ClF_4N_2O_2S$ 446.05, m/z found 447.0 $[M+H]^+$.

Compound 5: 4-Chloro-1-((4-(1, 1-difluoroethyl) phenyl) sulfonyl)-3-(3, 3-difluoropyrrolidin-1-yl)-1H-indazole



[00290] ***Step 1***: A mixture of tert-butyl 4-chloro-3-iodo-indazole-1-carboxylate (300 mg, 792 μmol, 1 eq), 3, 3-difluoropyrrolidine (137 mg, 951 μmol, 1.2 eq, HCl), $Pd_2(dba)_3$ (72.6 mg, 79.2 μmol, 0.1 eq), Cs_2CO_3 (775 mg, 2.38 mmol, 3 eq) and BINAP (49.3 mg, 79.2 μmol, 0.1 eq) in toluene (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 3 hours under N_2 atmosphere. LC-MS showed tert-butyl 4-chloro-3-iodo-indazole-1-carboxylate was consumed completely and the desired mass was detected. The crude was added H_2O (20 mL) and extracted with EtOAc (15 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ ethyl acetate = 3/1) give the desired tert-butyl 4-chloro-3-(3, 3-difluoropyrrolidin-1-yl) indazole-1-carboxylate (200 mg, 559 μmol, 70.5% yield) as a yellow oil. MS (ESI): mass calcd. For $C_{16}H_{18}ClF_2N_3O_2$ 357.11 m/z found 358.1 $[M+H]^+$.

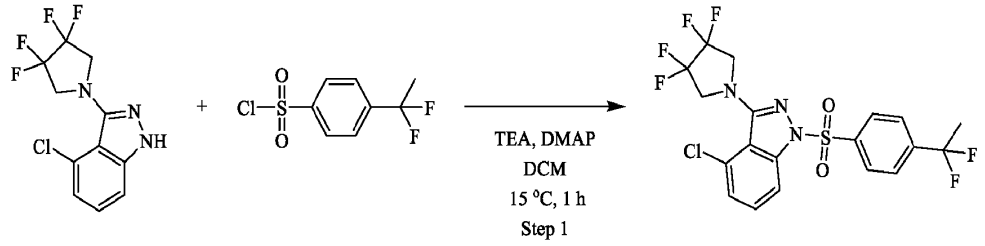
[00291] ***Step 2***: To a solution of tert-butyl 4-chloro-3-(3, 3-difluoropyrrolidin-1-yl) indazole-1-carboxylate (200 mg, 559 μmol, 1 eq) in DCM (2 mL) was added TFA (1.59 g, 14.0 mmol, 1.04 mL, 25 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed tert-butyl 4-chloro-3-(3, 3-difluoropyrrolidin-1-yl) indazole-1-carboxylate was consumed completely and the

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desired mass was detected. The reaction mixture was concentrated in vacuum to give the desired 4-chloro-3-(3, 3-difluoropyrrolidin-1-yl)-1H-indazole (200 mg, crude, TFA) as a brown oil. MS (ESI): mass calcd. For $C_{11}H_{10}ClF_2N_3$ 257.05 m/z found 258.1 $[M+H]^+$.

[00292] ***Step 3***: To a solution of 4-chloro-3-(3, 3-difluoropyrrolidin-1-yl)-1H-indazole (100 mg, 269 µmol, 1 eq, TFA) and 4-(1,1-difluoroethyl)benzenesulfonyl chloride (97.1 mg, 404 µmol, 1.5 eq) in DCM (2 mL) were added TEA (81.7 mg, 807 µmol, 112 µL, 3 eq) and DMAP (3.29 mg, 26.9 µmol, 0.1 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-chloro-3-(3, 3-difluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The crude was added H_2O (20 mL) and extracted with DCM (15 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition, column: Phenomenex Luna C18 75 * 30 mm * 3 µm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 55% - 85% B over 8.0 min) give the desired 4-chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(3,3-difluoropyrrolidin-1-yl)indazole (13.2 mg, 28.6 µmol, 10.6% yield, 100.00% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.65 (t, J = 8.1 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 3.88 (t, J = 13.1 Hz, 2H), 3.70 (t, J = 7.2 Hz, 2H), 2.50 - 2.41 (m, 2H), 1.92 (t, J = 19.1 Hz, 3H). HPLC: 100.00% (220 nm), 100.00% (215 nm), 100.00 (254 nm). MS (ESI): mass calcd. For $C_{19}H_{16}ClF_4N_3O_2S$ 461.06 m/z found 462.1 $[M+H]^-$.

Compound 6: 4-Chloro-1-((4-(1, 1-difluoroethyl) phenyl) sulfonyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole

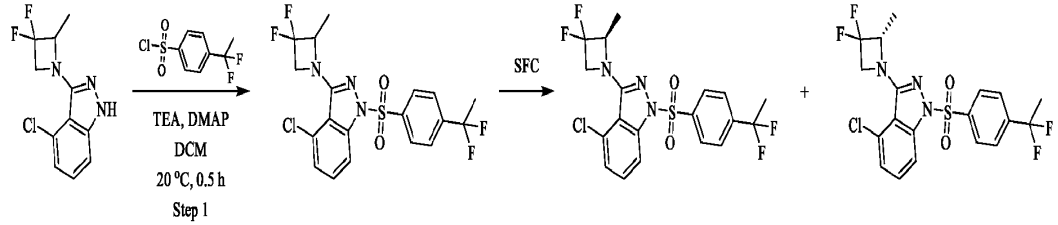


[00293] ***Step 1***: To a solution of 4-chloro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole (100 mg, 245 µmol, 1 eq, TFA) and 4-(1,1-difluoroethyl)benzenesulfonyl chloride (88.6 mg, 368 µmol, 1.5 eq) in DCM (2 mL) were added TEA (74.5 mg, 736 µmol, 102 µL, 3 eq) and DMAP (3.00 mg, 24.5 µmol, 0.1 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-

chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The crude was added H_2O (20 mL) and extracted with DCM (15 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition, column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 55% - 85% B over 8.0 min) give the desired 4-chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)indazole (14.6 mg, 29.1 μmol, 11.9% yield, 99.25% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, J = 8.5 Hz, 1H), 8.06 (d, J = 8.5 Hz, 2H), 7.82 (d, J = 8.5 Hz, 2H), 7.73 (t, J = 8.1 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 4.35 - 4.22 (m, 4H), 1.98 (t, J = 19.1 Hz, 3H). HPLC: 99.25% (220 nm), 98.53% (215 nm), 100.00 (254 nm). MS (ESI): mass calcd. For $C_{19}H_{14}ClF_6N_3O_2S$ 497.04 m/z found 498.1 $[M+H]^+$.

Compound 7: 4-Chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-[(2R)-3,3-difluoro-2-methyl-azetidin-1-yl]indazole

Compound 8: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2S)-3, 3-difluoro-2-methyl-azetidin-1-yl] indazole

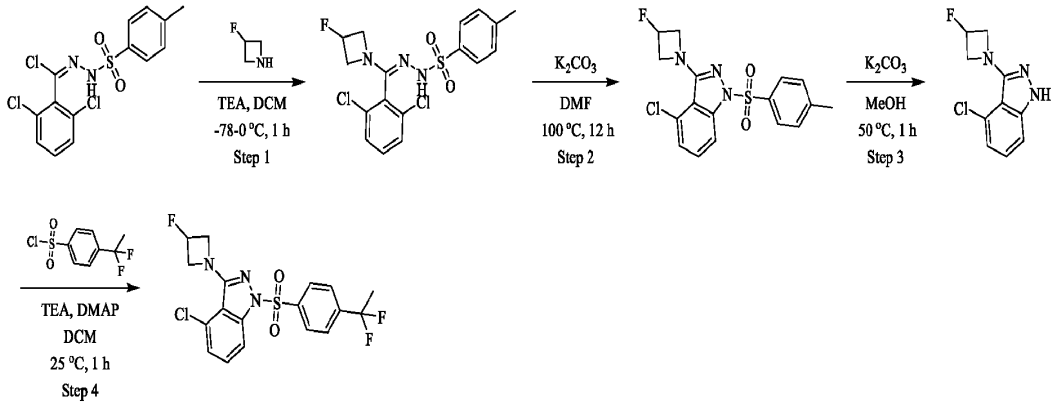


[00294] ***Step 1:*** To a solution of 4-chloro-3-(3,3-difluoro-2-methyl-cyclobutyl)-1H-indazole (110 mg, 429 μmol, 1 eq) and 4-(1,1-difluoroethyl)benzenesulfonyl chloride (155 mg, 643 μmol, 1.5 eq) in DCM (1 mL) were added TEA (130 mg, 1.29 mmol, 179 μL, 3 eq) and DMAP (5.24 mg, 42.9 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(3, 3-difluoro-2-methyl-cyclobutyl)-1H-indazole was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to water (20 mL), extracted with DCM (10 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ ethyl acetate = 2/1) to give the desired 4-

chloro-3-(3,3-difluoro-2-methylazetidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole (110 mg) as a white solid, which was further separated by SFC (condition: column: ChiralPak IH, 250*30mm, 10um;mobile phase: [CO_2-IPA(0.1%NH_3 H_2O)]; B%:15%, isocratic elution mode) to give two isomers. The structures were assigned arbitrarily. 4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2R)-3, 3-difluoro-2-methyl-azetidin-1-yl] indazole (21.0 mg, 44.5 μmol, 10.4% yield, 97.91% purity, Rt = 0.806 minutes; E.E. by chiral HPLC (%) = 99.98%) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.72 (t, J = 8.1 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 5.04 - 4.91 (m, 1H), 4.77 (q, J = 11.5 Hz, 1H), 4.57 - 4.41 (m, 1H), 1.98 (t, J = 19.1 Hz, 3H), 1.29 (d, J = 6.5 Hz, 3H). HPLC: 97.91% (220 nm), 97.64% (210 nm), 96.97% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{16}ClF_4N_3O_2S$ 461.06, m/z found 462.0 $[M+H]^+$.

4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2S)-3, 3-difluoro-2-methyl-azetidin-1-yl] indazole (21.1 mg, 45.0 μmol, 10.5% yield, 98.52% purity, Rt = 0.908 minutes; E.E. by chiral HPLC (%) = 94.60%) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.72 (t, J = 8.1 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 5.06 - 4.91 (m, 1H), 4.77 (q, J = 11.3 Hz, 1H), 4.57 - 4.42 (m, 1H), 1.98 (t, J = 19.1 Hz, 3H), 1.29 (d, J = 6.5 Hz, 3H). HPLC: 98.52% (220 nm), 98.41% (210 nm), 97.10% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{16}ClF_4N_3O_2S$ 461.06, m/z found 462.0 $[M+H]^+$.

Compound 9: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3-fluoroazetidin-1-yl) indazole



[00295] ***Step 1:*** To a solution of (1E)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (800 mg, 2.12 mmol, 1 eq) in DCM (10 mL) were added TEA (2.14 g, 21.2 mmol, 2.95

mL, 10 eq) and 3-fluoroazetidine hydrochloride (284 mg, 2.54 mmol, 1.2 eq) at -78 °C. The mixture was stirred for 0.5 hour and then the mixture was stirred at 0 °C for 0.5 hour. LCMS showed (1E)-2, 6-dichloro-4-fluoro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride was consumed completely and the desired mass was detected. The reaction mixture was concentrated to give the desired N-[(E)-[(2, 6-dichlorophenyl)-(3-fluoroazetidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (880 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{17}H_{16}Cl_2FN_3O_2S$ 415.03 m/z found 415.9 $[M+H]^+$.

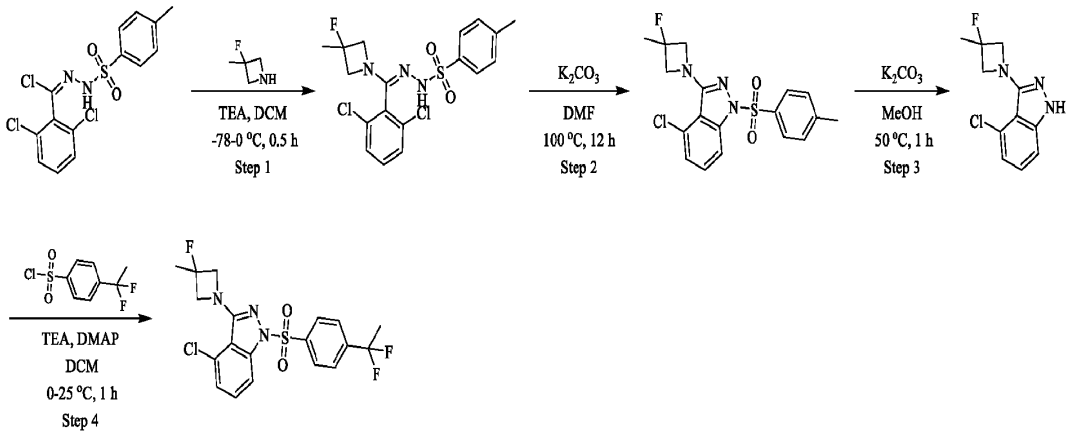
[00296] ***Step 2:*** To a solution of N-[(E)-[(2, 6-dichlorophenyl)-(3-fluoroazetidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (880 mg, 2.11 mmol, 1 eq) in DMF (10 mL) was added K_2CO_3 (876 mg, 6.34 mmol, 3 eq). The mixture was stirred at 100 °C for 12 hours. LCMS showed N-[(E)-[(2, 6-dichlorophenyl)-(3-fluoroazetidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. The residue was added water (10 mL) and extracted with EtOAc (3 X 10 mL). The combined organics were concentrated to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether/ ethyl acetate = 100/1 to 1/1) to give the desired 4-chloro-3-(3-fluoroazetidin-1-yl)-1-(p-tolylsulfonyl) indazole (280 mg, 737 μmol, 34.9% yield) as a yellow oil. MS (ESI): mass calcd. For $C_{17}H_{15}ClFN_3O_2S$ 379.06 m/z found 379.9 $[M+H]^+$.

[00297] ***Step 3:*** To a solution of 4-chloro-3-(3-fluoroazetidin-1-yl)-1-(p-tolylsulfonyl) indazole (280 mg, 737 μmol, 1 eq) in MeOH (3 mL) was added K_2CO_3 (204 mg, 1.47 mmol, 2 eq). The mixture was stirred at 50 °C for 1 hour. LCMS showed 4-chloro-3-(3-fluoroazetidin-1-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction was concentrated to get a residue. The residue was purified by column chromatography (silica gel, petroleum ether/ ethyl acetate = 100/1 to 3/1) to give the desired 4-chloro-3-(3-fluoroazetidin-1-yl)-1H-indazole (90 mg, 399 μmol, 54.1% yield) as a white solid. MS (ESI): mass calcd. For $C_{10}H_9ClFN_3$ 225.05 m/z found 225.9 $[M+H]^-$.

[00298] ***Step 4:*** To a solution of 4-chloro-3-(3-fluoroazetidin-1-yl)-1H-indazole (80 mg, 355 μmol, 1 eq) in DCM (1 mL) were added TEA (179 mg, 1.77 mmol, 247 μL, 5 eq) and DMAP (4 mg, 35.5 μmol, 0.1 eq), 4-(1,1-difluoroethyl)benzenesulfonyl chloride (171 mg, 709 μmol, 2 eq). The mixture was stirred at 25 °C for 1 hour. LCMS showed 4-chloro-3-(3-fluoroazetidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction was concentrated to get a residue. The residue was purified by *prep*-HPLC (column: Waters Xbridge

C18 150 * 50 mm * 10 μm; mobile phase: [H_2O(10mM NH_4HCO_3)-ACN]; gradient: 40% - 70% B over 8.0 min) to give the desired 4-chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(3-fluoroazetidin-1-yl)indazole (16 mg, 36.9 μmol, 10.4% yield, 99.23% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J = 8.4 Hz, 1H), 7.97 (br d, J = 8.1 Hz, 2H), 7.78 (br d, J = 8.2 Hz, 2H), 7.65 (br t, J = 8.1 Hz, 1H), 7.46 (br d, J = 7.7 Hz, 1H), 5.59 - 5.35 (m, 1H), 4.60 - 4.43 (m, 2H), 4.34 - 4.17 (m, 2H), 1.95 (br t, J = 19.1 Hz, 3H). MS (ESI): mass calcd. For $C_{18}H_{15}ClF_3N_3O_2S$ 429.05 m/z found 430.0 $[M+H]^+$.

Compound 10: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3-fluoro-3-methyl-azetidin-1-yl) indazole



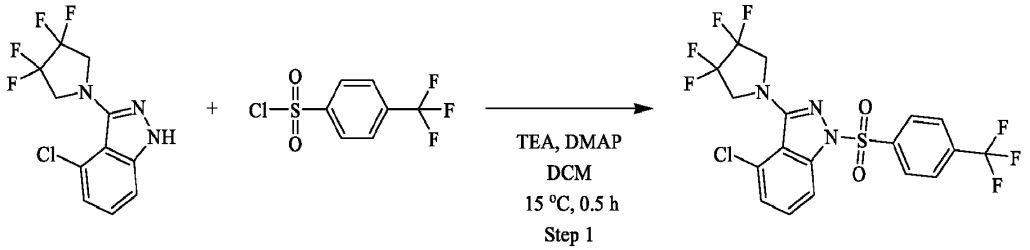
[00299] ***Step 1:*** The mixture of 3-fluoro-3-methyl-azetidine (319 mg, 2.54 mmol, 1.2 eq, HCl) in DCM (8 mL) were added TEA (1.07 g, 10.6 mmol, 1.47 mL, 5 eq) and (1E)-2,6-dichloro-N-(p-tolylsulfonyl)benzohydrazonoyl chloride (800 mg, 2.12 mmol, 1 eq) was added the mixture at -78 °C. The mixture was stirred at 0 °C for 0.5 hour. LCMS showed (1E)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride was consumed completely and the desired mass was detected. The reaction mixture was quenched by addition sat. aq. NH_4Cl (30 mL) at 0 °C, and extracted with DCM (3 X 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The reaction mixture was concentrated to give the desired N-[(E)-[(2, 6-dichlorophenyl)-(3-fluoro-3-methyl-azetidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (800 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{18}H_{18}Cl_2FN_3O_2S$ 429.05 m/z found 430.1 $[M+H]^+$.

[00300] ***Step 2:*** The mixture of N-[(E)-[(2, 6-dichlorophenyl)-(3-fluoro-3-methyl-azetidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (800 mg, 1.86 mmol, 1 eq) in DMF (6 mL) was added K_2CO_3 (771 mg, 5.58 mmol, 3 eq). The mixture was stirred at 100 °C for 12 hours. LCMS showed N-[(E)-[(2, 6-dichlorophenyl)-(3-fluoro-3-methyl-azetidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. The reaction mixture was concentrated to give the desired 4-chloro-3-(3-fluoro-3-methyl-azetidin-1-yl)-1-(p-tolylsulfonyl) indazole (700 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{18}H_{17}ClFN_3O_2S$ 393.07 m/z found 394.1 $[M+H]^+$.

[00301] ***Step 3:*** The mixture of 4-chloro-3-(3-fluoro-3-methyl-azetidin-1-yl)-1-(p-tolylsulfonyl) indazole (800 mg, 2.03 mmol, 1 eq) in MeOH (10 mL) was added K_2CO_3 (561 mg, 4.06 mmol, 2 eq). The mixture was stirred at 50 °C for 1 hour. LCMS showed 4-chloro-3-(3-fluoro-3-methyl-azetidin-1-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction was concentrated to get a residue. The residue was added water (30 mL) and extracted with EtOAc (3 X 50 mL). The residue was purified by column chromatography (silica gel, petroleum ether/ ethyl acetate = 10/1 to 5/1) The reaction mixture was concentrated to give the desired 4-chloro-3-(3-fluoro-3-methyl-azetidin-1-yl)-1H-indazole (200 mg, 834 μmol, 47.0% yield) as a yellow oil. MS (ESI): mass calcd. For $C_{11}H_{11}ClFN_3$ 239.06 m/z found 240.2 $[M+H]^+$.

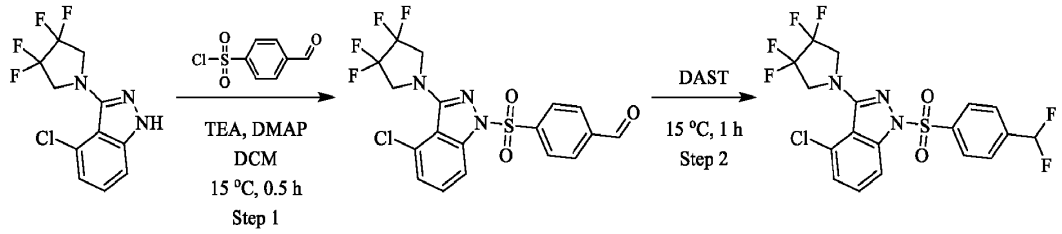
[00302] ***Step 4:*** The mixture of 4-chloro-3-(3-fluoro-3-methyl-azetidin-1-yl)-1H-indazole (200 mg, 834 μmol, 1 eq) in DCM (10 mL) were added TEA (253 mg, 2.50 mmol, 348 μL, 3 eq) and DMAP (10.2 mg, 83.5 μmol, 0.1 eq) at 0 °C. The mixture was stirred 25 °C for 1 hour. LCMS showed 4-chloro-3-(3-fluoro-3-methyl-azetidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction was concentrated to get a residue. The residue was purified by *prep*-HPLC (column: Waters Xbridge C18 150 * 50 mm * 10 μm; mobile phase: [H_2O(10mM NH_4HCO_3)-ACN]; gradient: 60% - 90% B over 8.0 min) to give the desired 4-chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(3-fluoro-3-methyl-azetidin-1-yl)indazole (82.2 mg, 171 μmol, 20.5% yield, 92.23% purity) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 8.6 Hz, 2H), 7.65 (t, J = 8.1 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 4.38 - 4.14 (m, 4H), 1.94 (t, J = 19.1 Hz, 3H), 1.68 - 1.49 (m, 3H) HPLC: 96.32% (220 nm), 96.20% (215 nm), 92.23% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{17}ClF_3N_3O_2S$ 443.07 m/z found 444.3 $[M+H]^+$.

Compound 11: 4-Chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-[4-(trifluoromethyl) phenyl] sulfonyl-indazole



[00303] ***Step 1***: To a solution of 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (50 mg, 170 μmol, 1 eq) and 4-(trifluoromethyl)benzenesulfonyl chloride (62.5 mg, 255 μmol, 1.5 eq) in DCM (1 mL) were added TEA (86.2 mg, 851 μmol, 119 μL, 5 eq) and DMAP (2.08 mg, 17.0 μmol, 0.1 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-[4-(trifluoromethyl) phenyl] sulfonyl-indazole (15.5 mg, 29.2 μmol, 17.2% yield, 94.67% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 8.4 Hz, 3H), 7.95 (d, J = 8.4 Hz, 2H), 7.69 (t, J = 8.1 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 4.23 (br t, J = 12.1 Hz, 4H). HPLC: 94.67% (220 nm), 100.0% (215 nm), 94.83% (254 nm). MS (ESI): mass calcd. For $C_{18}H_{11}ClF_7N_3O_2S$ 501.0, m/z found 502.0 $[M+H]^+$.

Compound 12: 4-Chloro-1-[4-(difluoromethyl) phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole

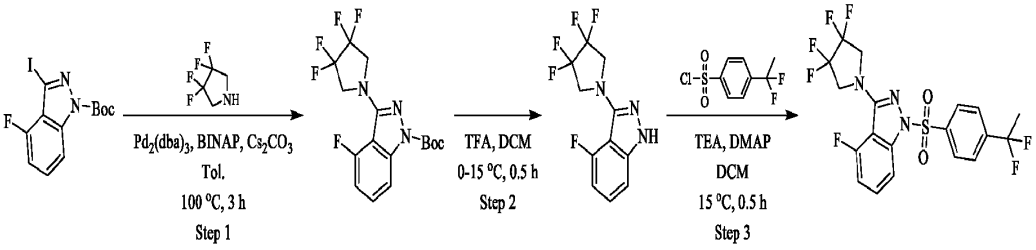


[00304] ***Step 1***: To a solution of 4-chloro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole (100 mg, 341 μmol, 1 eq) and 4-formylbenzenesulfonyl chloride (105 mg, 511 μmol, 1.5 eq) in DCM (1 mL) were added TEA (103 mg, 1.02 mmol, 142 μL, 3 eq) and DMAP (4.16 mg, 34.1 μmol, 0.1 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ ethyl acetate = 1/1) to give the desired 4-[4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazol-1-yl] sulfonylbenzaldehyde (27 mg, 58.5 μmol, 17.2% yield) as a white solid. MS (ESI): mass calcd. For $C_{18}H_{12}ClF_4N_3O_3S$ 461.1, m/z found 462.1 $[M+H]^+$.

[00305] ***Step 2***: To a solution of 4-[4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazol-1-yl] sulfonylbenzaldehyde (24 mg, 52.0 μmol, 1 eq) in DAST (0.3 mL). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-[4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazol-1-yl] sulfonylbenzaldehyde was consumed completely and the desired mass was detected. The reaction was quenched by Sodium bicarbonate in H_2O (10 ml), then the mixture was extracted with EtOAc (20 mL). The organic phase was separated, washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-1-[4-(difluoromethyl) phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole (12.3 mg, 24.4 μmol, 46.9% yield, 95.84% purity) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 8.3 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H), 7.67 (t, J = 8.1 Hz, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.25 - 6.93 (m, 1H), 4.23 (br t, J = 12.2 Hz, 4H). HPLC: 95.84% (220 nm), 94.80% (215 nm), 96.15% (254 nm). MS (ESI): mass calcd. For $C_{18}H_{12}ClF_6N_3O_2S$ 483.0, m/z found 484.0 $[M+H]^+$.

Compound 13: 1-((4-(1, 1-Difluoroethyl) phenyl) sulfonyl)-4-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole

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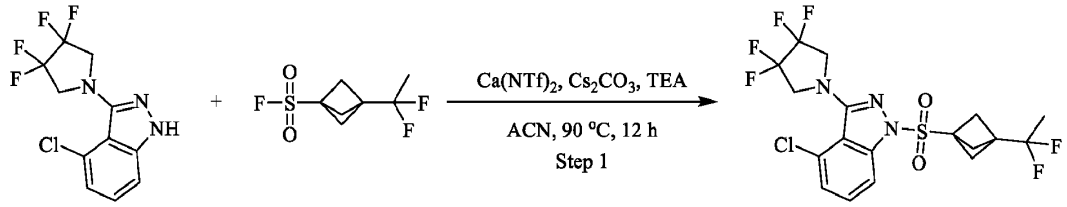
[00306] ***Step 1***: A mixture of tert-butyl 4-fluoro-3-iodo-indazole-1-carboxylate (100 mg, 278 μmol, 1 eq), 3, 3, 4, 4-tetrafluoropyrrolidine (50 mg, 278 μmol, 1 eq, HCl), $Pd_2(dba)_3$ (25.5 mg, 27.9 μmol, 0.1 eq), Cs_2CO_3 (272 mg, 835 μmol, 3 eq) and BINAP (17.3 mg, 27.9 μmol, 0.1 eq) in toluene (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 3 hours under N_2 atmosphere. LC-MS showed tert-butyl 4-fluoro-3-iodo-indazole-1-carboxylate was consumed completely and the desired mass was detected. The crude was added H_2O (20 mL) and extracted with EtOAc (15 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) give the desired tert-butyl 4-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole-1-carboxylate (100 mg, 265 μmol, 95.17% yield) as a yellow oil. MS (ESI): mass calcd. For $C_{16}H_{16}F_5N_3O_2$ 377.12 m/z found 378.1 $[M+H]^+$.

[00307] ***Step 2***: To a solution of tert-butyl 4-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)indazole-1-carboxylate (100 mg, 265 μmol, 1 eq) in DCM (1 mL) was added TFA (453 mg, 3.98 mmol, 295 μL, 15 eq) at 0 °C. The mixture was stirred at 15°C for 0.5 hour. LC-MS showed tert-butyl 4-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole-1-carboxylate was consumed completely and the desired mass was detected. The reaction mixture was concentrated in vacuum to give the desired 4-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (100 mg, crude, TFA) as a brown oil. MS (ESI): mass calcd. For $C_{11}H_8F_5N_3$ 277.06 m/z found 278.0 $[M+H]^+$.

[00308] ***Step 3***: To a solution of 4-fluoro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole (80 mg, 289 μmol, 1 eq) and 4-(1,1-difluoroethyl)benzenesulfonyl chloride (69.5 mg, 289 μmol, 1 eq) in DCM (0.5 mL) were added TEA (58.4 mg, 577 μmol, 80.3 μL, 2 eq) and DMAP (3.53 mg, 28.9 μmol, 0.1 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 4-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The crude was added H_2O (20 mL) and extracted with DCM (15 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and

concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) give the desired 1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-4-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole (3.2 mg, 6.65 μmol, 2.30% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.5 Hz, 2H), 7.79 - 7.73 (m, 1H), 7.31 (dd, J = 8.1, 11.3 Hz, 1H), 4.39 - 4.26 (m, 4H), 1.99 (t, J = 19.1 Hz, 3H). HPLC: 100.00% (220 nm), 100.00% (215 nm), 100.00 (254 nm). MS (ESI): mass calcd. For $C_{19}H_{14}F_7N_3O_2S$ 481.07 m/z found 482.1 $[M+H]^+$.

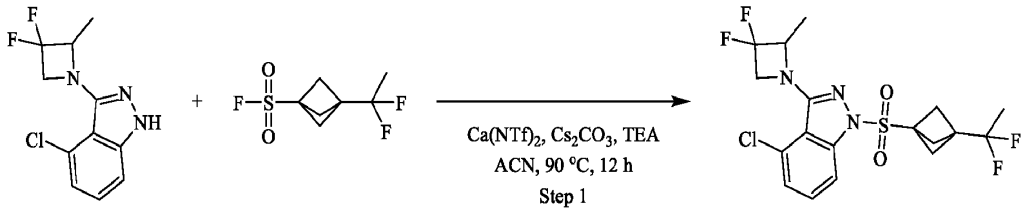
Compound 14: 4-Chloro-1-[[3-(1, 1-difluoroethyl)-1- bicycle [1.1.1] pentanyl] sulfonyl]-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole



[00309] ***Step 1:*** To a solution of 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (50 mg, 170 μmol, 1 eq) and 3-(1, 1-difluoroethyl) bicycle [1.1.1] pentane-1-sulfonyl fluoride (36.5 mg, 170 μmol, 1 eq) in ACN (3 mL) were added bis[bis(trifluoromethylsulfonyl) amino] calcium (307 mg, 511 μmol, 3 eq), TEA (86.2 mg, 851 μmol, 119 μL, 5 eq) and Cs_2CO_3 (277 mg, 851 μmol, 5 eq). The mixture was stirred at 90 °C for 12 hours. LC-MS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was filtered, and concentrated under reduced pressure to give a residue. The crude product was purified by *prep*-HPLC (column: Phenomenex Luna C18 75 * 30mm *3 μm; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 65% - 95% B over 8.0 minutes) to give the desired 4-chloro-1-[[3-(1, 1-difluoroethyl)-1-bicyclo [1.1.1] pentanyl] sulfonyl]-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole (6.7 mg, 13.7 μmol, 8.07% yield, 100.00% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 8.50 Hz, 1 H) 7.62 - 7.70 (m, 1 H) 7.55 (d, J = 7.63 Hz, 1 H) 4.27 (br t, J = 12.95 Hz, 4 H) 2.12 (s, 6 H) 1.51 (t, J = 18.89 Hz, 3 H). HPLC: 100.00% (220 nm), 100.00% (215 nm), 100.00% (254 nm). MS (ESI): mass calcd. For $C_{18}H_{16}ClF_6N_3O_2S$ 487.06 m/z found 488.1 $[M+H]^+$.

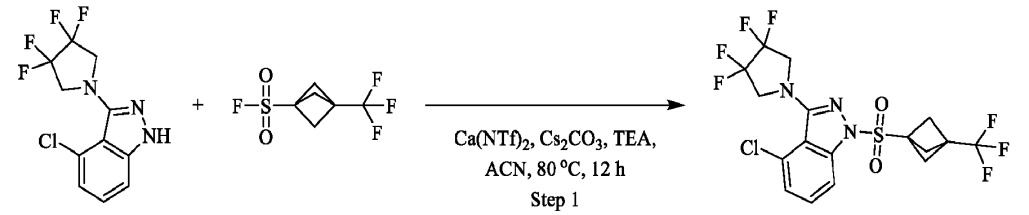
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Compound 15: 4-Chloro-1-[[3-(1, 1-difluoroethyl)-1-bicyclo [1.1.1] pentanyl] sulfonyl]-3-(3, 3-difluoro-2-methyl-azetidin-1-yl) indazole



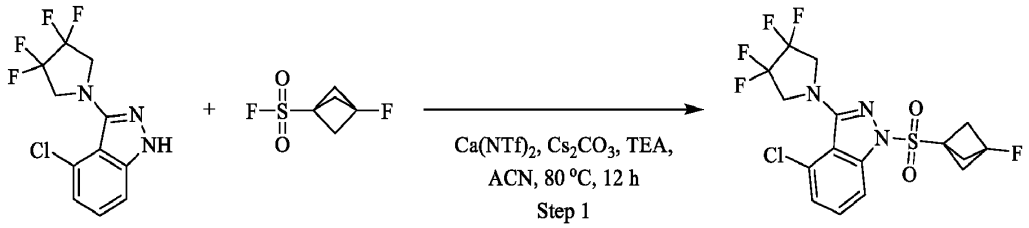
[00310] ***Step 1:*** To a solution of 4-chloro-3-(3, 3-difluoro-2-methyl-azetidin-1-yl)-1H-indazole (70 mg, 272 μmol, 1 eq) and 3-(1,1-difluoroethyl)bicyclo[1.1.1]pentane-1-sulfonyl fluoride (58.2 mg, 272 μmol, 1 eq) in ACN (3 mL) were added bis[bis(trifluoromethylsulfonyl)amino]calcium (163 mg, 272 μmol, 1 eq), TEA (137 mg, 1.36 mmol, 189 μL, 5 eq) and Cs_2CO_3 (443 mg, 1.36 mmol, 5 eq). The mixture was stirred at 90 °C for 12 hours. LC-MS showed 4-chloro-3-(3, 3-difluoro-2-methyl-azetidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; according to LCMS; method: column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O(0.1% TFA)-ACN]; gradient: 65%-95% B over 8.0 min) to give the desired 4-chloro-1-[[3-(1,1-difluoroethyl)-1-bicyclo[1.1.1]pentanyl]sulfonyl]-3-(3,3-difluoro-2-methyl-azetidin-1-yl)indazole (1.6 mg, 3.54 μmol, 1.33% yield, 100.0% purity) as a white solid. ^{1}H NMR (DMSO-d_6) δ 7.86 (br d, J = 8.4 Hz, 1H), 7.62 (br t, J = 8.0 Hz, 1H), 7.53 - 7.46 (m, 1H), 5.01 - 4.86 (m, 1H), 4.77 (q, J = 11.6 Hz, 1H), 4.62 - 4.48 (m, 1H), 2.09 (s, 6H), 1.51 (br t, J = 18.9 Hz, 3H), 1.35 (br d, J = 6.4 Hz, 3H). HPLC: 100.0% (220 nm), 99.72% (215 nm), 100.0% (254 nm). MS (ESI): mass calcd. For $C_{18}H_{18}ClF_4N_3O_2S$ 451.1 m/z found 452.1 $[M+H]^+$.

Compound 16: 4-Chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-[[3-(trifluoromethyl)-1-bicyclo [1.1.1] pentanyl] sulfonyl] indazole



[00311] ***Step 1:*** To a solution of 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (10 mg, 34.1 μmol, 1 eq) and 3-(trifluoromethyl) bicycle [1.1.1] pentane-1-sulfonyl fluoride (8.92 mg, 40.9 μmol, 1.2 eq) in ACN (1.5 mL) were added bis [bis (trifluoromethylsulfonyl) amino] calcium (24.5 mg, 40.9 μmol, 1.2 eq), Cs_2CO_3 (55.5 mg, 170 μmol, 5 eq) and TEA (17.2 mg, 170 μmol, 23.7 μL, 5 eq). The mixture was stirred at 80 °C for 12 hours. LCMS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O(0.1%TFA)-ACN]; gradient: 45% - 75% B over 8.0 min) to give the desired 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-[[3-(trifluoromethyl)-1-bicyclo [1.1.1] pentanyl] sulfonyl]indazole (5.9 mg, 12.0 μmol, 35.2% yield, 100.00% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, J = 8.3 Hz, 1H), 7.60 (t, J = 8.1 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 4.22 (br t, J = 12.2 Hz, 4H), 2.29 (s, 6H). HPLC: 99.75% (220 nm), 99.49% (215 nm), 100.00% (254 nm). MS (ESI): mass calcd. For $C_{17}H_{13}ClF_7N_3O_2S$ 491.03 m/z found 492.00 $[M+H]^+$.

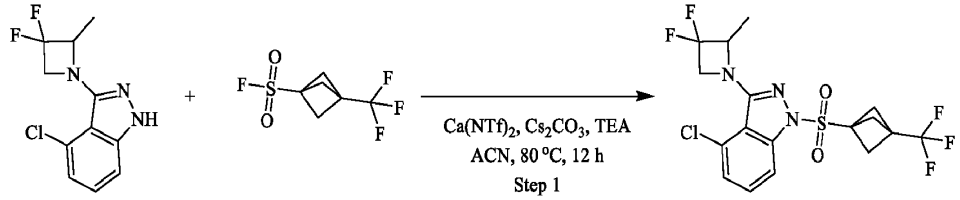
Compound 17: 4-Chloro-1-[(3-fluoro-1-bicyclo [1.1.1] pentanyl) sulfonyl]-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole



[00312] ***Step 1:*** To a solution of 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (10 mg, 34.1 μmol, 1 eq) and 3-fluorobicyclo [1.1.1] pentane-1-sulfonyl fluoride (6.9 mg, 40.9 μmol, 1.2 eq) in ACN (1.5 mL) were added bis [bis (trifluoromethylsulfonyl) amino] calcium (24.5 mg, 40.9 μmol, 1.2 eq), Cs_2CO_3 (55.5 mg, 170 μmol, 5 eq) and TEA (17.2 mg, 170 μmol, 23.7 μL, 5 eq). The mixture was stirred at 80 °C for 12 hours. LCMS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase:

[H_2O(0.1%TFA)-ACN]; gradient: 40% - 70% B over 8.0 min) to give the desired 4-chloro-1-[(3-fluoro-1-bicyclo [1.1.1] pentanyl)sulfonyl]-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole (4.9 mg, 11.1 μmol, 32.57% yield, 97.44% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 8.5 Hz, 1H), 7.67 (t, J = 8.1 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 4.34 - 4.20 (m, 4H), 2.45 (d, J = 2.3 Hz, 6H). HPLC: 97.44% (220 nm), 96.90% (215 nm), 99.84% (254 nm). MS (ESI): mass calcd. For $C_{16}H_{13}ClF_5N_3O_2S$ 441.03 m/z found 442.00 $[M+H]^+$.

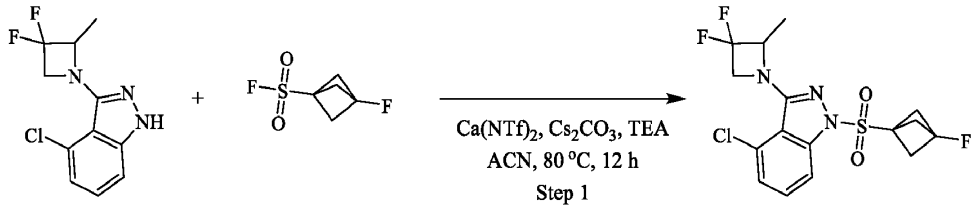
Compound 18: 4-Chloro-3-(3, 3-difluoro-2-methylazetidin-1-yl)-1-((3-(trifluoromethyl) bicycle [1.1.1] pentan-1-yl) sulfonyl) -1H-indazole



[00313] ***Step 1***: To a solution of 4-chloro-3-(3,3-difluoro-2-methyl-azetidin-1-yl)-1H-indazole (20 mg, 77.6 μmol, 1 eq) and 3-(trifluoromethyl)bicyclo[1.1.1]pentane-1-sulfonyl fluoride (25.4 mg, 116 μmol, 1.5 eq) in ACN (2 mL) were added bis [bis (trifluoromethylsulfonyl) amino] calcium (55.9 mg, 93.1 μmol, 1.2 eq), TEA (39.3 mg, 388 μmol, 54.0 μL, 5 eq) and Cs_2CO_3 (126 mg, 388 μmol, 5 eq). The mixture was stirred at 80 °C for 12 hours. LC-MS showed 4-chloro-3-(3, 3-difluoro-2-methyl-azetidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The crude was added H_2O (20 mL) and extracted with EtOAc (15 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition, column: Phenomenex Luna C18 75 * 30 mm *3 μm; mobile phase: [H_2O(0.1%TFA)-ACN]; gradient: 50% - 80% B over 8.0 min) give the desired 4-chloro-3-(3, 3-difluoro-2-methylazetidin-1-yl)-1-((3-(trifluoromethyl) bicycle [1.1.1] pentan-1-yl) sulfonyl) - 1H-indazole (10.5 mg, 23.0 μmol, 29.7% yield, 100.00% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 8.1 Hz, 1H), 7.51 (d, J = 7.1 Hz, 1H), 5.01 - 4.88 (m, 1H), 4.83 - 4.73 (m, 1H), 4.57 (dt, J = 10.7, 13.4 Hz, 1H), 2.33 (s, 6H), 1.36 (d, J = 6.5 Hz, 3H). HPLC: 100.00% (220 nm), 100.00% (215 nm), 100.00 (254 nm). MS (ESI): mass calcd. For $C_{17}H_{15}ClF_5N_3O_2S$ 455.05 m/z found 456.1 $[M+H]^-$.

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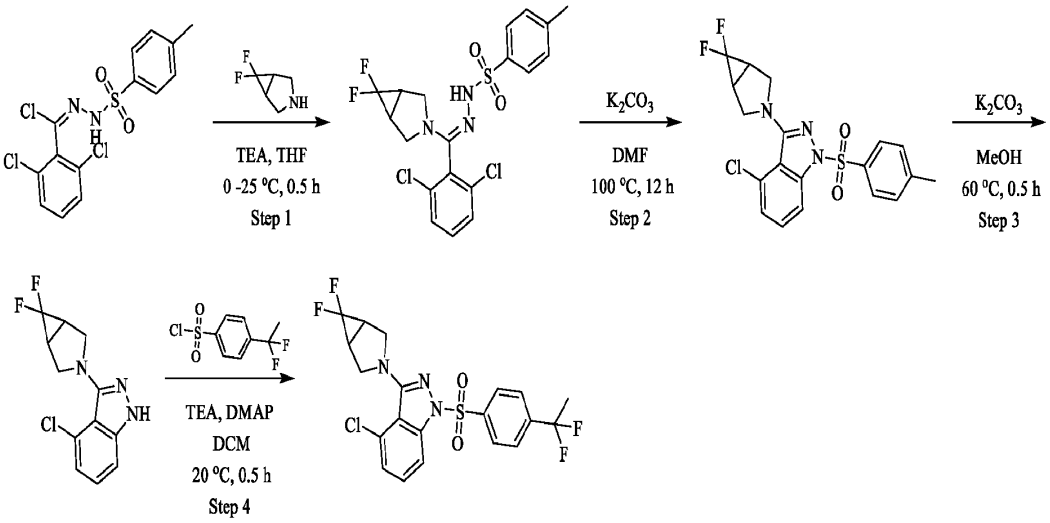
Compound 19: 4-Chloro-3-(3, 3-difluoro-2-methylazetidin-1-yl)-1-((3-fluorobicyclo [1.1.1] pentan-1-yl) sulfonyl)-1H-indazole



[00314] ***Step 1***: To a solution of 4-chloro-3-(3,3-difluoro-2-methyl-azetidin-1-yl)-1H-indazole (10 mg, 38.8 μmol, 1 eq) and 3-fluorobicyclo[1.1.1]pentane-1-sulfonyl fluoride (9.79 mg, 58.2 μmol, 1.5 eq) in ACN (2 mL) were added bis[bis(trifluoromethylsulfonyl) amino]calcium (28.0 mg, 46.6 μmol, 1.2 eq), TEA (19.6 mg, 194 μmol, 27.0 μL, 5 eq) and Cs_2CO_3 (63.2 mg, 194 μmol, 5 eq). The mixture was stirred at 80 °C for 12 hours. LC-MS showed 4-chloro-3-(3, 3-difluoro-2-methyl-azetidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The crude was added H_2O (20 mL) and extracted with EtOAc (15 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition, column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O(0.1%TFA)-ACN]; gradient: 45%-75% B over 8.0 min) to give the desired 4-chloro-3-(3,3-difluoro-2-methyl-azetidin-1-yl)-1-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)sulfonyl]indazole (6.5 mg, 16.0 μmol, 41.3 % yield, 100.00% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 8.3 Hz, 1H), 7.69 (t, J = 8.1 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 5.06 - 4.92 (m, 1H), 4.89 - 4.78 (m, 1H), 4.63 (dt, J = 10.8, 13.4 Hz, 1H), 2.49 (d, J = 2.3 Hz, 6H), 1.42 (d, J = 6.5 Hz, 3H). HPLC: 100.00% (220 nm), 100.00% (215 nm), 100.00 (254 nm). MS (ESI): mass calcd. For $C_{16}H_{15}ClF_3N_3O_2S$ 405.05 m/z found 406.1 $[M+H]^+$.

Compound 20: 4-Chloro-3-(6, 6-difluoro-3-azabicyclo [3.1.0] hexan-3-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole

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[00315] ***Step 1***: To a solution of 6, 6-difluoro-3-azabicyclo [3.1.0] hexane (150 mg, 964 μmol, 1 eq, HCl) in THF (2 mL) was added dropwise TEA (976 mg, 9.64 mmol, 1.34 mL, 10 eq) at 25 °C. After addition, the mixture was stirred at this temperature for 10 minutes. (1Z)-2,6-dichloro-N-(p-tolylsulfonyl)benzohydrazonoyl chloride (401 mg, 1.06 mmol, 1.1 eq) in THF (2 mL) was added dropwise to the mixture at 0 °C. The resulting mixture was stirred at 25 °C for 20 minutes. LC-MS showed 6, 6-difluoro-3-azabicyclo [3.1.0] hexane was consumed completely and one main peak with the desired mass was detected. The reaction mixture was separated between 20 mL of water and 40 mL of ethyl acetate. The organic phase was separated, washed with 30 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(Z)-[(2, 6-dichlorophenyl)-(6, 6-difluoro-3-azabicyclo [3.1.0] hexan-3-yl) methylene] amino]-4-methyl-benzenesulfonamide (440 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{19}H_{17}Cl_2F_2N_3O_2S$ 459.04 m/z found 460.2 $[M+H]^+$.

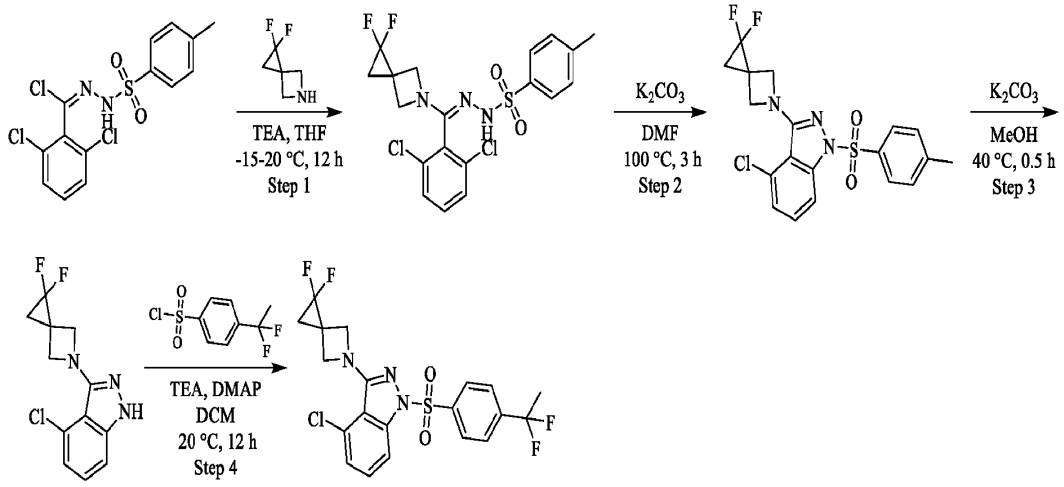
[00316] ***Step 2***: To a solution of N-[(Z)-[(2, 6-dichlorophenyl)-(6, 6-difluoro-3-azabicyclo [3.1.0] hexan-3-yl) methylene] amino]-4-methyl-benzenesulfonamide (440 mg, 956 μmol, 1 eq) in DMF (10 mL) was added K_2CO_3 (661 mg, 4.78 mmol, 5 eq). The mixture was stirred at 100 °C for 12 hours. LC-MS showed N-[(Z)-[(2, 6-dichlorophenyl)-(6, 6-difluoro-3-azabicyclo [3.1.0] hexan-3-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. The reaction mixture was added to water (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(6, 6-difluoro-3-azabicyclo [3.1.0] hexan-3-yl)-1-(p-tolylsulfonyl) indazole (400 mg,

crude) as a yellow oil. MS (ESI): mass calcd. For $C_{19}H_{16}ClF_2N_3O_2S$ 423.06 m/z found 424.1 $[M+H]^+$.

[00317] ***Step 3***: To a solution of 4-chloro-3-(6, 6-difluoro-3-azabicyclo [3.1.0] hexan-3-yl)-1-(p-tolylsulfonyl) indazole (400 mg, 944 μmol, 1 eq) in MeOH (10 mL) was added K_2CO_3 (652 mg, 4.72 mmol, 5 eq). The mixture was stirred at 60 °C for 0.5 hour. LC-MS showed 4-chloro-3-(6, 6-difluoro-3-azabicyclo [3.1.0] hexan-3-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-(6, 6-difluoro-3-azabicyclo [3.1.0] hexan-3-yl)-1H-indazole (80 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{12}H_{10}ClF_2N_3$ 269.05 m/z found 270.2 $[M+H]^+$.

[00318] ***Step 4***: To a solution of 4-chloro-3-(6, 6-difluoro-3-azabicyclo [3.1.0] hexan-3-yl)-1H-indazole (30 mg, 111 μmol, 1 eq) and 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (40.2 mg, 167 μmol, 1.5 eq) in DCM (1 mL) were added TEA (33.8 mg, 334 μmol, 46.5 μL, 3 eq) and DMAP (1.36 mg, 11.1 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(6, 6-difluoro-3-azabicyclo [3.1.0] hexan-3-yl)-1H-indazole was consumed completely and one main peak with the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 80 * 30 mm * 3 μm; mobile phase: $[H_2O(0.1\%TFA)$-ACN]; gradient: 50%-80% B over 8.0 min) to give the desired 4-chloro-3-(6, 6-difluoro-3-azabicyclo [3.1.0] hexan-3-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole (6.0 mg, 12.1 μmol, 10.9% yield, 95.51% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.6 Hz, 2H), 7.64 (t, J = 8.1 Hz, 1H), 7.49 (d, J = 7.7 Hz, 1H), 4.01 (d, J = 11.0 Hz, 2H), 3.84 - 3.75 (m, 2H), 2.62 (br d, J = 11.7 Hz, 2H), 1.94 (t, J = 19.1 Hz, 3H). HPLC: 95.51% (220 nm), 95.21% (215 nm), 96.48 (254 nm). MS (ESI): mass calcd. For $C_{20}H_{16}ClF_4N_3O_2S$ 473.06 m/z found 474.0 $[M+H]^-$.

Compound 21: 4-Chloro-3-(2, 2-difluoro-5-azaspiro [2.3] hexan-5-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole



[00319] ***Step 1:*** To a solution of (1E)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (364 mg, 964 μmol, 1 eq) and TEA (976 mg, 9.64 mmol, 1.34 mL, 10 eq) in THF (10 mL) was added 2, 2-difluoro-5-azaspiro [2.3] hexane (150 mg, 964 μmol, 1 eq, HCl) at -15 °C and the mixture was stirred at 20 °C for 12 hours. LCMS showed (1E)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give the desired N-[(E)-[(2, 6-dichlorophenyl)-(2, 2-difluoro-5-azaspiro [2.3] hexan-5-yl) methylene] amino]-4-methyl-benzenesulfonamide (443 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{19}H_{17}N_3SO_2Cl_2F_2$ 459.04 m/z found 460.1 $[M+H]^+$.

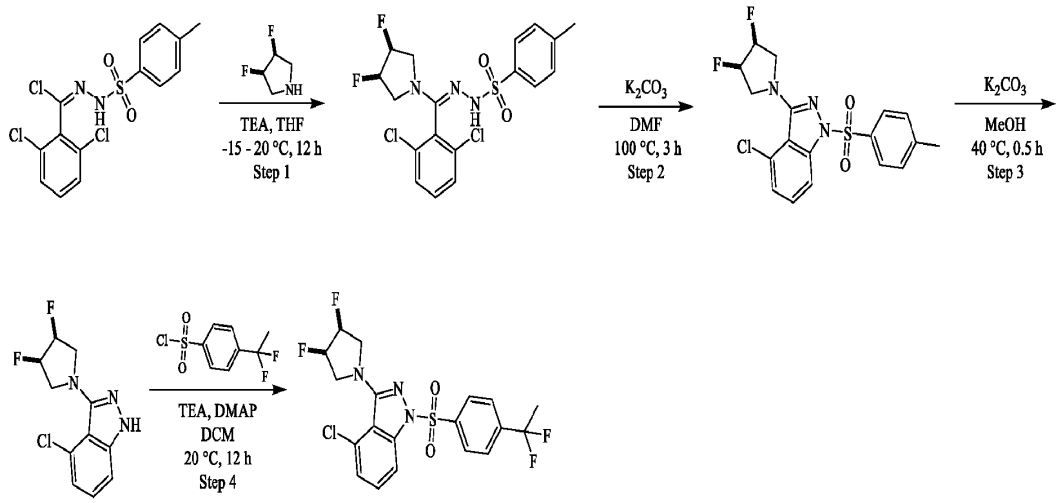
[00320] ***Step 2:*** The mixture of N-[(E)-[(2, 6-dichlorophenyl)-(2, 2-difluoro-5-azaspiro [2.3] hexan-5-yl) methylene] amino]-4-methyl-benzenesulfonamide (443 mg, 962 μmol, 1 eq) and K_2CO_3 (1.33 g, 9.62 mmol, 10 eq) in DMF (4 mL) was stirred at 100 °C for 3 hours. LCMS showed N-[(E)-[(2, 6-dichlorophenyl)-(2, 2-difluoro-5-azaspiro [2.3] hexan-5-yl) methylene] amino]-4-methyl-benzenesulfonamide remained and the desired mass was detected. The reaction was poured into ice-water (50 mL) and extracted with MTBE (3 X 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(2, 2-difluoro-5-azaspiro [2.3] hexan-5-yl)-1-(p-tolylsulfonyl) indazole (400 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{19}H_{16}N_3SO_2ClF_2$ 423.06 m/z found 424.2 $[M+H]^+$.

[00321] ***Step 3:*** The mixture of 4-chloro-3-(2, 2-difluoro-5-azaspiro [2.3] hexan-5-yl)-1-(p-tolylsulfonyl) indazole (400 mg, 944 μmol, 1 eq) and K_2CO_3 (261 mg, 1.89 mmol, 2 eq) in

MeOH (4 mL) was stirred at 40 °C for 0.5 hour. LCMS showed 4-chloro-3-(2, 2-difluoro-5-azaspiro [2.3] hexan-5-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was added water (50 mL) and extracted with MTBE (3 X 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-(2, 2-difluoro-5-azaspiro [2.3] hexan-5-yl)-1H-indazole (130 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{12}H_{10}N_3ClF_2$ 269.05 m/z found 270.1 $[M+H]^+$.

[00322] ***Step 4:*** To a solution of 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (66.9 mg, 278 μmol, 1.5 eq) in DCM (2 mL) and 4-chloro-3-(2, 2-difluoro-5-azaspiro [2.3] hexan-5-yl)-1H-indazole (50 mg, 185 μmol, 1 eq) in DCM (2 mL) were added TEA (56.3 mg, 556 μmol, 3 eq) and DMAP (2.27 mg, 18.5 μmol, 0.1 eq). The mixture was stirred at 20 °C for 12 hours. LCMS showed 4-chloro-3-(2, 2-difluoro-5-azaspiro [2.3] hexan-5-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired 4-chloro-3-(2, 2-difluoro-5-azaspiro [2.3] hexan-5-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole (20 mg, 41.3 μmol, 22.3% yield, 97.86% purity) as a white solid. ^1H NMR (DMSO-d_6) δ 8.06 (d, 1H), 7.95 (d, 2H), 7.76 (d, 2H), 7.64 (m, 1H), 7.45 (d, 1H), 4.27-4.37 (m, 4H), 1.93 (m, 3H), 1.75 (br m, 2H). HPLC: 97.86% (220 nm), 97.09% (215 nm), 95.74% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{16}ClN_3SO_2F_4$ 473.06 m/z found 474.1 $[M+H]^+$.

Compound 22: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3, 4-difluoropyrrolidin-1-yl) indazole



[00323] ***Step 1:*** To the mixture of (1E)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (921 mg, 2.44 mmol, 1 eq) and TEA (2.47 g, 24.4 mmol, 3.39 mL, 10 eq) in THF (10 mL) was added 3, 4-difluoropyrrolidine (350 mg, 2.44 mmol, 1 eq, HCl) at -15 °C. The mixture was stirred at 20 °C for 12 hours. LCMS showed (1E)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give the desired N-[(E)-[(2, 6-dichlorophenyl)-(3, 4-difluoropyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (1.09 g, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{18}H_{17}N_3SO_2Cl_2F_2$ 447.04 m/z found 448.1 $[M+H]^+$.

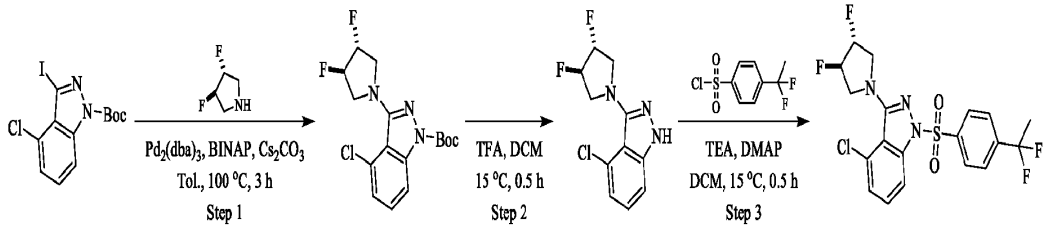
[00324] ***Step 2:*** The mixture of N-[(E)-[(2, 6-dichlorophenyl)-(3, 4-difluoropyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (1.09 g, 2.43 mmol, 1 eq) and K_2CO_3 (3.36 g, 24.3 mmol, 10 eq) in DMF (10 mL) was stirred at 100 °C for 3 hours. LCMS showed N-[(E)-[(2, 6-dichlorophenyl)-(3, 4-difluoropyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide remained and the desired mass was detected. The reaction was poured into ice-water (50 mL) and extracted with MTBE (3 X 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(3, 4-difluoropyrrolidin-1-yl)-1-(p-tolylsulfonyl) indazole (1 g, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{18}H_{16}N_3SO_2ClF_2$ 411.06 m/z found 412.1 $[M+H]^+$.

[00325] ***Step 3:*** The mixture of 4-chloro-3-(3, 4-difluoropyrrolidin-1-yl)-1-(p-tolylsulfonyl) indazole (1 g, 2.43 mmol, 1 eq) and K_2CO_3 (671 mg, 4.86 mmol, 2 eq) in MeOH (10 mL) was

stirred at 40 °C for 0.5 hour. LCMS showed 4-chloro-3-(3, 4-difluoropyrrolidin-1-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was added water (50 mL) and extracted with MTBE (3 X 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-(3, 4-difluoropyrrolidin-1-yl)-1H-indazole (250 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{11}H_{10}ClN_3F_2$ 257.05 m/z found 258.1 $[M+H]^+$.

[00326] ***Step 4:*** To a solution of 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (140 mg, 582 μmol, 1.5 eq) and 4-chloro-3-(3, 4-difluoropyrrolidin-1-yl)-1H-indazole (100 mg, 388 μmol, 1 eq) in DCM (2 mL) were added TEA (118 mg, 1.16 mmol, 3 eq) and DMAP (4.74 mg, 38.8 μmol, 0.1 eq). The mixture was stirred at 20 °C for 12 hours. LCMS showed 4-chloro-3-(3, 4-difluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired 4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3, 4-difluoropyrrolidin-1-yl) indazole (24.0 mg, 51.4 μmol, 13.2% yield, 98.87% purity) as a white solid. ^1H NMR (DMSO-d_6) δ 8.08 (d, 1H), 7.94 (d, 2H), 7.75 (d, 2H), 7.64 (m, 1H), 7.48 (d, 1H), 5.41-5.50 (m, 1H), 5.27-5.37 (m, 1H), 3.87-4.02 (m, 2H), 3.70-3.85 (m, 2H), 1.92 (m, 3H) HPLC: 98.87% (220 nm), 98.43% (215 nm), 99.38% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{16}ClF_4N_3O_2S$ 461.06 m/z found 462.1 $[M+H]^+$.

Compound 23: A meso form of 4-chloro-1-((4-(1, 1-difluoroethyl) phenyl) sulfonyl)-3-((3R, 4R)-3, 4-difluoropyrrolidin-1-yl)-1H-indazole



[00327] ***Step 1***: A mixture of tert-butyl 4-chloro-3-iodo-indazole-1-carboxylate (527 mg, 1.39 mmol, 1 eq), a meso form of 3, 4-difluoropyrrolidine (200 mg, 1.39 mmol, 1 eq, HCl), $Pd_2(dba)_3$

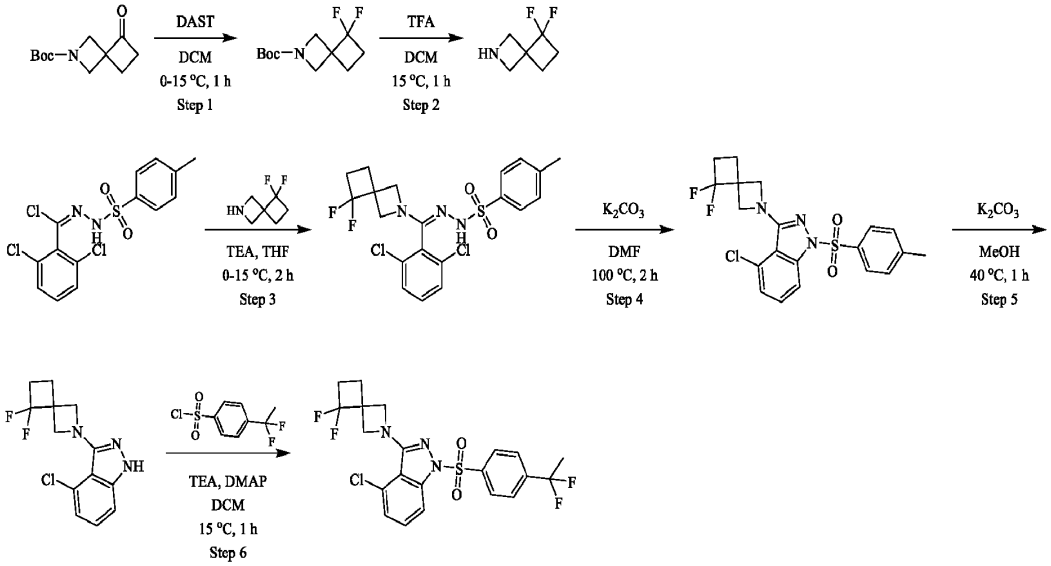
(128 mg, 139 μmol, 0.1 eq), Cs_2CO_3 (1.36 g, 4.18 mmol, 3 eq) and BINAP (86.8 mg, 139 μmol, 0.1 eq) in toluene (10 mL) was degassed and purged with N_2 for 3 times. The mixture was stirred at 100 °C for 3 hours under N_2 atmosphere. LC-MS showed tert-butyl 4-chloro-3-iodo-indazole-1-carboxylate was consumed completely and the desired mass was detected. The crude was added H_2O (20 mL) and extracted with EtOAc (20 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired meso form of tert-butyl 4-chloro-3-(3, 4-difluoropyrrolidin-1-yl) indazole-1-carboxylate (150 mg, 419 μmol, 30.1% yield) as a yellow oil. MS (ESI): mass calcd. For $C_{16}H_{18}ClF_2N_3O_2$ 357.11 m/z found 358.1 $[M+H]^+$.

[00328] ***Step 2***: To a solution of a meso form of tert-butyl 4-chloro-3-((3R, 4R)-3, 4-difluoropyrrolidin-1-yl) indazole-1-carboxylate (250 mg, 699 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 15 °C for 0.5 hour. TLC (petroleum ether/ ethyl acetate = 3/1) indicated a meso form of tert-butyl 4-chloro-3-((3R, 4R)-3, 4-difluoropyrrolidin-1-yl) indazole-1-carboxylate was consumed completely and one new spot was formed. The reaction mixture was concentrated in vacuum to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) give the desired meso form of 4-chloro-3-(3, 4-difluoropyrrolidin-1-yl)-1H-indazole (250 mg, crude, TFA) as a brown solid.

[00329] ***Step 3***: To a solution of a meso form of 4-chloro-3-((3R, 4R)-3, 4-difluoropyrrolidin-1-yl)-1H-indazole (20.0 mg, 53.8 μmol, 1 eq, TFA) and 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (13.0 mg, 53.8 μmol, 1 eq) in DCM (1 mL) were added TEA (27.2 mg, 269 μmol, 37.5 μL, 5 eq) and DMAP (657 μg, 5.38 μmol, 0.1 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed a meso form of 4-chloro-3-((3R, 4R)-3, 4-difluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The crude was added H_2O (20 mL) and extracted with DCM (15 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ ethyl acetate = 3/1) to give the desired meso form of 4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-((3R, 4R)-3, 4-difluoropyrrolidin-1-yl) indazole (2 mg, 4.14 μmol, 7.69 % yield, 95.53% purity) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 7.70 (t, J = 8.1 Hz, 1H), 7.54 (d, J = 7.4 Hz, 1H), 5.62 - 5.39 (m, 2H), 4.25 -

4.03 (m, 2H), 3.82 - 3.66 (m, 2H), 1.97 (t, J = 19.1 Hz, 3H). HPLC: 95.93% (220 nm), 95.88% (215 nm), 100.00 (254 nm). MS (ESI): mass calcd. For $C_{19}H_{16}ClF_4N_3O_2S$ 461.06 m/z found 462.1 $[M+H]^+$.

Compound 24: 4-Chloro-3-(7, 7-difluoro-2-azaspiro [3.3] heptan-2-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole



[00330] ***Step 1***: To a solution of tert-butyl 7-oxo-2-azaspiro [3.3] heptane-2-carboxylate (500 mg, 2.37 mmol, 1 eq) in DCM (6 mL) was added DAST (1.91 g, 11.8 mmol, 1.56 mL, 5 eq) at 0 °C. The mixture was stirred at 15 °C for 1 hour. TLC indicated tert-butyl 7-oxo-2-azaspiro [3.3] heptane-2-carboxylate was consumed completely one new spot was formed. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired tert-butyl 7, 7-difluoro-2-azaspiro [3.3] heptane-2-carboxylate (160 mg, 686 µmol, 28.9% yield) as a white oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.22 (d, J = 9.3 Hz, 2H), 3.76 (d, J = 9.3 Hz, 2H), 2.44 (tt, J = 8.6, 12.3 Hz, 2H), 2.05 - 1.94 (m, 2H), 1.43 (s, 9H).

[00331] ***Step 2***: To a solution of tert-butyl 7, 7-difluoro-2-azaspiro [3.3] heptane-2-carboxylate (160 mg, 686 µmol, 1 eq) in DCM (3 mL) was added TFA (1.96 g, 17.2 mmol, 1.27 mL, 25 eq). The mixture was stirred at 15 °C for 1 hour. TLC indicated tert-butyl 7, 7-difluoro-2-

azaspiro [3.3] heptane-2-carboxylate was consumed completely and one new spot was formed. The reaction mixture was filtered, and the filter liquor was concentrated under reduced pressure to give the desired 7, 7-difluoro-2-azaspiro [3.3] heptane (300 mg, crude, TFA) as a black oil.

[00332] ***Step 3***: To a solution of (1E)-2, 6-dichloro-N-(p-tolylsulfonyl)benzohydrazonoyl chloride (550 mg, 1.46 mmol, 1.2 eq) and 7, 7-difluoro-2-azaspiro[3.3]heptane (300 mg, 1.21 mmol, 1 eq, TFA) in THF (8 mL) was added TEA (614 mg, 6.07 mmol, 845 µL, 5 eq) at 0 °C. The mixture was stirred at 15 °C for 2 hours. LC-MS showed 7, 7-difluoro-2-azaspiro [3.3] heptane was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 30 mL of H_2O and 50 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2, 6-dichlorophenyl)-(7, 7-difluoro-2-azaspiro [3.3] heptan-2-yl)] amino]-4-methyl-benzenesulfonamide (490 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{20}H_{19}Cl_2F_2N_3O_2S$ 473.1, m/z found 474.1 $[M+H]^+$.

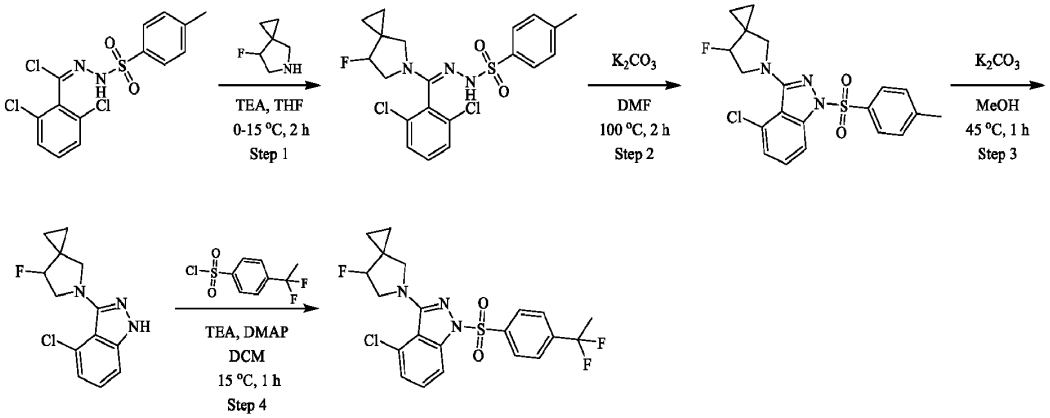
[00333] ***Step 4:*** To a solution of N-[(E)-[(2, 6-dichlorophenyl)-(7, 7-difluoro-2-azaspiro [3.3] heptan-2-yl) methylene] amino]-4-methyl-benzenesulfonamide (470 mg, 991 µmol, 1 eq) in DMF (5 mL) was added K_2CO_3 (685 mg, 4.95 mmol, 5 eq). The mixture was stirred at 100 °C for 2 hours. LC-MS showed N-[(E)-[(2, 6-dichlorophenyl)-(7, 7-difluoro-2-azaspiro [3.3] heptan-2-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 20 mL of H_2O and 30 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(7, 7-difluoro-2-azaspiro [3.3] heptan-2-yl)-1-(p-tolylsulfonyl)indazole (280 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{18}ClF_2N_3O_2S$ 437.1, m/z found 438.1 $[M+H]^+$.

[00334] ***Step 5:*** To a solution of 4-chloro-3-(7, 7-difluoro-2-azaspiro [3.3] heptan-2-yl)-1-(p-tolylsulfonyl) indazole (280 mg, 639 µmol, 1 eq) in MeOH (3 mL) was added K_2CO_3 (442 mg, 3.20 mmol, 5 eq). The mixture was stirred at 40 °C for 1 hour. LC-MS showed 4-chloro-3-(7, 7-difluoro-2-azaspiro [3.3] heptan-2-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was filtered, and the filter liquor was concentrated under reduced pressure to give a residue. The residue was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product.

The crude was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 1/1) to give the desired 4-chloro-3-(7, 7-difluoro-2-azaspiro [3.3] heptan-2-yl)-1H-indazole (70 mg, 247 µmol, 38.6% yield) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{12}ClF_2N_3$ 283.1 m/z found 284.1 $[M+H]^+$.

[00335] ***Step 6:*** To a solution of 4-chloro-3-(7, 7-difluoro-2-azaspiro [3.3] heptan-2-yl)-1H-indazole (30 mg, 106 µmol, 1 eq) and 4- (1,1-difluoroethyl)benzenesulfonyl chloride (38.2 mg, 159 µmol, 1.5 eq) in DCM (1 mL) were added TEA (21.4 mg, 212 µmol, 29.4 µL, 2 eq) and DMAP (1.29 mg, 10.6 µmol, 0.1 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-chloro-3-(7, 7-difluoro-2-azaspiro [3.3] heptan-2-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL X 3). The combined organic phase was washed with brine (10 mL X 3), dried over Na_2SO_4, filtered, and concentrated in vacuum to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-(7, 7-difluoro-2-azaspiro [3.3] heptan-2-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole (4.1 mg, 8.37 µmol, 13.6% yield, 99.62% purity) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.63 (t, J = 8.1 Hz, 1H), 7.45 (d, J = 7.7 Hz, 1H), 4.34 (d, J = 9.3 Hz, 2H), 4.13 (d, J = 9.3 Hz, 2H), 2.49 - 2.41 (m, 2H), 2.04 (br t, J = 8.3 Hz, 2H), 1.91 (t, J = 19.1 Hz, 3H). HPLC: 99.62% (220 nm), 99.38% (215 nm), 100.00% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{18}ClF_4N_3O_2S$ 487.1 m/z found 488.1 $[M+H]^+$.

Compound 25: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(7-fluoro-5-azaspiro [2.4] heptan-5-yl) indazole



[00336] ***Step 1:*** To a solution of 7-fluoro-5-azaspiro [2.4] heptane hydrochloride (100 mg, 660 μmol, 1 eq) in THF (10 mL) were added TEA (133 mg, 1.32 mmol, 184 μL, 2 eq) and (1E)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (299 mg, 792 μmol, 1.2 eq) at 0 °C. The mixture was stirred at 15 °C for 2 hours. LC-MS showed (1E)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride was consumed completely and the desired mass was detected. The reaction mixture was concentrated to give the desired N-[(Z)-[(2, 6-dichlorophenyl)-(7-fluoro-5-azaspiro [2.4] heptan-5-yl) methylene] amino]-4-methylbenzenesulfonamide (1 g, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{20}H_{20}Cl_2FN_3O_2S$ 455.06, m/z found 456.3 $[M+H]^+$.

[00337] ***Step 2:*** To a solution of N-[(Z)-[(2, 6-dichlorophenyl)-(7-fluoro-5-azaspiro [2.4] heptan-5-yl) methylene] amino]-4-methyl-benzenesulfonamide (1.0 g, 2.19 mmol, 1 eq) in DMF (10 mL) was added K_2CO_3 (3.03 g, 21.9 mmol, 10 eq). The mixture was stirred at 100 °C for 2 hours. LC-MS showed N-[(Z)-[(2, 6-dichlorophenyl)-(7-fluoro-5-azaspiro [2.4] heptan-5-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. The reaction mixture was diluted with H_2O (20 mL) and extracted with MTBE (20 mL X 3). The combined organic phase was washed with brine (20 mL X 3), dried over Na_2SO_4, filtered, and concentrated in vacuum to give the desired 4-chloro-3-(7-fluoro-5-azaspiro[2.4]heptan-5-yl)-1-(p-tolylsulfonyl)indazole (380 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{20}H_{19}ClFN_3O_2S$ 419.09, m/z found 420.3 $[M+H]^+$.

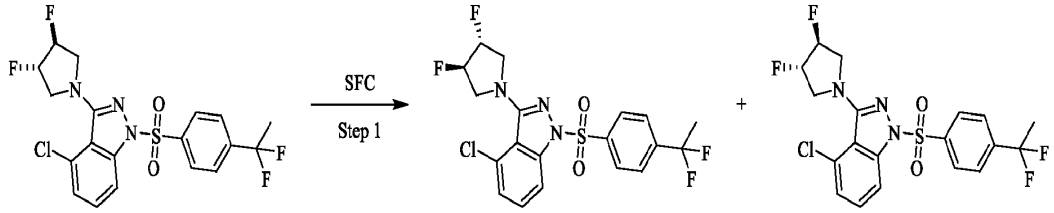
[00338] ***Step 3:*** To a solution of 4-chloro-3-(7-fluoro-5-azaspiro [2.4] heptan-5-yl)-1-(p-tolylsulfonyl) indazole (380 mg, 905 μmol, 1 eq) in MeOH (5 mL) was added K_2CO_3 (1.25 g, 9.05 mmol, 10 eq). The mixture was stirred at 45 °C for 1 hour. LC-MS showed 4-chloro-3-(7-fluoro-5-azaspiro [2.4] heptan-5-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL X 3). The combined organic phase was washed with brine (10 mL X 3), dried over Na_2SO_4, filtered, and concentrated in vacuum to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ ethyl acetate = 3/1) to give the desired 4-chloro-3-(7-fluoro-5-azaspiro [2.4] heptan-5-yl)-1H-indazole (90 mg, 338 μmol, 37.4% yield) as a white solid. MS (ESI): mass calcd. For $C_{13}H_{13}ClFN_3$ 265.08, m/z found 266.2 $[M+H]^+$.

[00339] ***Step 4:*** To a solution of 4-chloro-3-(7-fluoro-5-azaspiro[2.4]heptan-5-yl)-1H-indazole (90 mg, 338 μmol, 1 eq) and 4-(1,1- difluoroethyl)benzenesulfonyl chloride (122 mg, 508 μmol, 1.5 eq) in DCM (2 mL) were added TEA (68 mg, 677 μmol, 94 μL, 2 eq) and DMAP

(4.14 mg, 33 μmol, 0.1 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-chloro-3-(7-fluoro-5-azaspiro [2.4] heptan-5-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was added to H_2O (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:50%-80% B over 8.0 min) to give the desired 4-chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(7-fluoro-5-azaspiro[2.4]heptan-5-yl)indazole (6 mg, 12.3 μmol, 3.63% yield, 96.26% purity) as a white solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.13 - 8.03 (m, 1H), 7.92 (d, J = 8.3 Hz, 2H), 7.80 - 7.69 (m, 2H), 7.68 - 7.57 (m, 1H), 7.50 - 7.41 (m, 1H), 4.85 - 4.62 (m, 1H), 4.25 - 4.03 (m, 2H), 3.77 - 3.61 (m, 1H), 3.17 - 3.08 (m, 1H), 2.00 - 1.83 (m, 3H), 1.07 - 0.73 (m, 3H), 0.70 - 0.58 (m, 1H). HPLC: 96.81% (220 nm), 82.12% (215 nm), 96.26% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{19}ClF_3N_3O_2S$ 469.08 m/z found 470.0 $[M+H]^+$.

Compound 26: 4-Chloro-1-((4-(1, 1-difluoroethyl) phenyl) sulfonyl)-3-((3R, 4R)-3, 4-difluoropyrrolidin-1-yl)-1H-indazole

Compound 27: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(3S, 4S)-3, 4-difluoropyrrolidin-1-yl] indazole

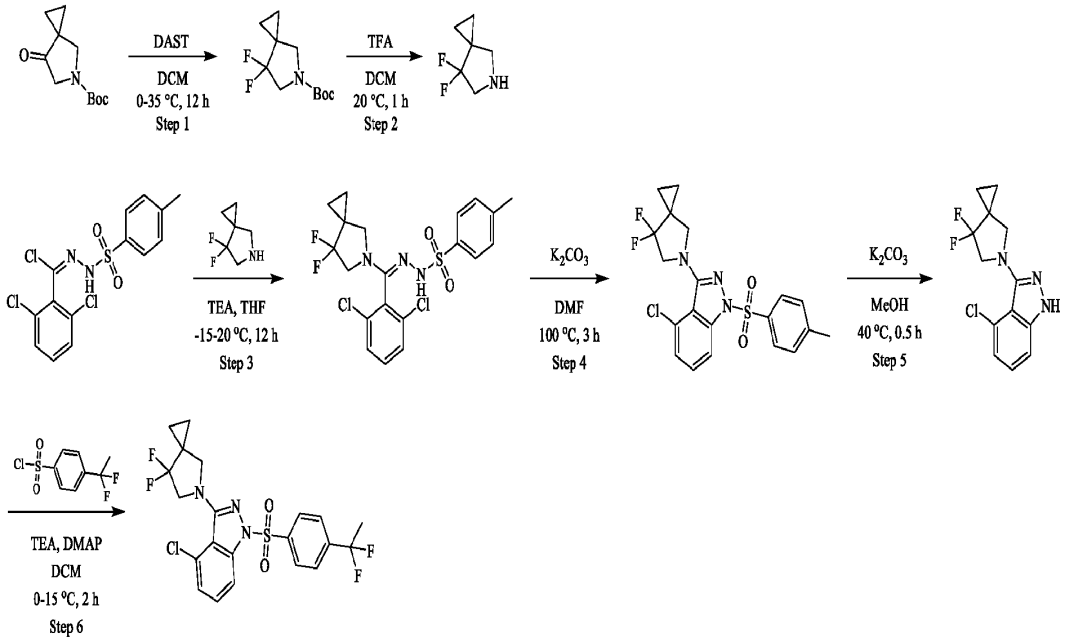


[00340] ***Step 1***: The meso form of 4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-((3S,4S)-3,4-difluoropyrrolidin-1-yl)-1H-indazole (60 mg, 130 μmol, 1 eq) was separated by chiral SFC (column: Daicel ChiralPak IG (250 * 30 mm, 10 μm); mobile phase: [Heptane-EtOH]; gradient: 5%-70% B over 12.0 min) to give two isomers. The structures were assigned arbitrarily. 4-Chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-((3R,4R)-3,4-difluoropyrrolidin-1-yl)-1H-indazole (11.3 mg, 24.0 μmol, 18.5% yield, 98.24% purity, Rt = 3.968 minutes; E.E. by chiral HPLC (%) = 100.00%) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.5 Hz,

2H), 7.70 (t, *J* = 8.1 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 5.62 - 5.38 (m, 2H), 4.25 - 4.04 (m, 2H), 3.82 - 3.66 (m, 2H), 1.97 (t, *J* = 19.1 Hz, 3H). HPLC: 98.24% (220 nm), 97.92% (215 nm), 98.66% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{16}ClF_4N_3O_2S$ 461.06 m/z found 462.1 $[M+H]^+$.

4-Chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-[(3S,4S)-3,4-difluoropyrrolidin-1-yl]indazole (9.7 mg, 20.8 µmol, 16.0% yield, 99.21% purity, Rt = 4.222 minutes; E.E. by chiral HPLC (%) = 95.68%) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.14 (br d, *J* = 8.5 Hz, 1H), 8.00 (br d, *J* = 8.0 Hz, 2H), 7.80 (br d, *J* = 7.9 Hz, 2H), 7.74 - 7.67 (m, 1H), 7.54 (br d, *J* = 7.7 Hz, 1H), 5.60 - 5.41 (m, 2H), 4.24 - 4.06 (m, 2H), 3.82 - 3.67 (m, 2H), 2.05 - 1.91 (m, 3H). HPLC: 99.21% (220 nm), 99.12% (215 nm), 97.45% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{16}ClF_4N_3O_2S$ 461.06 m/z found 462.1 $[M+H]^-$.

Compound 28: 4-Chloro-3-(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole



[00341] ***Step 1:*** To a solution of tert-butyl 7-oxo-5-azaspiro [2.4] heptane-5-carboxylate (1.61 g, 7.62 mmol, 1 eq) in DCM (17 mL) was added DAST (18.4 g, 114 mmol, 15.1 mL, 15 eq) at 0 °C. The mixture was stirred at 35 °C for 12 hours. TLC indicated tert-butyl 7-oxo-5-azaspiro [2.4] heptane-5-carboxylate remained and one major new spot with lower polarity was detected.

The reaction was quenched by sat. aq. $NaHCO_3$ (20 mL), then the mixture was extracted with DCM (40 mL). The organic phase was separated, washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 2 g SepaFlash® Silica Flash Column, Eluent of 0~15% ethyl acetate/petroleum ether gradient @ 60 mL/min) to give the desired tert-butyl 7, 7-difluoro-5-azaspiro [2.4] heptane-5-carboxylate (680 mg, 2.92 mmol, 38.3% yield) as a white solid.

[00342] ***Step 2:*** To the mixture of tert-butyl 7, 7-difluoro-5-azaspiro [2.4] heptane-5-carboxylate (580 mg, 2.49 mmol, 1 eq) in DCM (9 mL) was added TFA (4.61 g, 40.4 mmol, 3 mL, 16.2 eq). The mixture was stirred at 20 °C for 1 hour. TLC indicated tert-butyl 7, 7-difluoro-5-azaspiro [2.4] heptane-5-carboxylate was consumed completely and a new spot was formed. The reaction was concentrated under reduced pressure to give the desired 7, 7-difluoro-5-azaspiro [2.4] heptane (610 mg, crude, TFA) as a light brown oil.

[00343] ***Step 3:*** To the mixture of 7,7-difluoro-5-azaspiro[2.4]heptane (300 mg, 1.21 mmol, 1 eq, TFA) and TEA (2.18 g, 21.5 mmol, 3 mL, 17.8 eq) in THF (5 mL) was added (1E)-2,6-dichloro-N-(p-tolylsulfonyl)benzohydrazonoyl chloride (458 mg, 1.21 mmol, 1 eq) at -15 °C. The mixture was stirred at 20 °C for 12 hours. LCMS showed (1E)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give the desired N-[(E)-[(2, 6-dichlorophenyl)-(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl) methylene] amino]-4-methylbenzenesulfonamide (575 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{19}Cl_2F_2N_3O_2S$ 473.05, m/z found 474.1 $[M+H]^+$.

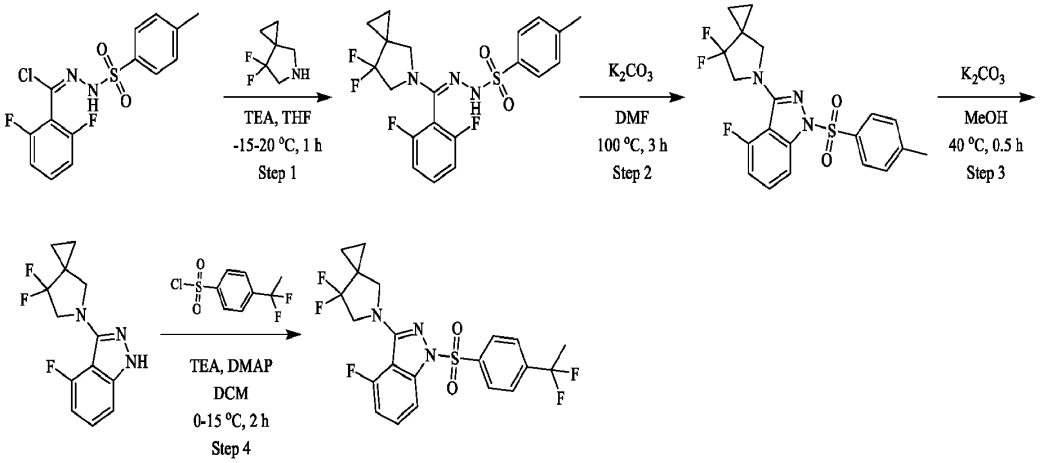
[00344] ***Step 4:*** The mixture of N-[(E)-[(2, 6-dichlorophenyl)-(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl) methylene] amino]-4-methylbenzenesulfonamide (575 mg, 1.21 mmol, 1 eq) and K_2CO_3 (3.35 g, 24.2 mmol, 20 eq) in DMF (10 mL) was stirred at 100 °C for 3 hours. LCMS showed N-[(E)-[(2, 6-dichlorophenyl)-(7, 7-difluoro-5-azaspiro [2.4] heptan-5- yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. The reaction was poured into ice-water (50 mL) and extracted with MTBE (3 X 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(7, 7-difluoro-5-azaspiro

[2.4] heptan-5-yl)-1-(p-tolylsulfonyl) indazole (530 mg, 1.21 mmol, 99.9% yield) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{18}ClF_2N_3O_2S$ 437.08 m/z found 438.1 $[M+H]^+$.

[00345] ***Step 5***: The mixture of 4-chloro-3-(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl)-1-(p-tolylsulfonyl) indazole (530 mg, 1.21 mmol, 1 eq) and K_2CO_3 (334 mg, 2.42 mmol, 2 eq) in MeOH (5 mL) was stirred at 40 °C for 0.5 hour. LCMS showed 4-chloro-3-(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction was concentrated to get a residue. The reaction was poured into ice-water (10 mL) and extracted with MTBE (3 X 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired 4-chloro-3-(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl)-1H-indazole (90 mg, 317 µmol, 26.2% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{13}H_{12}ClF_2N_3$ 283.07 m/z found 284.1 $[M+H]^+$.

[00346] ***Step 6***: To a solution of 4-chloro-3-(7,7-difluoro-5-azaspiro[2.4]heptan-5-yl)-1H-indazole (50 mg, 176 µmol, 1 eq) and 4- (1,1-difluoroethyl)benzenesulfonyl chloride (63.6 mg, 264 µmol, 1.5 eq) in DCM (2 mL) were added TEA (35.7 mg, 352 µmol, 49 µL, 2 eq) and DMAP (2.15 mg, 17.6 µmol, 0.1 eq) at 0 °C. The mixture was stirred at 15 °C for 2 hours. LC-MS showed 4-chloro-3-(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was added to H_2O (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ ethyl acetate = 3/1) to give the desired 4-chloro-3-(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole (35 mg, 71.5 µmol, 40.6% yield, 99.64% purity) as a white solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.14 - 8.05 (m, 1H), 8.00 - 7.92 (m, 2H), 7.81 - 7.72 (m, 2H), 7.69 - 7.61 (m, 1H), 7.53 - 7.44 (m, 1H), 4.12 - 4.00 (m, 2H), 3.74 - 3.66 (m, 2H), 1.99 - 1.85 (m, 3H), 1.02 - 0.95 (m, 2H), 0.91 - 0.82 (m, 2H). HPLC: 97.73% (220 nm), 97.61% (215 nm), 99.64% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{18}ClF_4N_3O_2S$ 487.07 m/z found 488.0 $[M+H]^+$.

Compound 29: 3-(7, 7-Difluoro-5-azaspiro [2.4] heptan-5-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-4-fluoro-indazole



[00347] ***Step 1:*** To the mixture of 7,7-difluoro-5-azaspiro[2.4]heptane (300 mg, 1.21 mmol, 1 eq, TFA) and TEA (2.18 g, 21.5 mmol, 3 mL, 17.8 eq) in THF (5 mL) was added (1E)-2,6-difluoro-N-(p-tolylsulfonyl)benzohydrazonoyl chloride (418 mg, 1.21 mmol, 1 eq) at -15 °C and the mixture was stirred at 20 °C for 1 hour. LCMS showed 7,7-difluoro-5-azaspiro[2.4]heptane was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give the desired N-[(E)-[(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl)-(2, 6-difluorophenyl) methylene] amino]-4-methylbenzenesulfonamide (535 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{19}F_4N_3O_2S$ 441.11, m/z found 442.1 $[M+H]^+$.

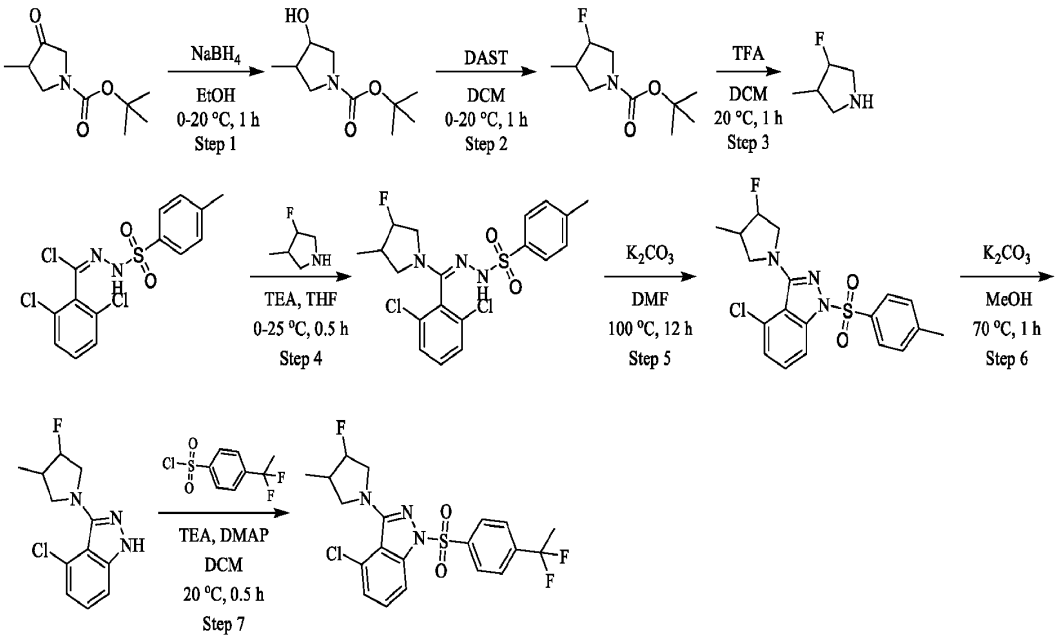
[00348] ***Step 2:*** The mixture of N-[(E)-[(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl)-(2, 6-difluorophenyl) methylene] amino]-4-methylbenzenesulfonamide (535 mg, 1.21 mmol, 1 eq) and K_2CO_3 (3.35 g, 24.2 mmol, 20 eq) in DMF (10 mL) was stirred at 100 °C for 3 hours. LCMS showed N-[(E)-[(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl)-(2, 6- difluorophenyl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. The reaction was poured into ice-water (50 mL) and extracted with MTBE (3 X 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 3-(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl)-4-fluoro-1-(p-tolylsulfonyl) indazole (510 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{18}F_3N_3O_2S$ 421.11, m/z found 422.1 $[M+H]^+$.

[00349] ***Step 3:*** The mixture of 3-(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl)-4-fluoro-1-(p-tolylsulfonyl) indazole (510 mg, 1.21 mmol, 1 eq) and K_2CO_3 (335 mg, 2.42 mmol, 2 eq) in

MeOH (5 mL) was stirred at 40 °C for 0.5 hour. LCMS showed 3-(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl)-4-fluoro-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired 3-(7,7-difluoro-5-azaspiro[2.4]heptan-5-yl)-4-fluoro-1H-indazole (130 mg, 486 µmol, 40.2% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{13}H_{12}F_3N_3$ 267.1, m/z found 268.1 $[M+H]^+$.

[00350] ***Step 4:*** To a solution of 3-(7,7-difluoro-5-azaspiro[2.4]heptan-5-yl)-4-fluoro-1H-indazole (50 mg, 187 µmol, 1 eq) and 4- (1,1-difluoroethyl)benzenesulfonyl chloride (67.5 mg, 281 µmol, 1.5 eq) in DCM (2 mL) were added TEA (37.9 mg, 374 µmol, 52.1 µL, 2 eq) and DMAP (2.29 mg, 18.7 µmol, 0.1 eq) at 0 °C. The mixture was stirred at 15 °C for 2 hours. LC-MS showed 3-(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl)-4-fluoro-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was added to H_2O (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate =3/1) to give the desired 3-(7, 7-difluoro-5-azaspiro [2.4] heptan-5-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-4-fluoro-indazole (44 mg, 93.0 µmol, 49.71% yield, 99.64% purity) as a white solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.00 - 7.89 (m, 3H), 7.79 - 7.63 (m, 3H), 7.26 - 7.16 (m, 1H), 4.15 - 4.04 (m, 2H), 3.79 - 3.64 (m, 2H), 2.01 - 1.85 (m, 3H), 1.04 - 0.89 (m, 4H). HPLC: 98.76% (220 nm), 98.93% (215 nm), 99.64% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{18}F_5N_3O_2S$ 471.1 m/z found 472.0 $[M+H]^+$.

Compound 30: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3-fluoro-4-methyl-pyrrolidin-1-yl) indazole



[00351] ***Step 1***: To a solution of tert-butyl 3-methyl-4-oxo-pyrrolidine-1-carboxylate (1 g, 5.02 mmol, 1 eq) in EtOH (10 mL) was added $NaBH_4$ (380 mg, 10.0 mmol, 2 eq) at 0 °C. The mixture was stirred at 20 °C for 1 hour. TLC indicated tert-butyl 3-methyl-4-oxo-pyrrolidine-1-carboxylate was consumed completely and one new spot was formed. The residue was diluted with HCl (1 N, 5 mL) and the resulting mixture was allowed to return to room temperature. The EtOH was evaporated in vacuum. The reaction mixture was added to water (20 mL) and extracted with DCM (20 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate =1/0 to 0/1) to give the desired tert-butyl 3-hydroxy-4-methyl-pyrrolidine-1-carboxylate (1 g, crude) as colorless oil.

[00352] ***Step 2***: To a solution of tert-butyl 3-hydroxy-4-methyl-pyrrolidine-1-carboxylate (1 g, 4.97 mmol, 1 eq) in DCM (20 mL) was added DAST (2.40 g, 14.9 mmol, 1.97 mL, 3 eq) at 0 °C. The mixture was stirred at 20 °C for 1 hour. TLC indicated tert-butyl 3-hydroxy-4-methyl-pyrrolidine-1-carboxylate was consumed completely and two new spots were formed. The reaction mixture was quenched by addition sat. $NaHCO_3$ aq. (40 mL) and extracted with DCM (10 mL X 4). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by

column chromatography (silica gel, petroleum ether / ethyl acetate = 1/0 to 0/1) to give the desired tert-butyl 3-fluoro-4-methyl-pyrrolidine-1-carboxylate (190 mg, crude) as a colorless oil.

[00353] ***Step 3***: To a solution of tert-butyl 3-fluoro-4-methyl-pyrrolidine-1-carboxylate (190 mg, 935 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 20 °C for 1 hour. TLC indicated tert-butyl 3-fluoro-4-methyl-pyrrolidine-1-carboxylate was consumed completely and one new spot was formed. The reaction mixture was concentrated to give the desired 3-fluoro-4-methyl-pyrrolidine (200 mg, crude, TFA) as a yellow oil.

[00354] ***Step 4***: To a solution of 3-fluoro-4-methyl-pyrrolidine (200 mg, 921 μmol, 1 eq, TFA) in THF (3 mL) was added dropwise TEA (932 mg, 9.21 mmol, 1.28 mL, 10 eq) at 25 °C. After addition, the mixture was stirred at this temperature for 10 minutes. (1Z)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (522 mg, 1.38 mmol, 1.5 eq) in THF (5 mL) was added dropwise to the mixture at 0 °C. The resulting mixture was stirred at 25 °C for 20 minutes. LC-MS showed 3-fluoro-4-methyl-pyrrolidine was consumed completely and one main peak with the desired mass was detected. The mixture was separated between 20 mL of water and 40 mL of ethyl acetate. The organic phase was separated, washed with 30 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2, 6-dichlorophenyl)-(3-fluoro-4-methyl-pyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (400 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{19}H_{20}Cl_2FN_3O_2S$ 443.06 m/z found 444.0 $[M+H]^+$.

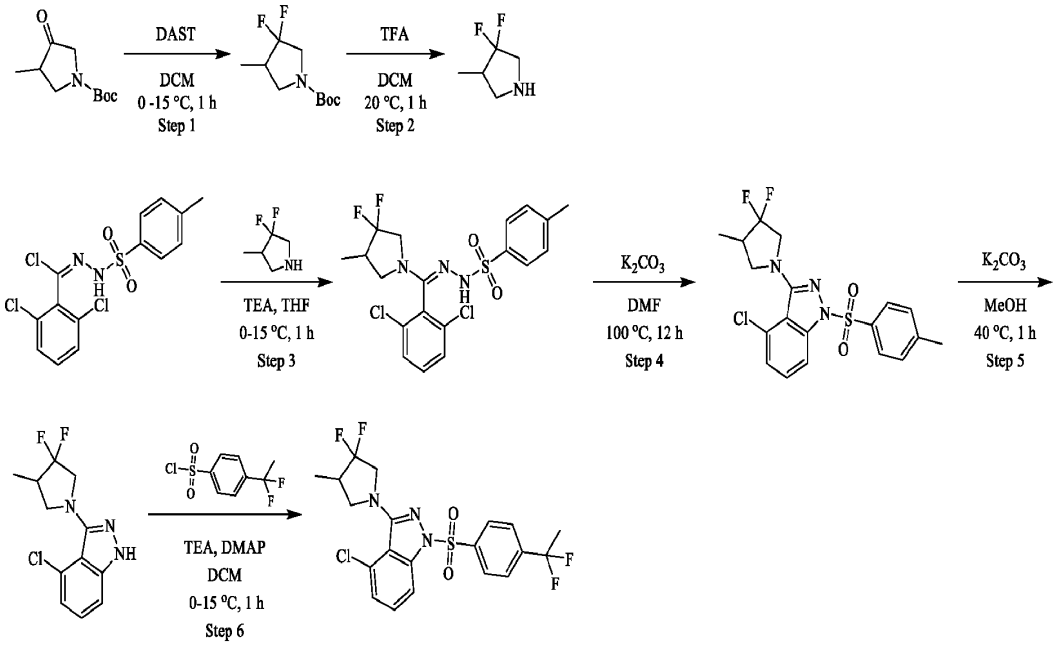
[00355] ***Step 5***: To a solution of N-[(E)-[(2, 6-dichlorophenyl)-(3-fluoro-4-methyl-pyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (400 mg, 900 μmol, 1 eq) in DMF (10 mL) was added K_2CO_3 (622 mg, 4.50 mmol, 5 eq). The mixture was stirred at 100 °C for 12 hours. LC-MS showed N-[(E)-[(2, 6-dichlorophenyl)-(3-fluoro-4-methyl-pyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. The reaction mixture was added to water (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(3-fluoro-4-methyl-pyrrolidin-1-yl)-1-(p-tolylsulfonyl)indazole (360 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{19}H_{19}ClFN_3O_2S$ 407.09 m/z found 408.1 $[M+H]^+$.

[00356] ***Step 6***: To a solution of 4-chloro-3-(3-fluoro-4-methyl-pyrrolidin-1-yl)-1-(p-tolylsulfonyl) indazole (460 mg, 1.13 mmol, 1 eq) in MeOH (10 mL) was added K_2CO_3 (779 mg,

5.64 mmol, 5 eq). The mixture was stirred at 70 °C for 1 hour. LC-MS showed 4-chloro-3-(3-fluoro-4-methyl-pyrrolidin-1-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ ethyl acetate = 2/1) to give the desired 4-chloro-3-(3-fluoro-4-methyl-pyrrolidin-1-yl)-1H-indazole (190 mg, 749 μmol, 66.4% yield) as a yellow oil. MS (ESI): mass calcd. For $C_{12}H_{13}ClFN_3$ 253.08 m/z found 254.1 $[M+H]^+$.

[00357] ***Step 7***: To a solution of 4-chloro-3-(3-fluoro-4-methyl-pyrrolidin-1-yl)-1H-indazole (190 mg, 749 μmol, 1 eq) and 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (270 mg, 1.12 mmol, 1.5 eq) in DCM (1 mL) were added TEA (227 mg, 2.25 mmol, 313 μL, 3 eq) and DMAP (9.15 mg, 74.9 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(3-fluoro-4-methyl-pyrrolidin-1-yl)-1H-indazole was consumed completely and one main peak with the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O(0.1%TFA)-ACN]; gradient: 50%-80% B over 8.0 min) to give the desired 4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3-fluoro-4-methyl-pyrrolidin-1-yl) indazole (28 mg, 60.4 μmol, 8.06% yield, 98.70% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J = 8.4 Hz, 1H), 7.92 (br d, J = 8.2 Hz, 2H), 7.73 (br d, J = 8.2 Hz, 2H), 7.61 (br t, J = 8.1 Hz, 1H), 7.45 (br d, J = 7.6 Hz, 1H), 5.28 - 4.94 (m, 1H), 4.18 - 3.68 (m, 2H), 3.62 - 3.53 (m, 1H), 3.52 - 3.43 (m, 1H), 2.41 - 2.03 (m, 1H), 1.91 (t, J = 19.1 Hz, 3H), 1.60 - 1.45 (m, 1H), 1.10 (br d, J = 6.7 Hz, 2H). HPLC: 98.70% (220 nm), 99.85% (215 nm), 98.73% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{19}ClF_3N_3O_2S$ 457.08 m/z found 458.0 $[M+H]^+$.

Compound 31: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3, 3-difluoro-4-methyl-pyrrolidin-1-yl) indazole



[00358] ***Step 1***: To a solution of tert-butyl 3-methyl-4-oxo-pyrrolidine-1-carboxylate (500 mg, 2.51 mmol, 1 eq) in DCM (5 mL) was added DAST (2.02 g, 12.6 mmol, 1.66 mL, 5 eq) at 0 °C. The mixture was stirred at 15 °C for 1 hour. TLC indicated tert-butyl 3-methyl-4-oxo-pyrrolidine-1-carboxylate was consumed completely and one new spot was formed. The reaction was quenched by sat. aq. $NaHCO_3$ (20 mL) and extracted with DCM (30 mL). The organic phase was separated, washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 1 g SepaFlash® Silica Flash Column, Eluent of 0~15% EtOAc/petroleum ether gradient @ 40 mL/min) to give the desired tert-butyl 3, 3-difluoro-4-methyl-pyrrolidine-1-carboxylate (400 mg, 1.81 mmol, 72.1% yield) as a yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 3.95 (br d, *J* = 4.5 Hz, 1H), 3.80 - 3.59 (m, 3H), 3.15 - 3.01 (m, 1H), 1.46 (s, 9H), 1.11 (br d, *J* = 6.8 Hz, 3H).

[00359] ***Step 2***: To a solution of tert-butyl 3, 3-difluoro-4-methyl-pyrrolidine-1-carboxylate (350 mg, 1.58 mmol, 1 eq) in DCM (5 mL) was added TFA (3.61 g, 31.6 mmol, 2.35 mL, 20 eq). The mixture was stirred at 20 °C for 1 hour. TLC indicated tert-butyl 3, 3-difluoro-4-methyl-pyrrolidine-1-carboxylate was consumed completely and one new spot was formed. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under

reduced pressure to give the desired 3, 3-difluoro-4-methyl-pyrrolidine (372 mg, crude, TFA) as a white solid.

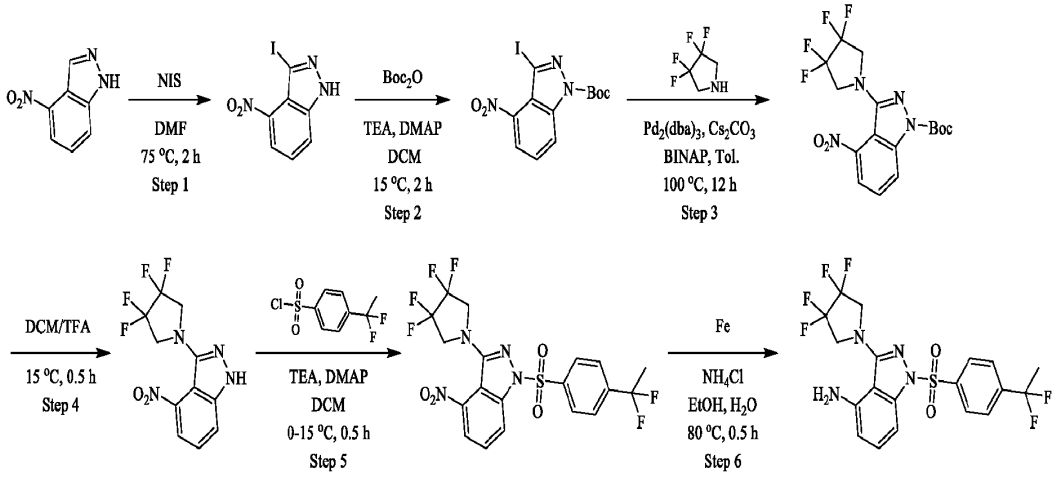
[00360] ***Step 3***: To a solution of 3, 3-difluoro-4-methyl-pyrrolidine (390 mg, 1.66 mmol, 1 eq, TFA) in THF (10 mL) were added TEA (168 mg, 1.66 mmol, 231 μL, 1 eq) and (1E)-2, 6-dichloro-N-(p-tolylsulfonyl)benzohydrazonoyl chloride (689 mg, 1.82 mmol, 1.1 eq) at 0 °C. The mixture was stirred at 15 °C for 1 hour. LC-MS showed 3, 3-difluoro-4-methyl-pyrrolidine was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2, 6-dichlorophenyl)-(3, 3-difluoro-4-methyl-pyrrolidin-1-yl)methylene]amino]-4-methyl-benzenesulfonamide (766 mg, crude) as a black solid. MS (ESI): mass calcd. For $C_{19}H_{19}Cl_2F_2N_3O_2S$ 461.1, m/z found 462.0 $[M+H]^+$.

[00361] ***Step 4:*** To a solution of N-[(E)-[(2, 6-dichlorophenyl)-(3, 3-difluoro-4-methyl-pyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (766 mg, 1.66 mmol, 1 eq) in DMF (8 mL) was added K_2CO_3 (1.14 g, 8.28 mmol, 5 eq). The mixture was stirred at 100 °C for 12 hours. LC-MS showed N-[(E)-[(2, 6-dichlorophenyl)-(3, 3-difluoro-4-methyl-pyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. The reaction mixture was partitioned between10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(3, 3-difluoro-4-methyl-pyrrolidin-1-yl)-1-(p-tolylsulfonyl) indazole (700 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{19}H_{18}ClF_2N_3O_2S$ 425.1, m/z found 426.1 $[M+H]^+$.

[00362] ***Step 5:*** To a solution of 4-chloro-3-(3, 3-difluoro-4-methyl-pyrrolidin-1-yl)-1-(p-tolylsulfonyl) indazole (700 mg, 1.64 mmol, 1 eq) in MeOH (8 mL) was added K_2CO_3 (1.14 g, 8.22 mmol, 5 eq). The mixture was stirred at 40 °C for 1 hour. LC-MS showed 4-chloro-3-(3, 3-difluoro-4-methyl-pyrrolidin-1-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was filtered, and the filter liquor was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-(3, 3-difluoro-4-methyl-pyrrolidin-1-yl)-1H-indazole (120 mg, 442 μmol, 26.9% yield) as a white solid. MS (ESI): mass calcd. For $C_{12}H_{12}ClF_2N_3$ 271.1 m/z found 272.1 $[M+H]^+$.

[00363] ***Step 6:*** To a solution of 4-chloro-3-(3, 3-difluoro-4-methyl-pyrrolidin-1-yl)-1H-indazole (120 mg, 442 μmol, 1 eq) and 4-(1, 1-difluoroethyl)benzenesulfonyl chloride (106 mg, 442 μmol, 1 eq) in DCM (2 mL) were added TEA (89.4 mg, 883 μmol, 123 μL, 2 eq) and DMAP (5.40 mg, 44.2 μmol, 0.1 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-chloro-3-(3, 3-difluoro-4-methyl-pyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O(0.1%TFA)-ACN]; gradient: 70%-95% B over 8.0 min to give the desired 4-chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(3,3-difluoro-4-methyl-pyrrolidin-1-yl)indazole (30 mg, 62.3 μmol, 14.1% yield, 98.80% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, J = 8.3 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.65 (t, J = 8.1 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 4.09 (br d, J = 18.0 Hz, 1H), 3.90 - 3.76 (m, 2H), 3.38 (s, 2H), 1.92 (t, J = 19.2 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H). HPLC: 98.80% (220 nm), 98.82% (215 nm), 98.44% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{18}ClF_4N_3O_2S$ 475.1 m/z found 476.1 $[M+H]^+$.

Compound 32: 1-[4-(1, 1-Difluoroethyl) phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazol-4-amine



[00364] ***Step 1:*** To a solution of 4-nitro-2H-indazole (100 mg, 613 μmol, 1 eq) in DMF (5 mL) was added NIS (152 mg, 674 μmol, 1.1 eq). The mixture was stirred at 75 °C for 2 hours.

TLC indicated 4-nitro-2H-indazole was consumed completely and one new spot was formed. The reaction mixture was diluted with H_2O (30 mL) and extracted with MTBE (20 mL X 3). The combined organic phase was washed with brine (20 mL X 3), dried over Na_2SO_4, filtered, and concentrated in vacuum to give the desired 3-iodo-4-nitro-2H-indazole (200 mg, crude) as a yellow solid.

[00365] ***Step 2:*** To a solution of 3-iodo-4-nitro-1H-indazole (200 mg, 692 μmol, 1 eq) and tert-butoxycarbonyl tert-butyl carbonate (151 mg, 692 μmol, 159 μL, 1 eq) in DCM (10 mL) were added TEA (140 mg, 1.38 mmol, 192 μL, 2 eq) and DMAP (8.45 mg, 69.2 μmol, 0.1 eq). The mixture was stirred at 15 °C for 2 hours. TLC indicated 3-iodo-4-nitro-1H-indazole was consumed completely and one new spot was formed. The reaction mixture was concentrated to give the residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/petroleum ether gradient @ 80 mL/min) to give the desired tert-butyl 3-iodo-4-nitro-indazole-1-carboxylate (140 mg, 360 μmol, 52.0% yield) as a yellow solid.

[00366] ***Step 3:*** A mixture of tert-butyl 3-iodo-4-nitro-indazole-1-carboxylate (100 mg, 257 μmol, 1 eq), 3, 3, 4, 4- tetrafluoropyrrolidine hydrochloride (46.1 mg, 257 μmol, 1 eq), $Pd_2(dba)_3$ (23.5 mg, 25.7 μmol, 0.1 eq), Cs_2CO_3 (251 mg, 771 μmol, 3 eq) and BINAP (16 mg, 25.7 μmol, 0.1 eq) in toluene (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. TLC indicated 3-iodo-4-nitro-indazole-1-carboxylate was consumed completely and one new spot was formed. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic phase was washed with brine (20 mL X 3), dried over Na_2SO_4, filtered, and concentrated in vacuum to give the desired tert-butyl 4-nitro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)indazole-1-carboxylate (320 mg, crude) as a yellow solid.

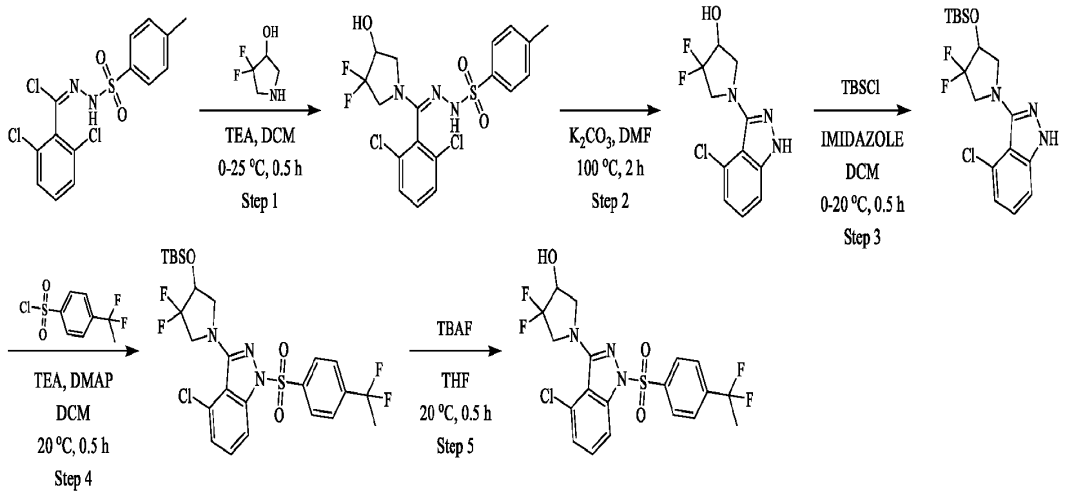
[00367] ***Step 4:*** To a solution of tert-butyl 4-nitro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole-1-carboxylate (270 mg, 668 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 15 °C for 0.5 hour. TLC (silica gel, petroleum ether / ethyl acetate =3/1) indicated tert-butyl 4-nitro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole-1-carboxylate was consumed completely and one new spot was formed. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic phase was washed with brine (20 mL X 2), dried over Na_2SO_4, filtered, and concentrated in vacuum to give a residue.

The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate =3/1) to give the desired 4-nitro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (30 mg, 98.6 μmol, 14.8% yield) as a yellow solid.

[00368] ***Step 5***: To a solution of 4-nitro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole (25 mg, 82.2 μmol, 1 eq) and 4-(1,1- difluoroethyl)benzenesulfonyl chloride (29.7 mg, 123 μmol, 1.5 eq) in DCM (3 mL) were added TEA (25 mg, 246 μmol, 34.3 μL, 3 eq) and DMAP (1.00 mg, 8.22 μmol, 0.1 eq) at 0 °C. The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 4-nitro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic phase was washed with brine (20 mL X 2), dried over Na_2SO_4, filtered, and concentrated in vacuum to give the desired 1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-4-nitro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)indazole (90 mg, crude) as a brown solid. MS (ESI): mass calcd. For $C_{19}H_{14}F_6N_4O_4S$ 508.06 m/z found 509.2 $[M+H]^+$.

[00369] ***Step 6***: To a solution of 1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-4-nitro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole (90 mg, 177 μmol, 1 eq) in EtOH (2 mL) and H_2O (0.4 mL) were added Fe (9.89 mg, 177 μmol, 1 eq) and NH_4Cl (9.47 mg, 177 μmol, 1 eq). The mixture was stirred at 80 °C for 0.5 hour. LC-MS showed 1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-4-nitro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole was consumed completely and the desired mass was detected. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL X 3). The combined organic phase was washed with brine (10 mL X 2), dried over Na_2SO_4, filtered, and concentrated in vacuum to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-CAN]; gradient:50%-75% B over 8.0 min) to give the desired 1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)indazol-4-amine (3 mg, 6.17 μmol, 3.49% yield, 98.45% purity) as a light yellow solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.93 - 7.89 (m, 2H), 7.75 - 7.70 (m, 2H), 7.35 - 7.28 (m, 1H), 7.24 - 7.20 (m, 1H), 6.61 - 6.56 (m, 1H), 5.62 - 5.57 (m, 2H), 4.20 - 4.01 (m, 4H), 1.98 - 1.87 (m, 3H). HPLC: 96.93% (220 nm), 96.30% (215 nm), 98.45% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{16}F_6N_4O_2S$ 478.09 m/z found 479.2 $[M+H]^+$.

Compound 33: 1-[4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazol-3-yl]-4, 4-difluoro-pyrrolidin-3-ol



[00370] ***Step 1***: To a solution of 5, 5-difluoropyrrolidin-3-ol (250 mg, 1.57 mmol, 1 eq, HCl) in THF (5 mL) was added dropwise TEA (1.59 g, 15.7 mmol, 2.18 mL, 10 eq) at 25 °C. After addition, the mixture was stirred at this temperature for 10 minutes. The solution of (1Z)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (888 mg, 2.35 mmol, 1.5 eq) in THF (2 mL) was added dropwise to the mixture at 0 °C. The resulting mixture was stirred at 25 °C for 20 minutes. TLC indicated 5, 5-difluoropyrrolidin-3-ol was consumed completely and one new spot was formed. Then it was separated between 20 mL of water and 40 mL of ethyl acetate. The organic phase was separated, washed with 30 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2, 6-dichlorophenyl)-(2, 2-difluoro-4-hydroxy-pyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (720 mg, crude) as a yellow solid.

[00371] ***Step 2***: To a solution of N-[(E)-[(2, 6-dichlorophenyl)-(3, 3-difluoro-4-hydroxy-pyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (720 mg, 1.55 mmol, 1 eq) in DMF (10 mL) was added K_2CO_3 (1.07 g, 7.75 mmol, 5 eq). The mixture was stirred at 100 °C for 2 hours. TLC indicated N-[(E)-[(2, 6-dichlorophenyl)-(3, 3-difluoro-4-hydroxy-pyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and one new spot was formed. The reaction mixture was added to water (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by

column chromatography (silica gel, petroleum ether / ethyl acetate =1/0 to 0/1) to give the desired 1-(4-chloro-1H-indazol-3-yl)-4, 4-difluoro-pyrrolidin-3-ol (400 mg, crude) as a yellow oil.

[00372] ***Step 3***: To a solution of 1-(4-chloro-1H-indazol-3-yl)-4,4-difluoro-pyrrolidin-3-ol (200 mg, 731 μmol, 1 eq) in DCM (2 mL) were added imidazole (99.5 mg, 1.46 mmol, 2 eq) and TBSCl (132 mg, 877 μmol, 108 μL, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 1-(4-chloro-1H-indazol-3-yl)-4, 4-difluoro-pyrrolidin-3-ol was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to sat. aq. $NaHCO_3$ (30 mL) and extracted with DCM (30 mL X 3). The combined organic layers were washed with brine (20 mL) , dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired tert-butyl-[1-(4-chloro-1H-indazol-3-yl)-4,4-difluoro-pyrrolidin-3-yl]oxy-dimethyl-silane (180 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{17}H_{24}ClF_2N_3OSi$ 387.13 m/z found 388.1 $[M+H]^+$.

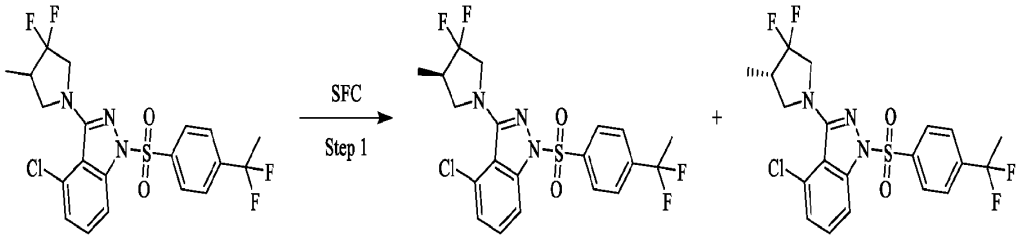
[00373] ***Step 4***: To a solution of tert-butyl-[1-(4-chloro-1H-indazol-3-yl)-4, 4-difluoro-pyrrolidin-3-yl] oxy-dimethyl-silane (100 mg, 258 μmol, 1 eq) and 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (93.1 mg, 387 μmol, 1.5 eq) in DCM (1 mL) were added TEA (78.3 mg, 773 μmol, 108 μL, 3 eq) and DMAP (3.15 mg, 25. 8 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed tert-butyl-[1-(4-chloro-1H-indazol-3-yl)-4, 4-difluoro-pyrrolidin-3-yl] oxy-dimethyl-silane was consumed completely and one main peak with the desired mass was detected. The reaction mixture was concentrated to give the desired tert-butyl-[1-[4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazol-3-yl]-4, 4-difluoro-pyrrolidin-3-yl] oxy-dimethyl-silane (150 mg, crude) as a white solid. MS (ESI): mass calcd. For $C_{25}H_{30}ClF_4N_3O_3SSi$ 591.14 m/z found 592.2 $[M+H]^+$.

[00374] ***Step 5***: To a solution of tert-butyl-[1-[4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazol-3-yl]-4, 4-difluoro-pyrrolidin-3-yl] oxy-dimethyl-silane (80 mg, 135 μmol, 1 eq) in THF (1 mL) was added TBAF (70.7 mg, 270 μmol, 2 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed tert-butyl-[1-[4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazol-3-yl]-4, 4-difluoro-pyrrolidin-3-yl] oxy-dimethyl-silane was consumed completely and one main peak with the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase:

[H_2O(0.1%TFA)-ACN]; gradient: 55%-80% B over 8.0 min) to give the desired 1-[4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazol-3-yl]-4, 4-difluoro-pyrrolidin-3-ol (1.1 mg, 2.28 μmol, 1.69% yield, 98.90% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.71 - 7.64 (m, 1H), 7.52 (d, J = 7.7 Hz, 1H), 6.33 - 6.04 (m, 1H), 4.40 - 4.29 (m, 1H), 4.14 - 3.74 (m, 4H), 1.95 (t, J = 19.1 Hz, 3H). HPLC: 98.90% (220 nm), 98.83% (215 nm), 100.00% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{16}ClF_4N_3O_3S$ 477.05 m/z found 478.0 $[M+H]^+$.

Compound 34: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(4R)-3, 3-difluoro-4-methyl-pyrrolidin-1-yl] indazole

Compound 35: 4-Chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-[(4S)-3,3-difluoro-4-methyl-pyrrolidin-1-yl]indazole



[00375] ***Step 1***: 4-Chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(3,3-difluoro-4-methyl-pyrrolidin-1-yl)indazole (20 mg, 62.3 μmol μmol, 1 eq) was separated by chiral SFC (column: Phenomenex Luna CN 100 * 30 mm * 5 μm; mobile phase: [Heptane-EtOH]; gradient: 20%-50% B over 10.0 min) to give two isomers. The structures were assigned arbitrarily. 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(4R)-3, 3-difluoro-4-methyl-pyrrolidin-1-yl] indazole (7 mg, 14.7 μmol, 34.9% yield, 98.98% purity, Rt = 4.948 minutes; E.E. by chiral HPLC (%) = 100.0%) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.5 Hz, 2H), 7.64 (t, J = 8.1 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 4.09 (br d, J = 17.9 Hz, 1H), 3.89 - 3.77 (m, 2H), 3.38 (s, 1H), 2.78 - 2.61 (m, 1H), 1.92 (t, J = 19.1 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H). HPLC: 98.98% (220 nm), 99.47% (215 nm), 99.10% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{18}ClF_4N_3O_2S$ 475.1 m/z found 476.1 $[M+H]^+$.

[00376] 4-Chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-[(4S)-3,3-difluoro-4-methyl-pyrrolidin-1-yl]indazole (8 mg, 16.61 μmol, 39.5% yield, 98.79% purity, Rt = 5.261 minutes; E.E. by chiral HPLC (%) = 97.88%) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-

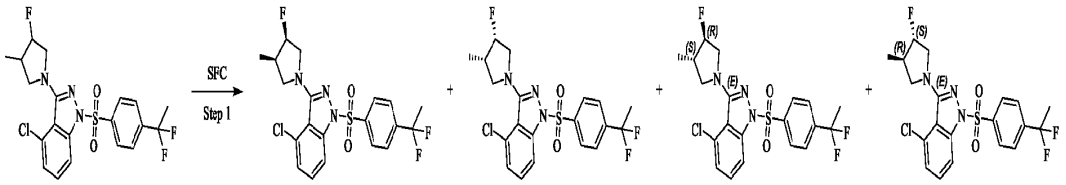
*d*6) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.64 (t, *J* = 8.1 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 4.09 (td, *J* = 11.6, 17.9 Hz, 1H), 3.90 - 3.77 (m, 2H), 3.41 - 3.36 (m, 1H), 2.75 - 2.65 (m, 1H), 1.92 (t, *J* = 19.1 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H). HPLC: 98.79% (220 nm), 98.92% (215 nm), 99.06% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{18}ClF_4N_3O_2S$ 475.1 m/z found 476.1 $[M+H]^+$.

Compound 36: 4-Chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-[(3R,4R)-3-fluoro-4-methyl-pyrrolidin-1-yl]indazole

Compound 37: 4-Chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-[(3S,4S)-3-fluoro-4-methyl-pyrrolidin-1-yl]indazole

Compound 38: 4-Chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-[(3R,4S)-3-fluoro-4-methyl-pyrrolidin-1-yl]indazole

Compound 39: 4-Chloro-1-[4-(1, 1-difluoroethyl)phenyl]sulfonyl-3-[(3S,4R)-3-fluoro-4-methyl-pyrrolidin-1-yl]indazole



[00377] ***Step 1:*** 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3-fluoro-4-methyl-pyrrolidin-1-yl) indazole (20 mg, 43.68 μmol, 1 eq) was separated by chiral SFC (column: Daicel ChiralPak IG (250 * 30 mm, 10 μm); mobile phase: [Heptane-IPA]; B%:20%, isocratic elution mode) to give four isomers. The structures were assigned arbitrarily. 4-Chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-[(3R,4R)-3-fluoro-4-methyl-pyrrolidin-1-yl]indazole (2.2 mg, 4.55 μmol, 10.4% yield, 94.67% purity, Rt = 3.919 minutes; E.E. by chiral HPLC (%) = 100.00%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.12 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.6 Hz, 2H), 7.66 (t, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 4.31 - 4.22 (m, 1H), 3.93 - 3.76 (m, 1H), 3.65 - 3.43 (m, 3H), 2.25 - 2.16 (m, 1H), 1.95 (t, *J* = 19.1 Hz, 3H), 1.32 (br d, *J* = 6.8 Hz, 3H). HPLC: 94.67% (220 nm), 95.53% (215 nm), 86.92% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{19}ClF_3N_3O_2S$ 457.08 m/z found 458.0 $[M+H]^+$.

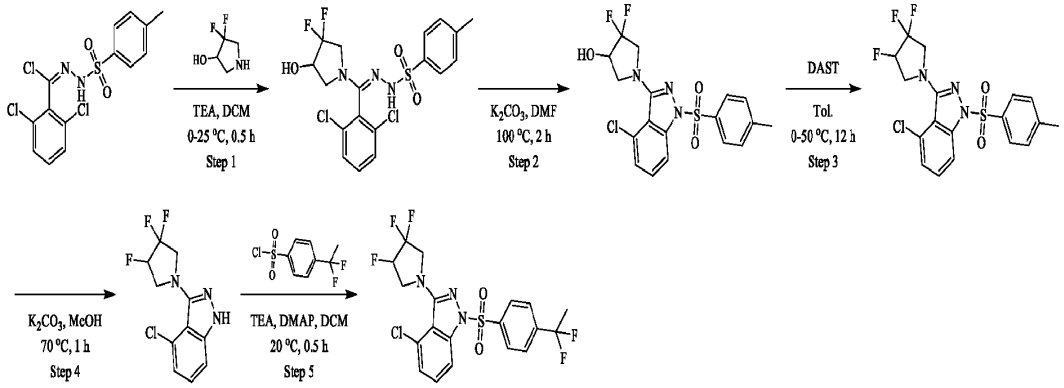
[00378] 4-Chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-[(3S,4S)-3-fluoro-4-methyl-pyrrolidin-1-yl]indazole (1.0 mg, 2.13 μmol, 4.87% yield, 97.38% purity, Rt = 4.352 minutes;

E.E. by chiral HPLC (%) = 93.52%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.67 - 7.60 (m, 1H), 7.51 - 7.45 (m, 1H), 5.25 - 5.07 (m, 1H), 3.94 (d, J = 5.6 Hz, 1H), 3.64 - 3.46 (m, 3H), 2.41 - 2.29 (m, 1H), 1.94 (t, J = 19.2 Hz, 3H), 1.13 (d, J = 6.7 Hz, 3H). HPLC: 97.38% (220 nm), 92.54% (215 nm), 97.31% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{19}ClF_3N_3O_2S$ 457.08 m/z found 458.0 $[M+H]^+$.

[00379] 4-Chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-[(3R,4S)-3-fluoro-4-methyl-pyrrolidin-1-yl]indazole (1.0 mg, 2.10 µmol, 4.82% yield, 96.33% purity, Rt = 4.561 minutes; E.E. by chiral HPLC (%) = 44.52%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.95 (br d, J = 7.8 Hz, 2H), 7.80 - 7.73 (m, 2H), 7.70 - 7.61 (m, 1H), 7.50 (dd, J = 3.9, 7.7 Hz, 1H), 5.19 - 4.92 (m, 1H), 4.26 (dd, J = 2.2, 5.3 Hz, 1H), 3.95 (d, J = 5.5 Hz, 4H), 1.94 (dt, J = 2.3, 19.2 Hz, 3H), 1.33 (br d, J = 7.0 Hz, 3H). HPLC: 96.33% (220 nm), 97.27% (215 nm), 73.24% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{19}ClF_3N_3O_2S$ 457.08 m/z found 458.0 $[M+H]^+$.

[00380] 4-Chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-[(3S,4R)-3-fluoro-4-methyl-pyrrolidin-1-yl]indazole (1.2 mg, 2.54 µmol, 5.83% yield, 97.10% purity, Rt = 6.393 minutes; E.E. by chiral HPLC (%) = 100.0%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.65 (s, 1H), 7.50 (s, 1H), 5.28 - 5.08 (m, 1H), 4.21 - 4.02 (m, 1H), 3.64 - 3.49 (m, 3H), 2.39 - 2.34 (m, 1H), 2.01 - 1.89 (m, 3H), 1.13 (d, J = 6.7 Hz, 3H). HPLC: 97.10% (220 nm), 98.03% (215 nm), 81.97% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{19}ClF_3N_3O_2S$ 457.08 m/z found 458.0 $[M+H]^+$.

Compound 40: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3, 3, 4-trifluoropyrrolidin-1-yl) indazole



[00381] ***Step 1***: To a solution of 5, 5-difluoropyrrolidin-3-ol (250 mg, 1.57 mmol, 1 eq, HCl) in THF (5 mL) was added dropwise TEA (1.59 g, 15.7 mmol, 2.18 mL, 10 eq) at 25 °C. After addition, the mixture was stirred at this temperature for 10 minutes. (1Z)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (888 mg, 2.35 mmol, 1.5 eq) in THF (2 mL) was added dropwise to the mixture at 0 °C. The resulting mixture was stirred at 25 °C for 20 minutes. TLC indicated 5, 5-difluoropyrrolidin-3-ol was consumed completely and one new spot was formed. Then it was separated between 20 mL of water and 40 mL of ethyl acetate. The organic phase was separated, washed with 30 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2, 6-dichlorophenyl)-(2, 2-difluoro-4-hydroxy-pyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (720 mg, crude) as a yellow solid.

[00382] ***Step 2***: To a solution of N-[(E)-[(2, 6-dichlorophenyl)-(3, 3-difluoro-4-hydroxy-pyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (720 mg, 1.55 mmol, 1 eq) in DMF (10 mL) was added K_2CO_3 (1.07 g, 7.75 mmol, 5 eq). The mixture was stirred at 100 °C for 2 hours. TLC indicated N-[(E)-[(2, 6-dichlorophenyl)-(3, 3-difluoro-4-hydroxy-pyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and one new spot was formed. The reaction mixture was added to water (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 35%-60% B over 8.0 min) to give the desired 1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-3-ol (60 mg, crude) as a yellow oil.

[00383] ***Step 3***: Two reactions were carried out in parallel. To a solution of 1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-3-ol (30 mg, 70.1 μmol, 1 eq) in toluene (1 mL) was added DAST (22.6 mg, 140 μmol, 18.5 μL, 2 eq) at 0 °C. The mixture was stirred at 50 °C for 12 hours. Two reactions were carried out in parallel. LC-MS showed 1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-3-ol remained. Several new peaks were shown on LC-MS and the desired compound was detected. Two reactions were combined for workup. The reaction mixture was added to water (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-1-(p-tolylsulfonyl)-3-(3,3,4-trifluoropyrrolidin-1-yl)indazole (60 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{18}H_{15}ClF_3N_3O_2S$ 429.05 m/z found 430.2 $[M+H]^+$.

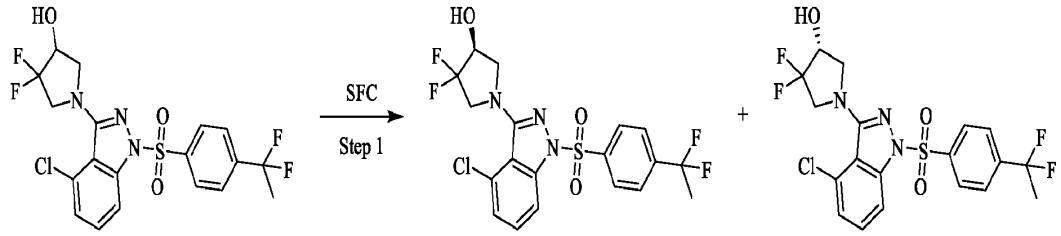
[00384] ***Step 4***: To a solution of 4-chloro-1-(p-tolylsulfonyl)-3-(3, 3, 4-trifluoropyrrolidin-1-yl) indazole (60 mg, 140 μmol, 1 eq) in MeOH (1 mL) was added K_2CO_3 (57.9 mg, 419 μmol, 3 eq). The mixture was stirred at 70 °C for 1 hour. LC-MS showed 4-chloro-1-(p-tolylsulfonyl)-3-(3, 3, 4-trifluoropyrrolidin-1-yl) indazole remained. Several new peaks were shown on LC-MS and the desired compound was detected. The reaction mixture was added to water (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 1/1) to give the desired 4-chloro-3-(3, 3, 4-trifluoropyrrolidin-1-yl)-1H-indazole (20 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{11}H_9ClF_3N_3$ 275.04 m/z found 276.0 $[M+H]^+$.

[00385] ***Step 5***: To a solution of 4-chloro-3-(3,3,4-trifluoropyrrolidin-1-yl)-1H-indazole (20 mg, 72.6 μmol, 1 eq) and 4-(1,1-difluoroethyl)benzenesulfonyl chloride (26.2 mg, 109 μmol, 1.5 eq) in DCM (1 mL) were added TEA (22.0 mg, 218 μmol, 30.3 μL, 3 eq) and DMAP (886 μg, 7.26 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(3, 3, 4-trifluoropyrrolidin-1-yl)-1H-indazole was consumed completely and one main peak with the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O(0.1%TFA)-ACN]; gradient: 50%-75% B over 8.0 min) to give the desired 4-chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(3,3,4-trifluoropyrrolidin-1-yl)indazole (1 mg, 2.04 μmol, 2.81% yield, 97.79% purity) as a pink solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 8.5 Hz, 1H), 7.98 (br d, J = 8.3 Hz, 2H), 7.76 (br d, J = 8.3 Hz, 2H), 7.67 (t, J = 8.1 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 5.59 - 5.32 (m, 1H), 4.28 - 3.94 (m, 3H), 3.91 - 3.78 (m, 1H), 1.93 (t, J = 19.1 Hz, 3H). HPLC: 97.79% (220 nm), 96.44% (215 nm), 96.90% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{15}ClF_5N_3O_2S$ 479.05 m/z found 480.0 $[M+H]^+$.

Compound 41: (3S)-1-[4-chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-indazol-3-yl]-4,4-difluoro-pyrrolidin-3-ol

Compound 42: (3R)-1-[4-chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-indazol-3-yl]-4,4-difluoro-pyrrolidin-3-ol



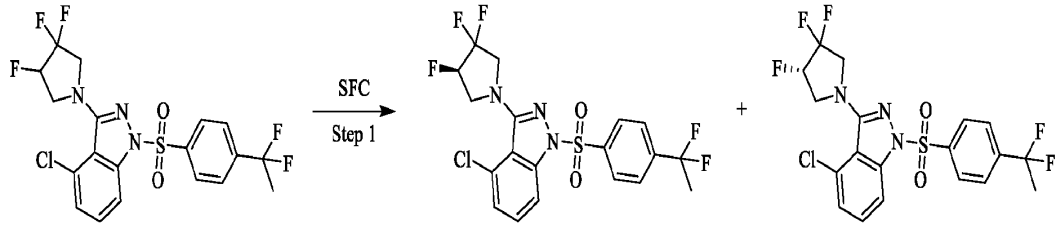
[00386] ***Step 1:*** 1-[4-Chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-indazol-3-yl]-4,4-difluoro-pyrrolidin-3-ol (60 mg, 126 µmol, 1 eq) was separated by chiral SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 µm); mobile phase: [Heptane-IPA]; B%: 20%, isocratic elution mode) to give two isomers. The structures were assigned arbitrarily. (3S)-1-[4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazol-3-yl]-4, 4-difluoro-pyrrolidin-3-ol (5.8 mg, 11.94 µmol, 9.51% yield, 98.41% purity, Rt = 4.278 minutes; E.E. by chiral HPLC (%) = 100.0%) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.70 (t, J = 8.1 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 6.17 (d, J = 5.1 Hz, 1H), 4.42 - 4.32 (m, 1H), 4.14 - 3.91 (m, 3H), 3.51 - 3.45 (m, 1H), 1.98 (t, J = 19.1 Hz, 3H). HPLC: 98.41% (220 nm), 98.26% (215 nm), 98.10% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{16}ClF_4N_3O_3S$ 477.05 m/z found 478.0 $[M+H]^+$.

[00387] (3R)-1-[4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazol-3-yl]-4, 4-difluoro-pyrrolidin-3-ol (4.5 mg, 9.24 µmol, 7.36% yield, 98.09% purity, Rt = 4.825 minutes; E.E. by chiral HPLC (%) = 91.20%) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.65 (t, J = 8.1 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 6.12 (d, J = 5.1 Hz, 1H), 4.37 - 4.27 (m, 1H), 4.06 - 3.86 (m,

3H), 3.43 (ddd, J = 2.1, 4.2, 11.3 Hz, 1H), 1.93 (t, J = 19.1 Hz, 3H). HPLC: 98.09% (220 nm), 98.26% (215 nm), 97.30% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{16}ClF_4N_3O_3S$ 477.05 m/z found 478.0 $[M+H]^+$.

Compound 43: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(4R)-3, 3, 4-trifluoropyrrolidin-1-yl] indazole

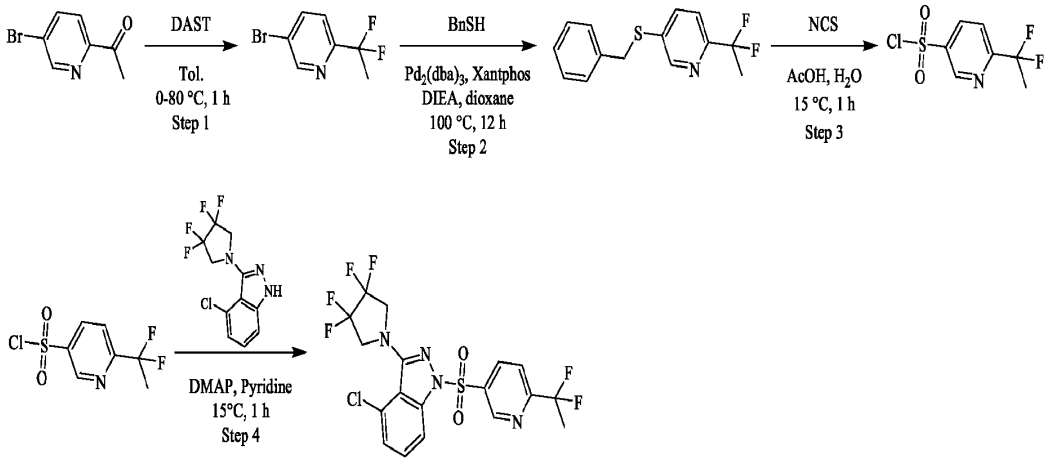
Compound 44: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(4S)-3, 3, 4-trifluoropyrrolidin-1-yl] indazole



[00388] ***Step 1:*** 4-Chloro-1-((4-(1, 1-difluoroethyl) phenyl) sulfonyl)-3-(3, 3, 4-trifluoropyrrolidin-1-yl)-1H-indazole (20 mg) was separated by SFC (column: Daicel ChiralPak IG (250 * 30 mm, 10 μm); mobile phase: [Heptane-EtOH]; B%:20%, isocratic elution mode) to give two isomers. The structures were assigned arbitrarily. 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(4R)-3, 3, 4-trifluoropyrrolidin-1-yl] indazole (1.0 mg, 1.89 μmol, 4.52% yield, 90.85% purity, Rt = 2.851 minutes; E.E. by chiral HPLC (%) = 100.00%) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.67 (t, J = 8.1 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 5.59 - 5.37 (m, 1H), 4.25 - 3.99 (m, 3H), 3.92 - 3.76 (m, 1H), 1.93 (t, J = 19.1 Hz, 3H). HPLC: 90.85% (220 nm), 91.20% (210 nm), 88.67% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{15}ClF_5N_3O_2S$ 479.05, m/z found 480.0 $[M+H]^+$.

[00389] 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(4S)-3, 3, 4-trifluoropyrrolidin-1-yl] indazole (1.2 mg, 2.41 μmol, 5.76% yield, 96.33% purity, Rt = 3.172 minutes; E.E. by chiral HPLC (%) = 100.00%) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.67 (t, J = 8.1 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 5.63 - 5.37 (m, 1H), 4.25 - 4.00 (m, 3H), 3.91 - 3.79 (m, 1H), 1.93 (t, J = 19.1 Hz, 3H). HPLC: 96.33% (220 nm), 96.57% (210 nm), 94.05% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{15}ClF_5N_3O_2S$ 479.05, m/z found 480.0 $[M+H]^+$.

Compound 45: 4-Chloro-1-[[6-(1, 1-difluoroethyl)-3-pyridyl] sulfonyl]-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole



[00390] ***Step 1***: To a solution of 1-(5-bromo-2-pyridyl) ethanone (1 g, 5.00 mmol, 1 eq) in toluene (10 mL) was added DAST (4.03 g, 25.0 mmol, 3.30 mL, 5 eq) at 0 °C. The mixture was stirred at 80 °C for 1 hour. TLC indicated 1-(5-bromo-2-pyridyl) ethanone was consumed completely one new spot was formed. The reaction was quenched with ice-water (10 g) and extracted with EtOAc (2 X 10 mL). The combined organics were concentrated to get a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 5/1) to give the desired 5-bromo-2-(1, 1-difluoroethyl) pyridine (330 mg, 1.49 mmol, 29.7% yield) as a yellow oil. MS (ESI): mass calcd. For $C_7H_6BrF_2N$ 221.0, m/z found 222.0 $[M+H]^+$.

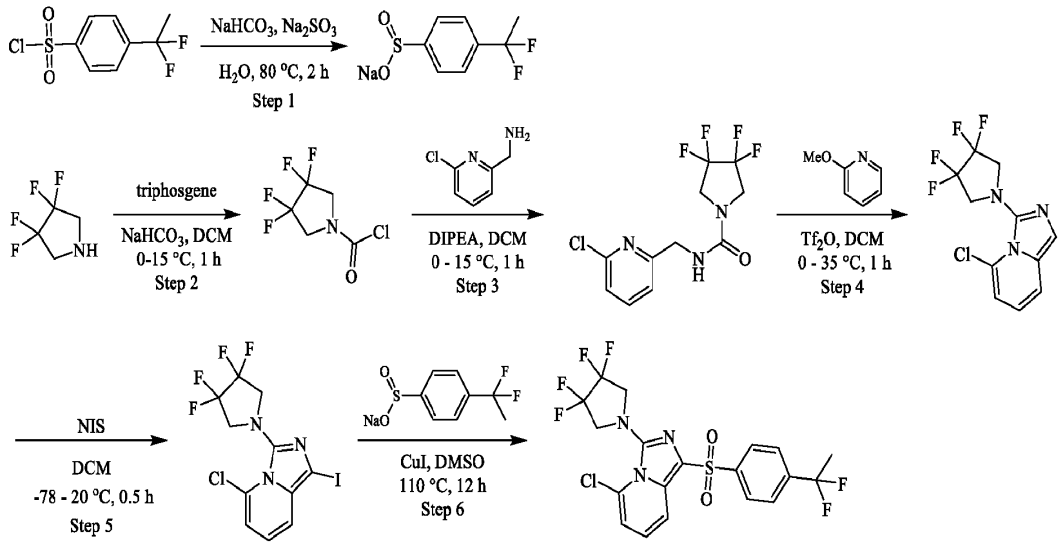
[00391] ***Step 2***: A mixture of 5-bromo-2-(1, 1-difluoroethyl)pyridine (330 mg, 1.49 mmol, 1 eq), phenylmethanethiol (277 mg, 2.23 mmol, 262 µL, 1.5 eq), DIEA (384 mg, 2.97 mmol, 518 µL, 2 eq), Xantphos (86.0 mg, 149 µmol, 0.1 eq) and $Pd_2(dba)_3$ (136 mg, 149 µmol, 0.1 eq) in dioxane (5 mL) was degassed and purged with N_2 for 3 times. The mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. LC-MS showed 5-bromo-2-(1, 1-difluoroethyl) pyridine was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 5/1) to give the desired 5-benzylsulfanyl-2-(1, 1-difluoroethyl) pyridine (230 mg, 867 µmol,

58.3% yield) as a yellow oil. MS (ESI): mass calcd. For $C_{14}H_{13}F_2NS$ 265.1, m/z found 266.1 $[M+H]^+$.

[00392] ***Step 3***: To a solution of 5-benzylsulfanyl- 2-(1, 1-difluoroethyl) pyridine (230 mg, 867 µmol, 1 eq) in AcOH (0.8 mL) and H_2O (0.2 mL) was added NCS (463 mg, 3.47 mmol, 4 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 5-benzylsulfanyl-2-(1, 1-difluoroethyl) pyridine was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 5/1) to give the desired 6-(1, 1-difluoroethyl) pyridine-3-sulfonyl chloride (80 mg, 331 µmol, 38.2% yield) as a white solid. MS (ESI): mass calcd. For $C_7H_6ClF_2NO_2S$ 241.0, m/z found 242.0 $[M+H]^+$.

[00393] ***Step 4:*** To a solution of 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (20 mg, 68.1 µmol, 1 eq) and 6-(1, 1-difluoroethyl) pyridine-3-sulfonyl chloride (32.9 mg, 136 µmol, 2 eq) in pyridine (1 mL) was added DMAP (83 µg, 6.81 µmol, 0.1 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was filtered, and the filter liquor was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; Method: column: Phenomenex Luna C18 75 * 30 mm * 3 µm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 50%-80% B over 8.0 min) to give the desired 4-chloro-1-[[6-(1,1-difluoroethyl)-3-pyridyl]sulfonyl]-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)indazole (4.3 mg, 8.48 µmol, 12.5% yield, 98.38% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (d, J = 1.3 Hz, 1H), 8.48 (dd, J = 2.1, 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 8.1 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 4.24 (br t, J = 12.3 Hz, 4H), 1.95 (t, J = 19.3 Hz, 3H). HPLC: 98.38% (220 nm), 98.29% (215 nm), 98.79% (254 nm). MS (ESI): mass calcd. For $C_{18}H_{13}ClF_6N_4O_2S$ 498.0 m/z found 499.0 $[M+H]^+$.

Compound 46: 5-Chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)imidazo[1,5-a]pyridine



[00394] ***Step 1:*** To a solution of 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (1 g, 4.16 mmol, 1 eq) in H_2O (10 mL) were added $NaHCO_3$ (698 mg, 8.31 mmol, 2 eq) and Na_2SO_3 (1.05 g, 8.31 mmol, 2 eq). The mixture was stirred at 80 °C for 2 hours. TLC indicated 4-(1, 1-difluoroethyl) benzenesulfonyl chloride was consumed completely and one new spot was formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was added MeOH (20 mL). The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give the desired [4-(1, 1-difluoroethyl) phenyl] sulfinyloxysodium (1 g, crude) as a white solid.

[00395] ***Step 2:*** To a solution of 3, 3, 4, 4-tetrafluoropyrrolidine (3 g, 16.7 mmol, 1 eq, HCl) in DCM (30 mL) were added $NaHCO_3$ (7.02 g, 83.6 mmol, 5 eq) and bis (trichloromethyl) carbonate (2.38 g, 8.02 mmol, 0.48 eq) at 0 °C. The mixture was stirred at 15 °C for 1 hour. The reaction was filtered, and the filtrate was concentrated to give the desired 3, 3, 4, 4-tetrafluoropyrrolidine-1-carbonyl chloride (3.3 g, crude) as a white oil.

[00396] ***Step 3:*** To a solution of (6-chloro-2-pyridyl) methanamine (1.83 g, 12.8 mmol, 0.8 eq) in DCM (35 mL) were added DIEA (10.4 g, 80.3 mmol, 14.0 mL, 5 eq) and 3, 3, 4, 4-tetrafluoropyrrolidine-1-carbonyl chloride (3.3 g, 16.1 mmol, 1 eq) at 0 °C. The mixture was stirred at 15 °C for 1 hour. LCMS showed (6-chloro-2-pyridyl) methanamine was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 30 mL of H_2O and 60 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The

residue was purified by purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate / petroleum ether gradient @60 mL/min) to give the desired N-[(6-chloro-2-pyridyl) methyl]-3, 3, 4, 4-tetrafluoro-pyrrolidine-1-carboxamide (2.74 g, 8.79 mmol, 54.8% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{11}H_{10}ClN_3F_4O$ 311.04 m/z found 312.0 $[M+H]^+$.

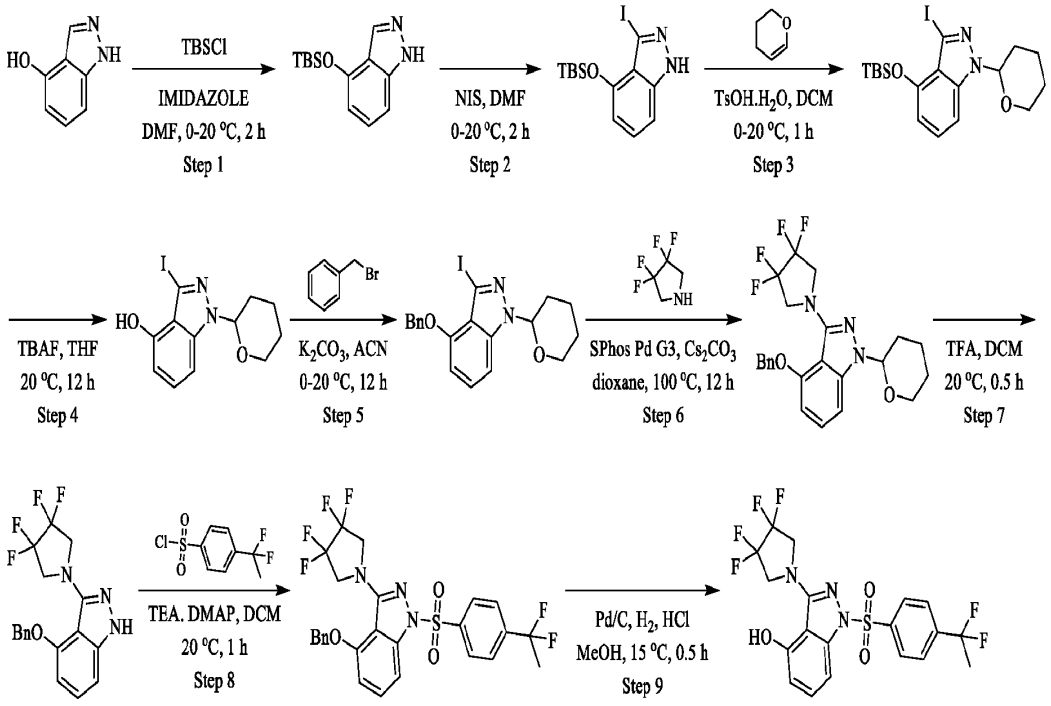
[00397] ***Step 4:*** To a solution of N-[(6-chloro-2-pyridyl)methyl]-3,3,4,4-tetrafluoro-pyrrolidine-1-carboxamide (2.74 g, 8.79 mmol, 1 eq) in DCM (30 mL) were added trifluoromethylsulfonyl trifluoromethanesulfonate (2.98 g, 10.6 mmol, 1.74 mL, 1.2 eq) and 2-methoxypyridine (1.06 g, 9.67 mmol, 1.01 mL, 1.1 eq) at 0 °C. The mixture was stirred at 35 °C for 1 hour. LCMS showed N-[(6-chloro-2-pyridyl) methyl]-3, 3, 4, 4-tetrafluoro-pyrrolidine-1-carboxamide was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 20 mL of H_2O and 30 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 15 % ethyl acetate/petroleum ether gradient @60 mL/min) to give the desired 5-chloro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)imidazo[1,5-a]pyridine (2.55 g, 8.68 mmol, 98.8% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{11}H_8N_3ClF_4$ 293.03 m/z found 294.0 $[M+H]^+$.

[00398] ***Step 5:*** To the mixture of NIS (613 mg, 2.72 mmol, 1.0 eq) in THF (10 mL) was added 5-chloro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)imidazo[1,5-a]pyridine (800 mg, 2.72 mmol, 1 eq) at -78 °C. The mixture was stirred at 20 °C for 0.5 hour. TLC indicated 5-chloro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)imidazo[1,5-a]pyridine was consumed completely and a new spot with lower polarity was detected. The reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with MTBE (2 X 20 mL). The combined organics were dried over Na_2SO_4 and concentrated to get a residue. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~10% ethyl acetate/petroleum ether gradient @ 50 mL/min) to give the desired 5-chloro-1-iodo-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)imidazo[1,5-a]pyridine (230 mg, 548 μmol, 20.1% yield) as a yellow solid.

[00399] ***Step 6:*** A mixture of 5-chloro-1-iodo-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) imidazo [1, 5-a] pyridine (50 mg, 119 μmol, 1 eq), [4-(1, 1-difluoroethyl) phenyl] sulfinyloxysodium

(81.6 mg, 358 μmol, 3 eq), CuI (90.8 mg, 477 μmol, 4 eq) in DMSO (3 mL) under N_2 atmosphere. The mixture was stirred at 110 °C for 12 hours. LCMS showed 5-chloro-1-iodo-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)imidazo[1,5-a]pyridine was consumed completely and the desired mass was detected. The reaction was poured into water (15 mL) and extracted with MTBE (2 X 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O(0.1%TFA)-ACN]; gradient: 40%-60% B over 8.0 minutes) to give the desired 5-chloro-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)imidazo[1,5-a]pyridine (13.4 mg, 26.9 μmol, 22.5% yield, 99.75% purity) as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.00-8.15 (m, 3H), 7.78 (d, 2H), 7.25 (m, 1H), 7.15 (m, 1H), 3.98-4.11 (m, 4H), 1.96 (m, 3H). HPLC: 99.75% (220 nm), 99.72% (215 nm), 99.67% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{14}SN_3ClF_6O_2$ 497.04 m/z found 498.0 $[M+H]^+$.

Compound 47: 1-((4-(1, 1-Difluoroethyl) phenyl) sulfonyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazol-4-ol



[00400] ***Step 1***: To the solution of 1H-indazol-4-ol (1 g, 7.46 mmol, 1 eq) in DMF (10 mL) were added imidazole (761 mg, 11.2 mmol, 1.5 eq) and TBSCl (1.69 g, 11.2 mmol, 1.38 mL, 1.5

eq) at 0 °C and the reaction mixture was stirred at 20 °C for 2 hours. TLC (silica gel, petroleum ether / EtOAc = 1/1) showed 1H-indazol-4-ol was consumed completely and a new spot was formed. The reaction mixture was poured into water (120 mL) and stirred at 20 °C for 0.5 hour. The mixture was filtered, and the cake was dried over reduce pressure to give the desired tert-butyl-(1H-indazol-4-yloxy)-dimethyl-silane (1.85 g, crude) as a black oil.

[00401] ***Step 2***: To the solution of tert-butyl-(1H-indazol-4-yloxy)-dimethyl-silane (1.85 g, 7.45 mmol, 1 eq) in DCM (20 mL) was added NIS (1.84 g, 8.19 mmol, 1.1 eq) at 0 °C and the solution was stirred at 20 °C for 2 hours. LC-MS showed tert-butyl-(1H-indazol-4-yloxy)-dimethyl-silane was consumed completely and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give the desired tert-butyl-[(3-iodo-1H-indazol-4-yl) oxy]-dimethyl-silane (2.79 g, crude) as a black oil. MS (ESI): mass calcd. For $C_{13}H_{19}IN_2OSi$ 374.03 m/z found 375.0 $[M+H]^+$.

[00402] ***Step 3***: To the solution of tert-butyl-[(3-iodo-1H-indazol-4-yl)oxy]-dimethyl-silane (2.75 g, 7.35 mmol, 1 eq) and $TsOH.H_2O$ (140 mg, 735 μmol, 0.1 eq) in DCM (30 mL) was added 3,4-dihydro-2H-pyran (927 mg, 11.0 mmol, 1.01 mL, 1.5 eq) at 0 °C. The solution was stirred at 20 °C for 1 hour. LC-MS showed tert-butyl-[(3-iodo-1H-indazol-4-yl) oxy]-dimethyl-silane was consumed completely and the desired mass was detected. The reaction was poured into water (30 mL) and extracted with MTBE (2 X 30 mL). The combined organics were dried over anhydrous sodium sulfate and concentrated to get a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate/petroleum ether gradient @ 80 mL/min) to give the desired tert-butyl-(3-iodo-1-tetrahydropyran-2-yl-indazol-4-yl) oxy-dimethyl-silane (980 mg, 2.14 mmol, 29.1% yield) as a colorless oil. MS (ESI): mass calcd. For $C_{18}H_{27}IN_2O_2Si$ 458.09 m/z found 459.0 $[M+H]^+$.

[00403] ***Step 4***: To the solution of tert-butyl-(3-iodo-1-tetrahydropyran-2-yl-indazol-4-yl) oxy-dimethyl-silane (780 mg, 1.70 mmol, 1 eq) in THF (8 mL) was added TBAF (1 M, 2.04 mL, 1.2 eq) at 20 °C. The mixture was stirred at 20 °C for 12 hours. TLC (silica gel, petroleum ether / EtOAc = 3/1) showed tert-butyl-(3-iodo-1-tetrahydropyran-2-yl-indazol-4-yl) oxy-dimethyl-silane was consumed completely and a new spot was formed. The reaction was concentrated to get a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate / petroleum ether gradient @

100 mL/min) to give the desired 3-iodo-1-tetrahydropyran-2-yl-indazol-4-ol (0.8 g, crude) as a black oil.

[00404] ***Step 5***: To the mixture of 3-iodo-1-tetrahydropyran-2-yl-indazol-4-ol (0.8 g, 2.32 mmol, 1 eq) and K_2CO_3 (964 mg, 6.97 mmol, 3 eq) in ACN (10 mL) was added benzyl bromide (477 mg, 2.79 mmol, 331 μL, 1.2 eq) at 0 °C and the solution was stirred at 20 °C for 12 hours. LC-MS showed 3-iodo-1-tetrahydropyran-2-yl-indazol-4-ol was consumed completely and the desired mass was detected. The reaction was concentrated to get a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% ethyl acetate / petroleum ether gradient @ 50 mL/min) to give the desired 4-benzyloxy-3-iodo-1-tetrahydropyran-2-yl-indazole (600 mg, crude) as a colorless oil. MS (ESI): mass calcd. For $C_{19}H_{19}IN_2O_2$ 434.05 m/z found 435.0 $[M+H]^+$.

[00405] ***Step 6***: A mixture of 4-benzyloxy-3-iodo-1-tetrahydropyran-2-yl-indazole (450 mg, 1.04 mmol, 1 eq), 3,3,4,4- tetrafluoropyrrolidine (186 mg, 1.04 mmol, 1 eq, HCl), Cs_2CO_3 (675 mg, 2.07 mmol, 2 eq), SPhos Pd G3 (80.9 mg, 104 μmol, 0.1 eq) in dioxane (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. LC-MS showed 4-benzyloxy-3-iodo-1-tetrahydropyran-2-yl-indazole was consumed completely and the desired mass was detected. The crude was added H_2O (20 mL) and extracted with EtOAc (15 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc = 3/1) to give the desired 4-benzyloxy-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-2-yl-indazole (0.4 g, 890 μmol, 85.9% yield) as a brown oil. MS (ESI): mass calcd. For $C_{23}H_{23}F_4N_3O_2$ 449.17 m/z found 450.3 $[M+H]^+$.

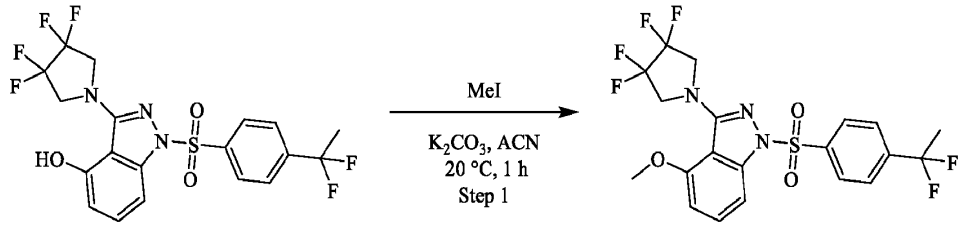
[00406] ***Step 7***: To a solution of 4-benzyloxy-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-2-yl-indazole (0.4 g, 890 μmol, 1 eq) in DCM (1 mL) was added TFA (0.5 mL). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-benzyloxy-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-2-yl-indazole was consumed completely and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc = 2/1) to give the desired 4-benzyloxy-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (0.2 g,

crude, TFA) as a brown solid. MS (ESI): mass calcd. For $C_{18}H_{15}F_4N_3O$ 365.12 m/z found 366.2 $[M+H]^+$.

[00407] ***Step 8***: To a solution of 4-benzyloxy-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (0.2 g, 417 μmol, 1 eq, TFA) and 4-(1, 1-difluoroethyl)benzenesulfonyl chloride (100 mg, 417 μmol, 1 eq) in DCM (1 mL) were added TEA (127 mg, 1.25 mmol, 174 μL, 3 eq) and DMAP (5.10 mg, 41.7 μmol, 0.1 eq). The mixture was stirred at 20 °C for 1 hour. TLC (silica gel, petroleum ether / EtOAc=3/1) showed 4-benzyloxy-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and a new spot was formed. The crude was added H_2O (20 mL) and extracted with EtOAc (15 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc = 3/1) to give the desired 4-benzyloxy-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)indazole (0.2 g, 351 μmol, 84.2% yield) as a brown oil.

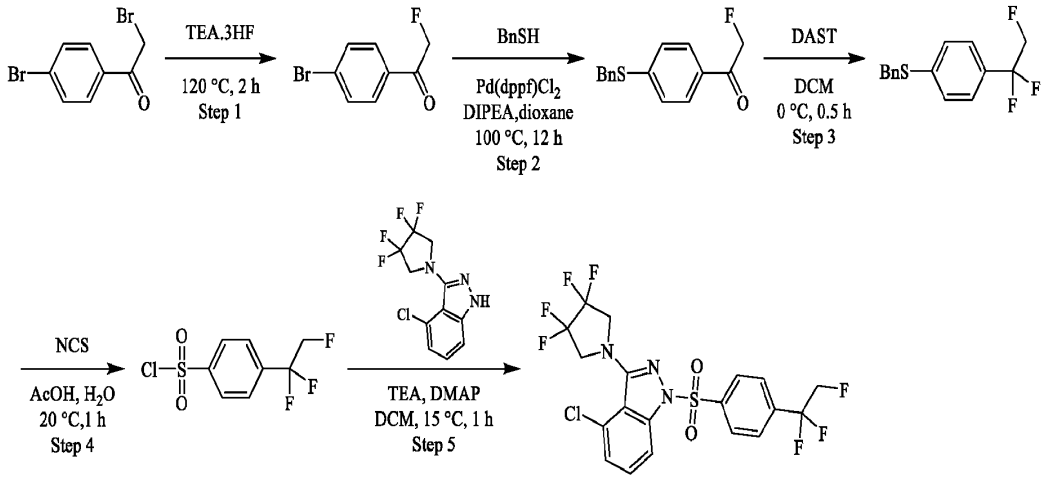
[00408] ***Step 9***: To a solution of 4-benzyloxy-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)indazole (0.2 g, 351 μmol, 1 eq) and 4-benzyloxy-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(3,3,4,4-tetrafluoropyrrolidin-1- yl)indazole (0.2 g, 351 μmol, 1 eq) in MeOH (5 mL) and HCl (0.1 mL) was added Pd/C (37.4 mg, 35.1 μmol, 10% purity, 0.1 eq). The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 Psi) at 15 °C for 0.5 hour. LC-MS showed 4-benzyloxy-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)indazole was consumed completely and the desired mass was detected. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc = 2/1) to give the desired 1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazol-4-ol (5.2 mg, 10.7 μmol, 3.06% yield, 98.97% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.25 (s, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.5 Hz, 2H), 7.58 - 7.47 (m, 2H), 6.80 (dd, J = 0.8, 7.6 Hz, 1H), 4.40 - 4.25 (m, 4H), 1.98 (t, J = 19.1 Hz, 3H). HPLC: 94.85% (220 nm), 93.11% (215 nm), 98.97% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{15}F_6N_3O_3S$ 479.07 m/z found 480.1 $[M+H]^+$.

Compound 48: 1-[4-(1, 1-Difluoroethyl) phenyl] sulfonyl-4-methoxy-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole



[00409] ***Step 1***: To a solution of 1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazol-4-ol (10 mg, 20.9 μmol, 1 eq) in ACN (0.5 mL) were added K_2CO_3 (14.4 mg, 104 μmol, 5 eq) and MeI (14.8 mg, 104 μmol, 6.49 μL, 5 eq). The mixture was stirred at 20 °C for 1 hour. LC-MS showed 1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazol-4-ol was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to HCl (1 mL, 1M) and extracted with EtOAc (3 mL X 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O(0.1%TFA)-ACN]; gradient: 55%-90% B over 8.0 min) to give the desired 1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-4-methoxy-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole (5 mg, 10.0 μmol, 48.0% yield, 98.85% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (br d, J = 8.1 Hz, 2H), 7.73 (br d, J = 8.3 Hz, 2H), 7.66 - 7.56 (m, 2H), 6.93 (br d, J = 7.4 Hz, 1H), 4.20 (br t, J = 12.2 Hz, 4H), 3.91 (s, 3H), 1.92 (br t, J = 19.1 Hz, 3H). HPLC: 98.85% (220 nm), 99.10% (215 nm), 99.33% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{17}F_6N_3O_3S$ 493.09 m/z found 494.1 $[M+H]^+$.

Compound 49: 4-Chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-[4-(1, 1, 2-trifluoroethyl) phenyl] sulfonyl-indazole



[00410] ***Step 1***: To a mixture of 2-bromo-1-(4-bromophenyl) ethanone (3 g, 10.8 mmol, 1 eq) was added 3HF.TEA (19.8 g, 128 mmol, 20 mL, 11.4 eq). The mixture was stirred at 120 °C for 2 hours. TLC indicated 2-bromo-1-(4-bromophenyl) ethanone was consumed completely and one new spot was formed. The reaction mixture was added to ice water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether / EtOAc = 1/0 to 5/1) to give the desired 1-(4-bromophenyl)-2-fluoro-ethanone (1.8 g, crude) as a white solid.

[00411] ***Step 2***: A mixture of phenylmethanethiol (504 mg, 4.05 mmol, 475 µL, 1.1 eq), 1-(4-bromophenyl)-2-fluoro-ethanone(800 mg, 3.69 mmol, 1 eq), DIEA (953 mg, 7.37 mmol, 1.28 mL, 2 eq), Xantphos (213 mg, 369 µmol, 0.1 eq) and $Pd_2(dba)_3$ (84.4 mg, 92.2 µmol, 0.025 eq) in dioxane (10 mL) was degassed and purged with N_2 for 3 times. The mixture was stirred at 100 °C for 3 hours under N_2 atmosphere. TLC indicated phenylmethanethiol was consumed completely and one new spot was formed. The reaction mixture was added to water (20 mL) and extracted with EtOAc (20 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether / EtOAc = 1/0 to 1/1) to give the desired 1-(4-benzylsulfanylphenyl)-2-fluoro-ethanone (840 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{15}H_{13}FOS$ 260.1, m/z found 261.1 $[M+H]^+$.

[00412] ***Step 3***: To a solution of 1-(4-benzylsulfanylphenyl)-2-fluoro-ethanone (300 mg, 1.15 mmol, 1 eq) in DCM (3 mL) was added DAST (929 mg, 5.76 mmol, 761 µL, 5 eq) at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. TLC (silica gel, petroleum ether/ EtOAc = 5/1)

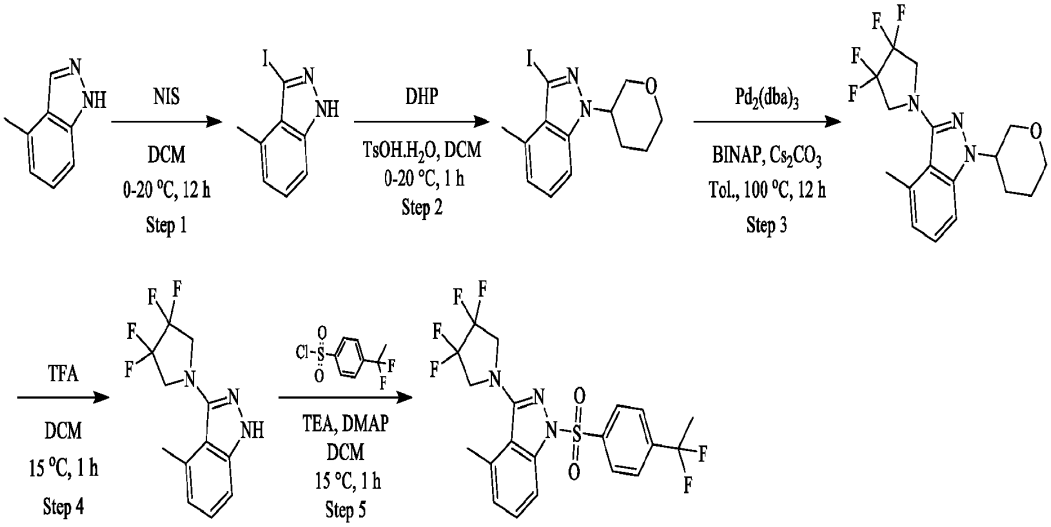
indicated 1-(4-benzylsμLfanylphenyl)-2-fluoro-ethanone was consumed completely and one new spot was formed. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether / EtOAc = 1/0 to 1/1) to give the desired 1-benzylsulfanyl-4-(1, 1, 2-trifluoroethyl) benzene (160 mg, crude) as a colourless oil. MS (ESI): mass calcd. For $C_{15}H_{13}F_3S$ 282.1, m/z found 283.1 $[M+H]^+$.

[00413] ***Step 4***: To a solution of 1-benzylsulfanyl-4-(1, 1, 2-trifluoroethyl) benzene (50 mg, 177 μmol, 1 eq) in AcOH (2 mL) and H_2O (0.4 mL) was added NCS (71.0 mg, 531 μmol, 3 eq). The mixture was stirred at 20 °C for 1 hour. LC-MS (the sample quenched with piperidine) showed 1-benzylsulfanyl-4-(1, 1, 2-trifluoroethyl) benzene was consumed completely and the desired compound was detected. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ EtOAc= 5/1) to give the desired 4-(1, 1, 2-trifluoroethyl) benzenesulfonyl chloride (30 mg, crude) as a colourless oil. MS (ESI): mass calcd. For $C_8H_6ClF_3O_2S$ 258.0, m/z found 308.0 $[M+H+49]^+$.

[00414] ***Step 5***: To a solution of 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (8 mg, 27.2 μmol, 1 eq) and 4-(1, 1, 2-trifluoroethyl)benzenesulfonyl chloride (7.05 mg, 27.2 μmol, 1 eq) in DCM (1 mL) were added TEA (2.76 mg, 27.2 μmol, 3.79 μL, 1 eq) and DMAP (3.33 mg, 27.2 μmol, 1 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 5 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 55%-75% B over 8.0 min) to give the desired 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-[4-(1, 1, 2-trifluoroethyl)phenyl] sulfonyl-indazole (2 mg, 3.62 μmol, 13.3% yield, 93.36% purity) as a little yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.12 - 8.02 (m, 3H), 7.80 (d, J = 8.5 Hz, 2H), 7.68 (t, J = 8.1 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 5.06 - 4.83 (m, 2H), 4.23 (br t, J = 12.2 Hz, 4H). HPLC: 93.36%

(220 nm), 92.65% (215 nm), 92.83% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{13}ClF_7N_3O_2S$ 515.0, m/z found 516.0 $[M+H]^+$.

Compound 50: 1-[4-(1, 1-Difluoroethyl) phenyl] sulfonyl-4-methyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole



[00415] ***Step 1***: To a solution of 4-methyl-1H-indazole (3 g, 22.7 mmol, 1 eq) in DCM (30 mL) was added NIS (5.62 g, 25.0 mmol, 1.1 eq) at 0 °C. The mixture was stirred at 20 °C for 12 hours. LC-MS showed 4-methyl-1H-indazole remained and the desired mass was detected. The reaction mixture was concentrated to give the desired 3-iodo-4-methyl-1H-indazole (5.8 g, crude) as a yellow solid. MS (ESI): mass calcd. For $C_8H_7IN_2$ 258.0, m/z found 259.0 $[M+H]^+$.

[00416] ***Step 2***: To a solution of 3-iodo-4-methyl-1H-indazole (5.8 g, 22.5 mmol, 1 eq) in DCM (60 mL) were added $TsOH.H_2O$ (428 mg, 2.25 mmol, 0.1 eq) and 3, 4-dihydro-2H-pyran (2.84 g, 33.7 mmol, 3.08 mL, 1.5 eq) at 0 °C. The mixture was stirred at 20 °C for 1 hour. LC-MS showed 3-iodo-4-methyl-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 3-iodo-4-methyl-1-tetrahydropyran-3-yl-indazole (7.6 g, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{14}H_{13}F_2NS$ 265.1, m/z found 266.1 $[M+H]^+$.

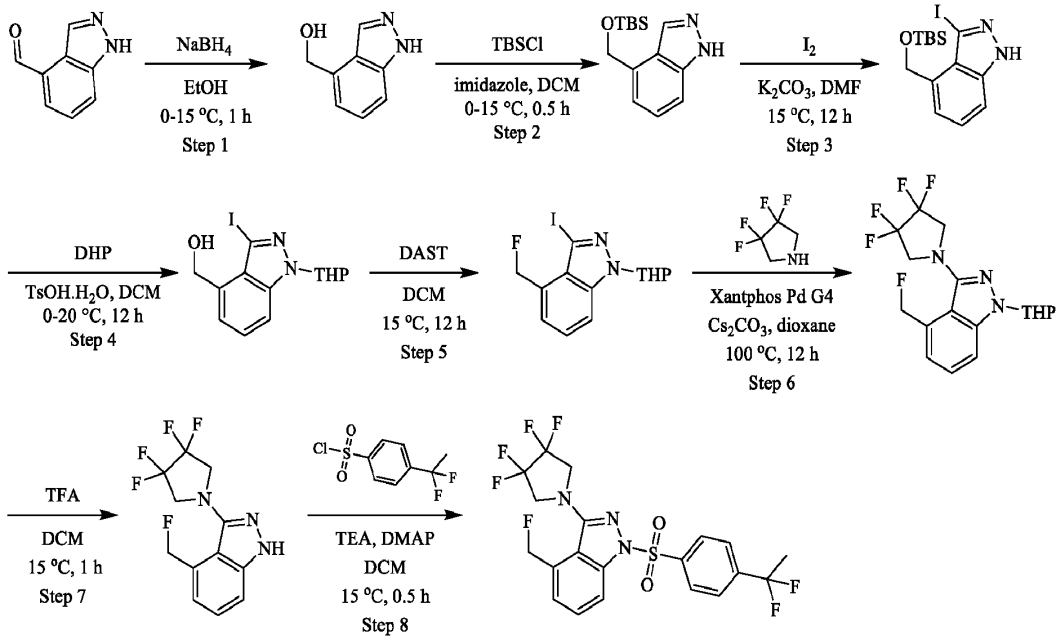
[00417] ***Step 3***: A mixture of 3-iodo-4-methyl-1-tetrahydropyran-3-yl-indazole (300 mg, 876 μmol, 1 eq), 3, 3, 4, 4-tetrafluoropyrrolidine (157 mg, 877 μmol, 1 eq, HCl), Cs_2CO_3 (571 mg, 1.75 mmol, 2 eq), BINAP (54.6 mg, 87.7 μmol, 0.1 eq) and $Pd_2(dba)_3$ (80.3 mg, 87. 7 μmol, 0.1 eq) in toluene (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. LC-MS showed 3-iodo-4-methyl-1-tetrahydropyran-3-yl-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc = 4/1) to give the desired 4-methyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-3-yl-indazole (150 mg, 420 μmol, 47.9% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{17}H_{19}F_4N_3O$ 357.1, m/z found 358.1 $[M+H]^+$.

[00418] ***Step 4***: To a solution of 4-methyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-3-yl-indazole (150 mg, 420 μmol, 1 eq) in DCM (2 mL) was added TFA (239 mg, 2.10 mmol, 156 μl, 5 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-methyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-3-yl-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc = 2/1) to give the desired 4-methyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (80 mg, 293 μmol, 69.8 % yield) as a white solid. MS (ESI): mass calcd. For $C_{12}H_{11}F_4N_3$ 273.1, m/z found 274.1 $[M+H]^-$.

[00419] ***Step 5***: To a solution of 4-methyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (38 mg, 139 μmol, 1 eq) and 4-(1, 1-difluoroethyl)benzenesulfonyl chloride (50.2 mg, 209 μmol, 1.5 eq) in DCM (1 mL) were added TEA (28.2 mg, 278 μmol, 38.7 μl, 2 eq) and DMAP (1.70 mg, 13.9 μmol, 0.1 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-methyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of DCM. The organic phase was separated, washed with 20 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30mm * 3μm;

mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 50%-80% B over 8.0 min) to give the desired 1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-4-methyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)indazole (12.9 mg, 24.9 μmol, 17.9% yield, 92.20% purity) as a little yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 - 7.88 (m, 3H), 7.73 (d, J = 8.5 Hz, 2H), 7.59 - 7.52 (m, 1H), 7.21 (d, J = 7.3 Hz, 1H), 4.19 - 4.04 (m, 4H), 2.61 - 2.54 (m, 3H), 1.91 (t, J = 19.1 Hz, 3H). HPLC: 92.20% (220 nm), 91.74% (215 nm), 89.46% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{17}F_6N_3O_2S$ 477.1, m/z found 478.1 $[M+H]^+$.

Compound 51: 1-[4-(1, 1-Difluoroethyl) phenyl] sulfonyl-4-(fluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole



[00420] ***Step 1***: To a solution of 1H-indazole-4-carbaldehyde (2 g, 13.7 mmol, 1 eq) in EtOH (20 mL) was added $NaBH_4$ (1.04 g, 27.4 mmol, 2 eq) at 0 °C. The mixture was stirred at 15 °C for 1 hour. LC-MS showed 1H-indazole-4-carbaldehyde was consumed completely and the desired mass was detected. To the reaction mixture was added 1 N HCl dropwise to pH = 1, and then concentrated under reduced pressure to give a residue. To the residue was added sat. aq. $NaHCO_3$ to pH = 6, and then extracted with ethyl acetate (50 mL). The combined organic layers were washed with brine (20mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressurefiltered, to give the desired 1H-indazol-4-ylmethanol (3.3 g, crude) as a white solid. MS (ESI): mass calcd. For $C_8H_8N_2O$ 148.1, m/z found 149.1 $[M+H]^+$.

[00421] ***Step 2***: To a solution of 1H-indazol-4-ylmethanol (3.3 g, 22.3 mmol, 1 eq) in DCM (35 mL) were added TBSCl (4.03 g, 26.7 mmol, 3.29 mL, 1.2 eq) and imidazole (3.03 g, 44.6 mmol, 2 eq) at 0 °C. The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 1H-indazol-4-ylmethanol was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 50 mL of H_2O and 50 mL of DCM. The organic phase was separated, washed with 10 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired tert-butyl-(1H-indazol-4-ylmethoxy)-dimethyl-silane (4.48 g, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{14}H_{22}N_2OSi$ 262.2, m/z found 263.2 $[M+H]^+$.

[00422] ***Step 3***: To a solution of tert-butyl-(1H-indazol-4-ylmethoxy)-dimethyl-silane (4.48 g, 17.1 mmol, 1 eq) in DMF (45 mL) were added I_2 (6.50 g, 25.6 mmol, 5.16 mL, 1.5 eq) and K_2CO_3 (4.72 g, 34.1 mmol, 2 eq). The mixture was stirred at 15 °C for 12 hours. LC-MS showed tert-butyl-(1H-indazol-4-ylmethoxy)-dimethyl-silane was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired tert-butyl-[(3-iodo-1H-indazol-4-yl) methoxy]-dimethyl-silane (6.6 g, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{14}H_{21}IN_2OSi$ 388.0, m/z found 389.0 $[M+H]^+$.

[00423] ***Step 4***: To the solution of tert-butyl-[(3-iodo-1H-indazol-4-yl) methoxy]-dimethyl-silane (6.6 g, 17.0 mmol, 1 eq) and $TsOH.H_2O$ (323 mg, 1.70 mmol, 0.1 eq) in DCM (70 mL) was added 3, 4-dihydro-2H-pyran (2.14 g, 25.5 mmol, 2.33 mL, 1.5 eq) at 0 °C. The reaction mixture was stirred at 20 °C for 12 hours. LC-MS showed tert-butyl-[(3-iodo-1H-indazol-4-yl) methoxy]-dimethyl-silane was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 20 mL of H_2O and 40 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~22% EtOAc/petroleum ether gradient @ 60 mL/min) to give the desired (3-iodo-1-tetrahydropyran-2-yl-indazol-4-yl) methanol (1.92 g, 5.36 mmol, 31.5% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{13}H_{15}IN_2O_2$ 358.0, m/z found 359.0 $[M+H]^+$.

[00424] ***Step 5***: To a solution of (3-iodo-1-tetrahydropyran-2-yl-indazol-4-yl) methanol (1.92 g, 5.36 mmol, 1 eq) in DCM (20 mL) was added DAST (4.32 g, 26.8 mmol, 3.54 mL, 5 eq). The

mixture was stirred at 15 °C for 12 hours. LC-MS showed (3-iodo-1-tetrahydropyran-2-yl-indazol-4-yl) methanol was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 32 g SepaFlash® Silica Flash Column, Eluent of 0~10% EtOAc/petroleum ether gradient @ 40 mL/min).) to give the desired 4-(fluoromethyl)-3-iodo-1-tetrahydropyran-2-yl-indazole (730 mg, 2.03 mmol, 37.8% yield) as a light yellow solid. MS (ESI): mass calcd. For $C_{13}H_{14}FIN_2O$ 360.0, m/z found 361.0 $[M+H]^+$.

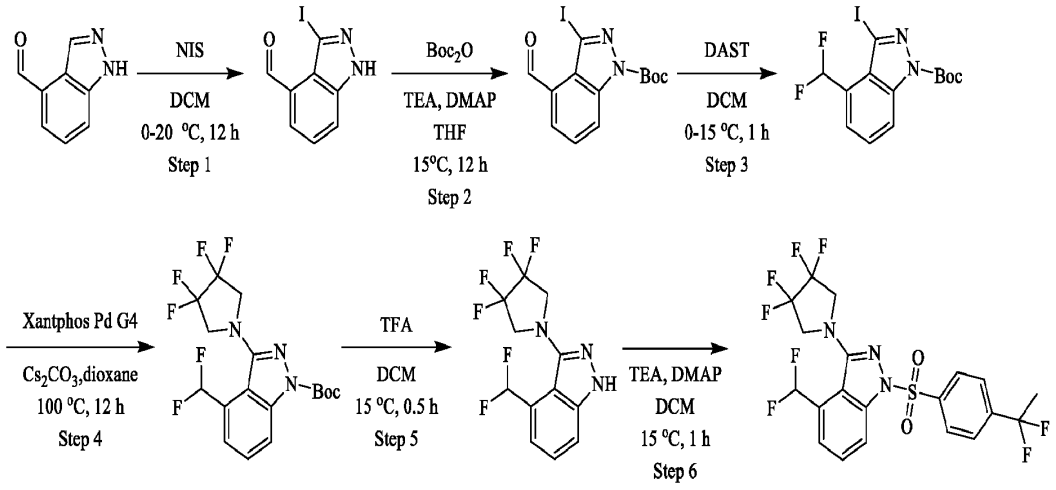
[00425] ***Step 6***: Three reactions were carried out in parallel. A mixture of 4-(fluoromethyl)-3-iodo-1-tetrahydropyran-2-yl-indazole (240 mg, 666 μmol, 1 eq), 3, 3, 4, 4-tetrafluoropyrrolidine (144 mg, 800 μmol, 1.2 eq, HCl), Xantphos Pd G_4 (64.1 mg, 66.6 μmol, 0.10 eq), Cs_2CO_3 (434 mg, 1.33 mmol, 2 eq) in dioxane (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. LC-MS showed 4-(fluoromethyl)-3-iodo-1-tetrahydropyran-2-yl-indazole was consumed completely and the desired mass was detected. Three reactions were combined. The reaction mixture was partitioned between 30 mL of H_2O and 40 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ EtOAc = 3/1) to give the desired 4-(fluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-2-yl-indazole (180 mg, 480 μmol, 24.0% yield) as a black solid. MS (ESI): mass calcd. For $C_{17}H_{18}F_5N_3O$ 375.1, m/z found 376.1 $[M+H]^+$.

[00426] ***Step 7***: To a solution of 4-(fluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-2-yl-indazole (130 mg, 346 μmol, 1 eq) in DCM (2 mL) was added TFA (3.07 g, 26.9 mmol, 2.00 mL, 77.7 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-(fluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-2-yl-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between10 mL of H_2O and 10 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc = 1/1) to give the desired 4-(fluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (80 mg,

275 µmol, 79.3% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{17}H_{18}F_5N_3O$ 291.1, m/z found 292.1 $[M+H]^+$.

[00427] ***Step 8***: To a solution of 4-(fluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (40 mg, 137 µmol, 1 eq) and 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (49.6 mg, 206 µmol, 1.5 eq) in DCM (1 mL) were added TEA (27.8 mg, 275 µmol, 38.2 µL, 2 eq) and DMAP (1.68 mg, 13.7 µmol, 0.1 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 4-(fluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30mm * 3 µm; mobile phase: [H_2O(0.1%TFA)-ACN]; gradient:70%-90% B over 8.0 min) to give the desired 1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-4-(fluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)indazole (2 mg, 3.59 µmol, 2.61% yield, 88.87% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.78 - 7.71 (m, 3H), 7.52 (br d, J = 7.1 Hz, 1H), 5.81 - 5.65 (m, 2H), 4.20 - 4.05 (m, 4H), 1.92 (t, J = 19.1 Hz, 3H). HPLC: 88.87% (220 nm), 89.36% (215 nm), 98.82% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{16}F_7N_3O_2S$ 495.1, m/z found 496.1 $[M+H]^+$.

Compound 52: 1-[4-(1, 1-Difluoroethyl) phenyl] sulfonyl-4-(difluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole



[00428] ***Step 1***: To a solution of 1H-indazole-4-carbaldehyde (3 g, 20.5 mmol, 1 eq) in DCM (30 mL) was added NIS (5.08 g, 22.6 mmol, 1.1 eq) at 0 °C. The mixture was stirred at 20 °C for 12 hours. LC-MS showed 1H-indazole-4-carbaldehyde remained and the desired mass was detected. The reaction mixture was concentrated to give the desired 3-iodo-1H-indazole-4-carbaldehyde (5.58 g, crude) as a yellow solid. MS (ESI): mass calcd. For $C_8H_5IN_2O$ 271.9, m/z found 273.0 $[M+H]^+$.

[00429] ***Step 2***: To a solution of 3-iodo-1H-indazole-4-carbaldehyde (4.5 g, 16.5 mmol, 1 eq) in THF (45 mL) were added TEA (5.02 g, 49.6 mmol, 6.91 mL, 3 eq), DMAP (202 mg, 1.65 mmol, 0.1 eq) and tert-butoxycarbonyl tert-butyl carbonate (4.33 g, 19.9 mmol, 4.56 mL, 1.2 eq). The mixture was stirred at 15 °C for 12 hours. LC-MS showed 3-iodo-1H-indazole-4-carbaldehyde was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 200 mL of H_2O and 130 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/petroleum ether gradient @ 60 mL/min) to give the desired tert-butyl 4-formyl-3-iodo-indazole-1-carboxylate (1.96 g, 5.27 mmol, 31.8% yield) as a white solid. MS (ESI): mass calcd. For $C_{13}H_{13}IN_2O_3$ 372.0, m/z found 373.0 $[M+H]^+$.

[00430] ***Step 3***: To a solution of tert-butyl 4-formyl-3-iodo-indazole-1-carboxylate (1 g, 2.69 mmol, 1 eq) in DCM (1 mL) was added DAST (2.17 g, 13.4 mmol, 1.78 mL, 5 eq) at 0 °C. The mixture was stirred at 15 °C for 1 hour. LC-MS showed tert-butyl 4-formyl-3-iodo-indazole-1-carboxylate was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc = 4/1) to give the desired tert-butyl 4-(difluoromethyl)-3-iodo-indazole-1-carboxylate (900 mg, 2.28 mmol, 85.0% yield) as a white solid. MS (ESI): mass calcd. For $C_{13}H_{13}F_2IN_2O_2$ 394.0, m/z found 395.0 $[M+H]^+$.

[00431] ***Step 4***: Three reactions were carried out in parallel. A mixture of tert-butyl 4-(difluoromethyl)-3-iodo-indazole-1-carboxylate (200 mg, 507 µmol, 1 eq), 3, 3, 4, 4-tetrafluoropyrrolidine (109 mg, 609 µmol, 1.2 eq, HCl), Xantphos Pd G_4 (48.8 mg, 50.7 µmol,

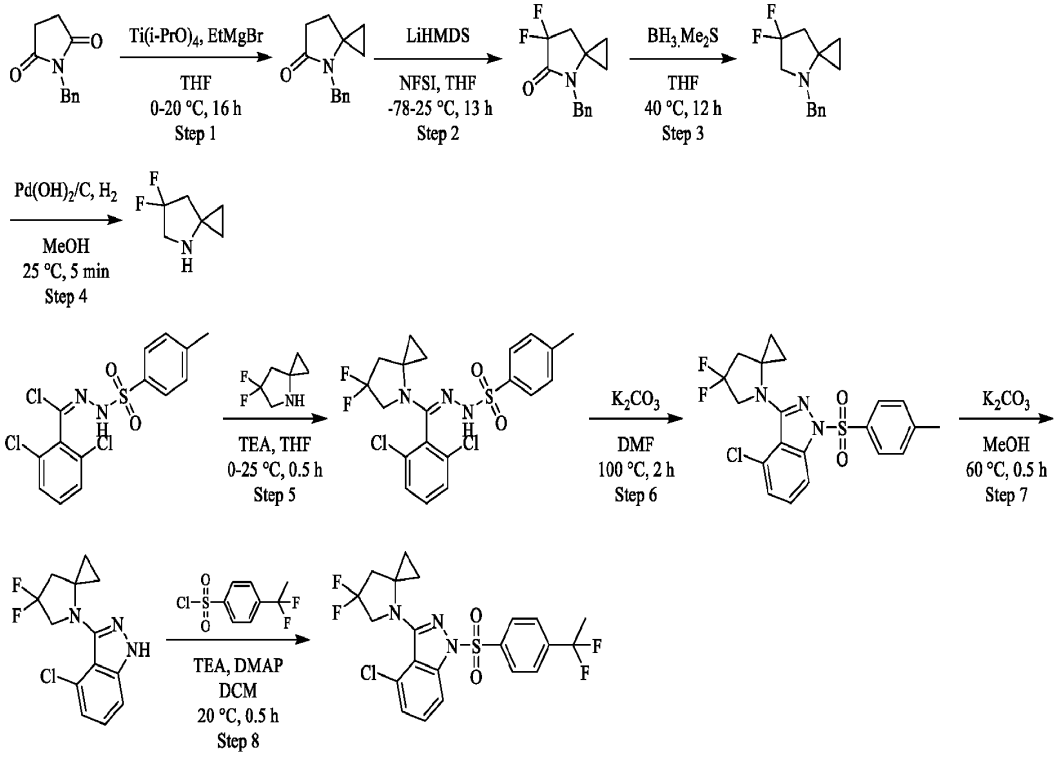
0.1 eq), Cs_2CO_3 (331 mg, 1.01 mmol, 2 eq) in dioxane (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. LC-MS showed tert-butyl 4-(difluoromethyl)-3-iodo-indazole-1-carboxylate was consumed completely and the desired mass was detected. Three reactions were combined. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc = 3/1) to give the desired tert-butyl 4-(difluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole-1-carboxylate (100 mg, 244 µmol, 16.1% yield) as a little yellow oil. MS (ESI): mass calcd. For $C_{17}H_{17}F_6N_3O_2$ 409.1, m/z found 410.1 $[M+H]^+$.

[00432] ***Step 5***: To a solution of tert-butyl 4-(difluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole-1-carboxylate (100 mg, 244 µmol, 1 eq) in DCM (3 mL) was added TFA (1.54 g, 13.5 mmol, 1 mL, 55.1 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed tert-butyl 4-(difluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole-1-carboxylate was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 5 mL of H_2O and 10 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether : ethyl acetate = 2:1) to give the desired 4-(difluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (40 mg, 129 µmol, 53.0% yield) as a white solid. MS (ESI): mass calcd. For $C_{12}H_9F_6N_3$ 309.1, m/z found 310.1 $[M+H]^+$.

[00433] ***Step 6:*** To a solution of 4-(difluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (20 mg, 64.7 µmol, 1 eq) and 4-(1,1-difluoroethyl)benzenesulfonyl chloride (23.4 mg, 97.1 µmol, 1.5 eq) in DCM (2 mL) were added TEA (13.1 mg, 129 µmol, 18.0 µL, 2 eq) and DMAP (790 µg, 6.47 µmol, 0.1 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-(difluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex luna C18 100 * 40mm * 3 µm; mobile phase: [H_2O(0.1%TFA)-ACN]; gradient:50%-90% B over 8.0 min) to

give the desired 1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-4-(difluoromethyl)-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole (11 mg, 21.0 μmol, 32.4% yield, 97.93% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (d, J = 8.6 Hz, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.84 (t, J = 8.1 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 7.6 Hz, 1H), 7.53 - 7.23 (m, 1H), 4.17 - 4.07 (m, 4H), 1.92 (t, J = 19.2 Hz, 3H). HPLC: 97.93% (220 nm), 97.17% (215 nm), 98.32% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{15}F_8N_3O_2S$ 513.1 m/z found 514.1 $[M+H]^+$.

Compound 56: 4-Chloro-3-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole



[00434] ***Step 1***: To a solution of 1-benzylpyrrolidine-2, 5-dione (3 g, 15.9 mmol, 1 eq) in THF (30 mL) were added Ti(i-PrO)$_4$ (22.5 g, 79.3 mmol, 23.4 mL, 5 eq) and EtMgBr (3 M, 18.5 mL, 3.5 eq) at 0 °C. The mixture was stirred at 20 °C for 12 hours. LC-MS showed 1-benzylpyrrolidine-2, 5-dione was consumed completely. $BF_3.Et_2O$ (11.3 g, 79.3 mmol, 9.75 mL, 5 eq) was added to the mixture. The mixture was stirred at 20 °C for 4 hours. LC-MS showed 1-benzylpyrrolidine-2, 5-dione was consumed completely and one main peak with the desired mass was detected. The reaction mixture was quenched by 3N hydrochloric acid (30 mL) and

extracted with EtOAc (60 mL X 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (0.1% TFA condition) to give the desired 4-benzyl-4-azaspiro [2.4] heptan-5-one (2 g, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{15}NO$ 201.0, m/z found 202.2 $[M+H]^+$.

[00435] ***Step 2***: To a solution of 4-benzyl-4-azaspiro [2.4] heptan-5-one (450 mg, 2.24 mmol, 1 eq) in THF (20 mL) was added LiHMDS (1 M, 8.94 mL, 4 eq) at -78 °C under N_2. The mixture was stirred at -78 °C for 1 hour. NFSI (2.82 g, 8.94 mmol, 4 eq) in THF (10 mL) was added to the mixture at -78 °C. The mixture was stirred at 25 °C for 12 hours. LC-MS showed 4-benzyl-4-azaspiro [2.4] heptan-5-one remained. Several new peaks were shown on LC-MS and the desired compound was detected. The reaction mixture was quenched by addition saturated aqueous NH_4Cl (200 mL) at 0 °C and extracted with EtOAc (300 mL X 3). The combined organic phase was washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 30%-55% B over 8.0 min) to give the desired 4-benzyl-6, 6-difluoro-4-azaspiro [2.4] heptan-5-one (100 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{13}F_2NO$ 237.10, m/z found 238.2 $[M+H]^-$.

[00436] ***Step 3***: To a solution of 4-benzyl-6, 6-difluoro-4-azaspiro [2.4] heptan-5-one (110 mg, 464 μmol, 1 eq) in THF (3 mL) was added BH_3-Me_2S (10 M, 92.7 μL, 2 eq). The mixture was stirred at 40 °C for 12 hours. LC-MS showed 4-benzyl-6, 6-difluoro-4-azaspiro [2.4] heptan-5-one was consumed completely and the desired compound was detected. MeOH (1 mL) was added dropwise to the mixture at 0 °C, then the mixture was stirred at 80 °C for 0.5 hour. The reaction mixture was quenched by addition HCl (1M, 1 mL) and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 20%-45% B over 8.0 min) to give the desired 4-benzyl-6, 6-difluoro-4-azaspiro [2.4] heptane (85 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{15}F_2N$ 223.12, m/z found 224.2 $[M+H]^+$.

[00437] ***Step 4***: Two reactions were carried out in parallel. A mixture of 4-benzyl-6, 6-difluoro-4-azaspiro [2.4] heptane (30 mg, 134 μmol, 1 eq), $Pd(OH)_2/C$ (40 mg, 28.5 μmol, 10% purity, 2.12 e^{-1} eq) in MeOH (5 mL) was degassed and purged with H_2(15 psi) for 3 times, and

then the mixture was stirred at 25 °C for 5 min under H_2 atmosphere. LC-MS showed 4-benzyl-6, 6-difluoro-4-azaspiro [2.4] heptane was consumed completely and the desired mass was detected. Two reactions were combined for workup. The reaction mixture was filtered, and concentrated under reduced pressure to give the desired 6, 6-difluoro-4-azaspiro [2.4] heptane (40 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_6H_9F_2N$ 133.07, m/z found 134.2 $[M+H]^+$.

[00438] ***Step 5***: To a solution of 6, 6-difluoro-4-azaspiro [2.4] heptane (35 mg, 263 μmol, 1 eq) in THF (1 mL) was added dropwise TEA (266 mg, 2.63 mmol, 366 μL, 10 eq) at 25 °C. After addition, the mixture was stirred at this temperature for 10 min. The solution of (1Z)-2,6-dichloro-N-(p-tolylsulfonyl)benzohydrazonoyl chloride (99.3 mg, 263 μmol, 1 eq) in THF (1 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 20 min. LC-MS showed 6, 6-difluoro-4-azaspiro [2.4] heptane was consumed completely and one main peak with the desired mass was detected. Then it was separated between 20 mL of water and 40 mL of ethyl acetate. The organic phase was separated, washed with 30 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2,6-dichlorophenyl)-(6,6-difluoro-4-azaspiro[2.4]heptan-4-yl)methylene]amino]-4-methyl-benzenesulfonamide (140 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{20}H_{19}Cl_2F_2N_3O_2S$ 473.05, m/z found 474.0 $[M+H]^+$.

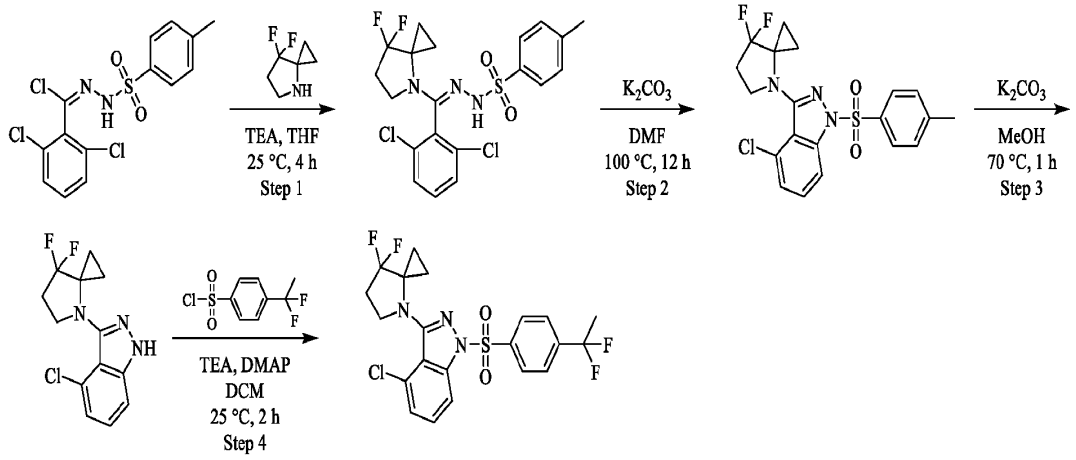
[00439] ***Step 6***: Two reactions were carried out in parallel. To a solution of N-[(E)-[(2, 6-dichlorophenyl)-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl) methylene] amino]-4-methyl-benzenesulfonamide (70 mg, 148 μmol, 1 eq) in DMF (3 mL) was added K_2CO_3 (102 mg, 738 μmol, 5 eq). The mixture was stirred at 100 °C for 2 hours. LC-MS showed N-[(E)-[(2, 6-dichlorophenyl)-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. Two reactions were combined for workup. The reaction mixture was added to water (5 mL) and extracted with EtOAc (3 mL X 3). The combined organic layers were washed with brine (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(6,6-difluoro-4-azaspiro[2.4]heptan-4-yl)-1-(p-tolylsulfonyl)indazole (120 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{18}ClF_2N_3O_2S$ 437.08, m/z found 438.1 $[M+H]^+$.

[00440] ***Step 7***: To a solution of 4-chloro-3-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl)-1-(p-tolylsulfonyl) indazole (120 mg, 274 μmol, 1 eq) in MeOH (3 mL) was added K_2CO_3 (189 mg,

1.37 mmol, 5 eq). The mixture was stirred at 60 °C for 0.5 hour. LC-MS showed 4-chloro-3-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (5 mL) and extracted with EtOAc (3 mL X 3). The combined organic layers were washed with brine (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl)-1H-indazole (25 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{12}ClF_2N_3$ 283.07, m/z found 284.0 $[M+H]^+$.

[00441] ***Step 8***: To a solution of 4-(1,1-difluoroethyl)benzenesulfonyl chloride (25.5 mg, 106 μmol, 1.5 eq) and 4-chloro-3-(6,6-difluoro-4-azaspiro[2.4]heptan-4-yl)-1H-indazole (20 mg, 70.5 μmol, 1 eq) in DCM (2 mL) were added TEA (35.7 mg, 352 μmol, 49.1 μL, 5 eq) and DMAP (861 μg, 7.05 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (2 mL) and extracted with EtOAc (1 mL X 3). The combined organic layers were washed with brine (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:55%-85% B over 8.0 min) to give the desired 4-chloro-3-(6,6-difluoro-4-azaspiro[2.4]heptan-4-yl)-1-[4-(1,1-difluoroethyl)phenyl]sulfonyl-indazole (16 mg, 32.8 μmol, 46.5% yield, 99.87% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.66 (t, J = 8.1 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 3.85 (br t, J = 12.9 Hz, 2H), 2.58 (br t, J = 14.7 Hz, 2H), 1.92 (t, J = 19.1 Hz, 3H), 0.90 (s, 2H), 0.70 - 0.55 (m, 2H). HPLC: 99.87% (220 nm), 99.92% (215 nm), 99.90% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{18}ClF_4N_3O_2S$ 487.07, m/z found 487.7 $[M+H]^+$.

Compound 57: 4-Chloro-3-(7,7-difluoro-4-azaspiro[2.4]heptan-4-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole



[00442] ***Step 1***: To a solution of 7,7-difluoro-4-azaspiro[2.4]heptane (130 mg, 767 μmol, 1 eq, HCl) in THF (10 mL) was added TEA (233 mg, 2.30 mmol, 3 eq) and (1Z)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (289 mg, 767 μmol, 1 eq) at 25 °C. The mixture was stirred at 25 °C for 4 hours. LCMS indicated starting material consumed and detected the desired mass of product. Then it was quenched by H_2O (10 mL) and extracted with ethyl acetate (10 mLx 2). The combined organic phase was washed brine (10 mL) and concentrated to give the desired (E)-N'-((2,6-dichlorophenyl)(7,7-difluoro-4-azaspiro[2.4]heptan-4-yl)methylene)-4-methylbenzenesulfonohydrazide (250 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{20}H_{19}Cl_2F_2N_3O_2S$ 473.05 m/z found 474.1 $[M+H]^+$.

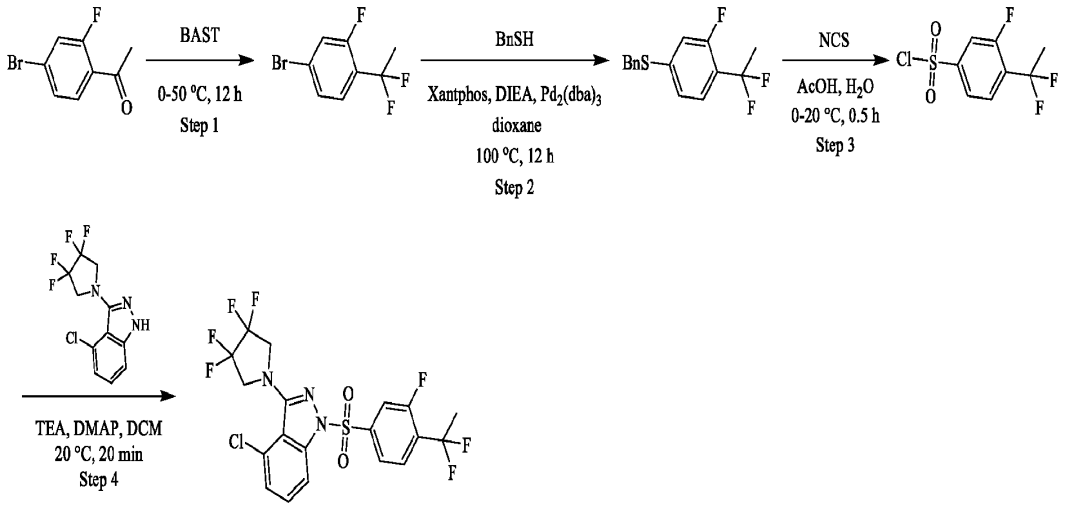
[00443] ***Step 2***: To a solution of (E)-N'-((2,6-dichlorophenyl)(7,7-difluoro-4-azaspiro[2.4]heptan-4-yl)methylene)-4-methylbenzenesulfonohydrazide (250 mg, 527 μmol, 1 eq) in DMF (10 mL) was added K_2CO_3 (219 mg,1.58 mmol,3 eq). The mixture was stirred at 100 °C for 12 h. LCMS indicated starting material consumed and detected the desired product. The mixture was quenched by NH_4Cl (10 mL), extracted with ethyl acetate (10 mL X 2), the combined organic phase was washed with brine (10 mL X 2), dried over MgSO4, filtered and concentrated under reduced pressure to give desired 4-chloro-3-(7,7-difluoro-4-azaspiro[2.4]heptan-4-yl)-1-tosyl-1H-indazole (220 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{20}H_{18}ClF_2N_3O_2S$ 437.08 m/z found 438.1 $[M+H]^+$.

[00444] ***Step 3***: To a solution of 4-chloro-3-(7,7-difluoro-4-azaspiro[2.4]heptan-4-yl)-1-tosyl-1H-indazole (220 mg, 502 μmol, 1 eq) in MeOH (10 mL) was added K_2CO_3 (208 mg, 1.51 mmol, 3 eq). The mixture was stirred at 70 °C for 1 h. LCMS indicated starting material consumed and detected the desired product. The solvents were removed under reduced pressure

then H_2O (10 mL) was added, extracted with ethyl acetate (10 mL X 2), the combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate =10/1 to 3/1) to give desired 4-chloro-3-(7,7-difluoro-4-azaspiro[2.4]heptan-4-yl)-1H-indazole (130 mg) as a light-yellow solid. MS (ESI): mass calcd. For $C_{13}H_{12}ClF_2N_3$ 283.07 m/z found 284.1 $[M+H]^+$.

[00445] ***Step 4***: To a solution of 4-chloro-3-(7,7-difluoro-4-azaspiro[2.4]heptan-4-yl)-1H-indazole (130 mg, 458 μmol, 1 eq) in DCM (10 mL) was added 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (165 mg, 687 μmol, 1.5 eq), TEA (92.7 mg, 916 μmol, 2 eq) and DMAP (5.60 mg, 45.8 μmol, 0.1 eq). The mixture was stirred at 25 °C for 2 hours. LCMS indicated starting material consumed and detected the desired product. The mixture was quenched by NH_4Cl (10 mL), extracted with ethyl acetate (10 mL X 2), the combined organic phase was washed with brine (10 mL), dried over MgSO4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate =50/1 to 10/1) to give desired 4-chloro-3-(7,7-difluoro-4-azaspiro[2.4]heptan-4-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole (103 mg,211 μmol,46%, 98.10 purity) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.43 (t, J = 8.1 Hz, 1H), 7.31 – 7.24 (m, 1H), 3.68 (t, J = 7.1 Hz, 2H), 2.53 – 2.38 (m, 2H), 1.88 (t, J = 18.2 Hz, 3H), 1.21 – 1.14 (m, 2H), 0.90 – 0.82 (m, 2H). HPLC: 98.10% (220 nm), 98.87% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{18}ClF_4N_3O_2S$ 487.07 m/z found 488.1 $[M+H]^+$.

Compound 58: 4-Chloro-1-[4-(1, 1-difluoroethyl)-3-fluoro-phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole



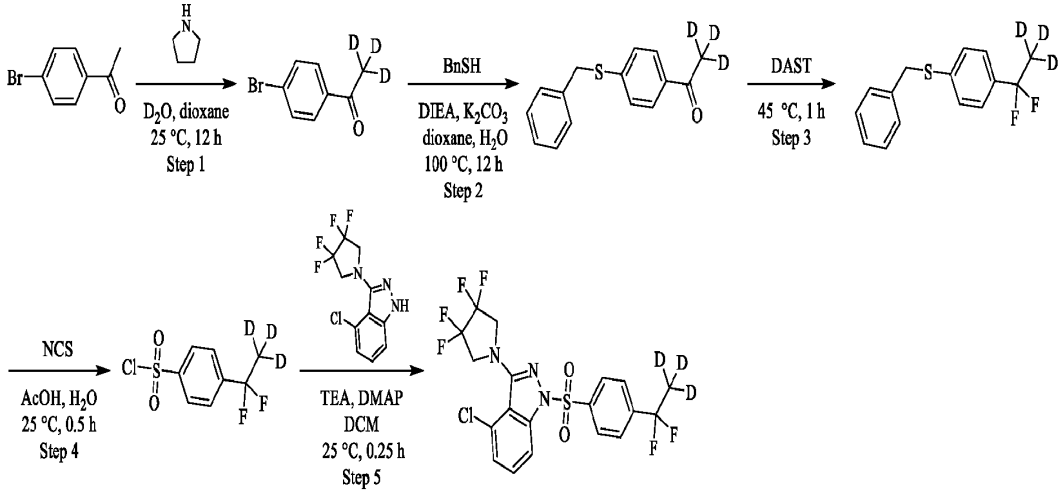
[00446] ***Step 1***: To a mixture of 1-(4-bromo-2-fluoro-phenyl) ethanone (1 g, 4.61 mmol, 1 eq) was added BAST (17 mL) at 0 °C. The mixture was stirred at 50 °C for 12 hours. TLC (petroleum ether / ethyl acetate = 1/0) showed 1-(4-bromo-2-fluoro-phenyl) ethanone remained and one new spot was formed. The reaction mixture was quenched by sat. aq. $NaHCO_3$ (300 mL) at 0 °C and extracted with EtOAc (150 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~100% EtOAc/petroleum ether gradient @ 80 mL/min) to give the desired 4-bromo-1-(1,1-difluoroethyl)-2-fluoro-benzene (540 mg, 2.26 mmol, 49.0% yield) as a colourless liquid.

[00447] ***Step 2***: A mixture of 4-bromo-1-(1, 1-difluoroethyl)-2-fluoro-benzene (540 mg, 2.26 mmol, 1 eq), BnSH (0.44 g, 3.54 mmol, 416 µL, 1.57 eq), Xantphos (131 mg, 226 µmol, 0.1 eq), DIEA (584 mg, 4.52 mmol, 787 µL, 2 eq) and $Pd_2(dba)_3$ (207 mg, 226 µmol, 0.1 eq) in dioxane (6 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. TLC (Petroleum ether / ethyl acetate = 1/0) showed 4-bromo-1-(1, 1-difluoroethyl)-2-fluoro-benzene remained and one new spot was formed. The reaction mixture was partitioned between water (20 mL) and EtOAc (15 mL). The organic phase was separated, washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (petroleum ether / acetate ethyl = 1/0) to give the desired 4-benzylsulfanyl-1-(1, 1-difluoroethyl)-2-fluoro-benzene (548 mg, 1.94 mmol, 85.9% yield) as a yellow oil.

[00448] ***Step 3***: To a solution of 4-benzylsulfanyl-1-(1, 1-difluoroethyl)-2-fluoro-benzene (300 mg, 1.06 mmol, 1 eq) in AcOH (4 mL) and H_2O (1 mL) was added NCS (568 mg, 4.25 mmol, 4 eq) at 0 °C. The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-benzylsulfanyl-1-(1,1-difluoroethyl)-2-fluoro-benzene was consumed completely and the desired compound was detected (quenched by piperidine). The reaction mixture was concentrated under reduced pressure to remove AcOH. The residue was diluted with H_2O (15 mL) and extracted with EtOAc (10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (petroleum ether / acetate ethyl = 5/1) to give the desired 4-(1,1-difluoroethyl)-3-fluoro-benzenesulfonyl chloride (113 mg, 437 μmol, 41.1% yield) as a yellow liquid. MS (ESI): mass calcd. For $C_{14}H_{14}ClFO_2$ 257.97 m/z found 308.1 $[M+H+49]^+$.

[00449] ***Step 4***: To a solution of 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (30 mg, 102 μmol, 1 eq), 4-(1,1-difluoroethyl)-3-fluoro-benzenesulfonyl chloride (34.4 mg, 133 μmol, 1.3 eq) in DCM (2 mL) were added TEA (20.7 mg, 204 μmol, 28.4 μL, 2 eq) and DMAP (1.25 mg, 10.2 μmol, 0.1 eq). The mixture was stirred at 20 °C for 20 min. LC-MS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired compound was detected. The reaction mixture was filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75*30mm*3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:65%-75% B over 10.0 min) to give the desired 4-chloro-1-[4-(1, 1-difluoroethyl)-3-fluoro-phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole (6.6 mg, 12.6 μmol, 98.66% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 8.5 Hz, 1H), 7.94 (br d, J = 10.0 Hz, 1H), 7.86 - 7.76 (m, 2H), 7.70 (t, J = 8.1 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 4.25 (br t, J = 12.2 Hz, 4H), 1.97 (t, J = 19.4 Hz, 3H) HPLC: 98.66% (220 nm), 98.62% (215 nm), 98.19% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{13}ClF_7N_3O_2S$ 515.03 m/z found 516.0 $[M+H]^+$.

Compound 59: 4-Chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-[4-(2, 2, 2-trideuterio-1, 1-difluoro-ethyl) phenyl] sulfonyl-indazole



[00450] ***Step 1***: To a solution of 1-(4-bromophenyl) ethanone (5 g, 25.1 mmol, 1 eq) in deuterated water (30 mL) and dioxane (30 mL) was added pyrrolidine (179 mg, 2.51 mmol, 210 μL, 0.1 eq) under N_2. The mixture was stirred at 25 °C for 12 hours. LC-MS showed 1-(4-bromophenyl) ethanone was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 100 mL of H_2O and 80 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/petroleum ether gradient @ 80 mL/min) to give the desired 1-(4-bromophenyl)-2, 2, 2-trideuterio-ethanone (4.7 g, 23.3 mmol, 92.6% yield) as a colorless oil. MS (ESI): mass calcd. For $C_8H_4D_3BrO$ 201.0, m/z found 202.1 $[M+H]^+$.

[00451] ***Step 2***: A mixture of 1-(4-bromophenyl)-2, 2, 2-trideuterio-ethanone (4.7 g, 23.3 mmol, 1 eq), phenylmethanethiol (3.18 g, 25.6 mmol, 3.00 mL, 1.1 eq), DIEA (6.01 g, 46.5 mmol, 8.10 mL, 2 eq), Xantphos (1.35 g, 2.33 mmol, 0.1 eq) and $Pd_2(dba)_3$ (1.06 g, 1.16 mmol, 0.05 eq) in dioxane (30 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. LC-MS showed 1-(4-bromophenyl)-2, 2, 2-trideuterio-ethanone was consumed completely and the desired mass was detected. The reaction mixture was partitioned between H_2O (60 mL) and EtOAc (100 mL). The organic phase was separated, washed with brine (100 mL X 2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl

acetate/petroleum ether gradient @ 60 mL/min) to give the desired 1-(4-benzylsulfanylphenyl)-2, 2, 2-trideuterio-ethanone (1.7 g, 6.93 mmol, 29.8% yield) as a little yellow solid. MS (ESI): mass calcd. For $C_{15}H_{11}D_3OS$ 245.1, m/z found 246.1 $[M+H]^+$.

[00452] ***Step 3***: To the mixture of 1-(4-benzylsulfanylphenyl)-2, 2, 2-trideuterio-ethanone (0.6 g, 2.45 mmol, 1 eq) was added DAST (7.32 g, 45.4 mmol, 6.00 mL, 18.6 eq). The mixture was stirred at 45 °C for 1 hour. TLC (petroleum ether / ethyl acetate = 5/1) indicated 1-(4-benzylsulfanylphenyl)-2, 2, 2-trideuterio-ethanone was consumed completely and two new spots were formed. The reaction mixture was quenched by sat. aq. $NaHCO_3$ (300 mL) at 0 °C and extracted with EtOAc (350 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/petroleum ether gradient @ 60 mL/min) to give the desired 1-benzylsulfanyl-4-(2, 2, 2-trideuterio-1, 1-difluoro-ethyl) benzene (0.128 g, 479 µmol, 19.6% yield) as a yellow solid.

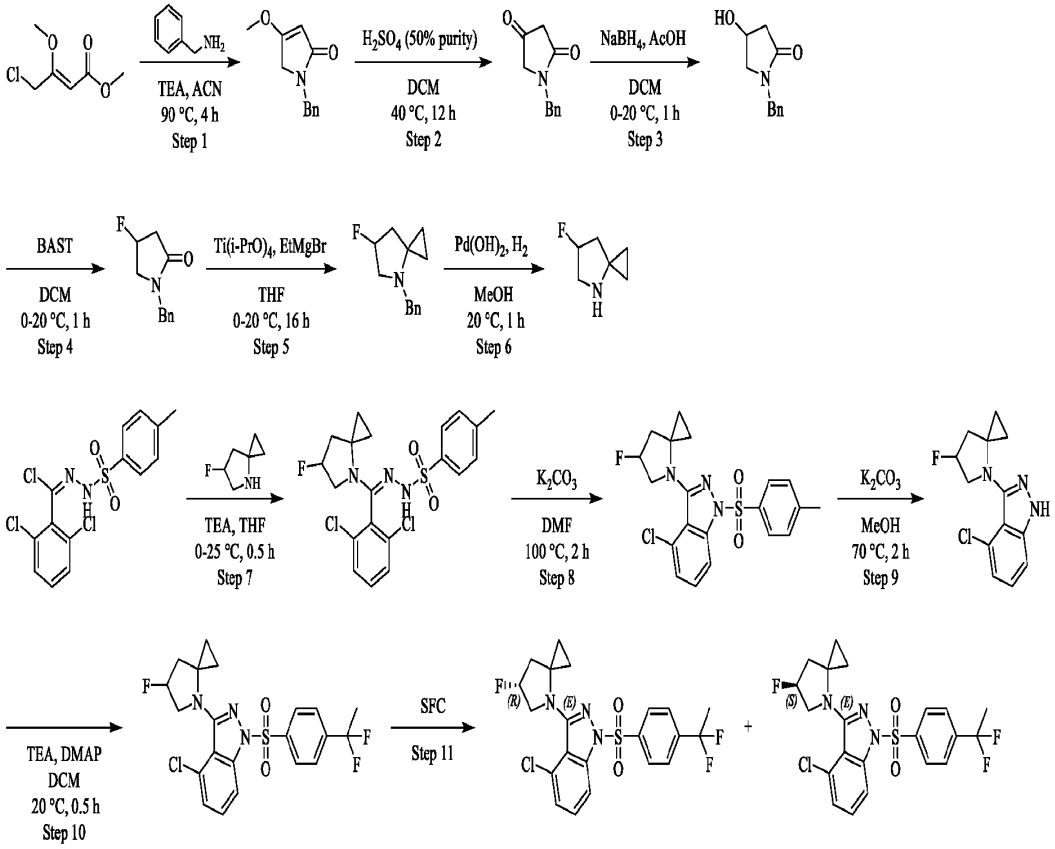
[00453] ***Step 4***: To a solution of 1-benzylsulfanyl-4-(2, 2, 2-trideuterio-1, 1-difluoro-ethyl) benzene (120 mg, 449 µmol, 1 eq) in AcOH (1.8 mL) and H_2O (0.6 mL) was added NCS (180 mg, 1.35 mmol, 3 eq). The mixture was stirred at 25 °C for 0.5 hour. LC-MS showed 1-benzylsulfanyl-4-(2, 2, 2-trideuterio-1, 1-difluoro-ethyl) benzene was consumed completely and the desired mass was detected (quenched by piperidine). The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether : ethyl acetate = 5:1) to give the desired 4-(2, 2, 2-trideuterio-1, 1-difluoro-ethyl) benzenesulfonyl chloride (90 mg, 370 µmol, 82.3% yield) as a colorless oil. MS (ESI): mass calcd. For $C_8H_4D_3ClF_2O_2S$ 243.0, m/z found 293.1 $[M+H+49]^+$.

[00454] ***Step 5***: To a solution of 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (20 mg, 68.1 µmol, 1 eq) and 4-(2, 2, 2-trideuterio-1, 1-difluoro-ethyl) benzenesulfonyl chloride (49.8 mg, 204 µmol, 3 eq) in DCM (1 mL) were added TEA (13.8 mg, 136 µmol, 19.0 µL, 2 eq) and DMAP (832 µg, 6.81 µmol, 0.1 eq). The mixture was stirred at 25 °C for 0.25 hour. LC-MS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O

and 10 mL of DCM. The organic phase was separated, washed with 5 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:60%-80% B over 8.0 min) to give the desired 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-[4-(2, 2, 2-trideuterio-1, 1-difluoro-ethyl) phenyl]sulfonyl-indazole (10 mg, 18.9 μmol, 27.7% yield, 94.48% purity) as a little yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.67 (t, J = 8.1 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 4.27 - 4.17 (m, 4H). HPLC: 94.48% (220 nm), 94.62% (215 nm), 91.32% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{11}D_3ClF_6N_3O_2S$ 500.1, m/z found 501.0 $[M+H]^+$.

Compound 60: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(6R)-6-fluoro-4-azaspiro [2.4] heptan-4-yl] indazole

Compound 61: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(6S)-6-fluoro-4-azaspiro [2.4] heptan-4-yl] indazole



[00455] ***Step 1***: To a refluxing solution of phenylmethanamine (8.46 g, 79.0 mmol, 8.61 mL, 1.3 eq) in ACN (85 mL) were added dropwise methyl (E)-4-chloro-3-methoxy-but-2-enoate (10 g, 60.8 mmol, 1 eq) in ACN (100 mL) and a solution of TEA (7.99 g, 79.0 mmol, 11.0 mL, 1.3 eq) in ACN (100 mL) in parallel. The mixture was stirred at 90 °C for 4 hours. LC-MS showed phenylmethanamine was consumed completely and one main peak with the desired mass was detected. The reaction mixture was partitioned between water (150 mL) and EtOAc (300 mL). The organic phase was separated, washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~100% ethyl acetate/petroleum ether gradient @ 80 mL/min) to give the desired 1-benzyl-3-methoxy-2H-pyrrol-5-one (8.5 g, 41.8 mmol, 65.4% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{12}H_{13}NO_2$ 203.09 m/z found 204.1 $[M+H]^+$.

[00456] ***Step 2***: To a solution of 1-benzyl-3-methoxy-2H-pyrrol-5-one (4 g, 19.7 mmol, 1 eq) in DCM (40 mL) was added H_2SO_4 (20.0 g, 102 mmol, 10.9 mL, 50% purity, 5.18 eq). The mixture was stirred at 40 °C for 12 hours. LC-MS showed 1-benzyl-3-methoxy-2H-pyrrol-5-one remained. Several new peaks were shown on LC-MS and the desired compound was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (0.1% TFA condition) to give the desired 1-benzylpyrrolidine-2, 4-dione (1.9 g, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{11}H_{11}NO_2$ 189.08 m/z found 190.1 $[M+H]^+$.

[00457] ***Step 3***: To a solution of 1-benzylpyrrolidine-2,4-dione (1 g, 5.29 mmol, 1 eq) and AcOH (3.17 g, 52.9 mmol, 3.03 mL, 10 eq) in DCM (20 mL) was added $NaBH_4$ (400 mg, 10.6 mmol, 2 eq) at 0 °C. The mixture was stirred at 20 °C for 1 hour. LC-MS showed 1-benzylpyrrolidine-2, 4-dione was consumed completely and the desired mass was detected. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 1-benzyl-4-hydroxy-pyrrolidin-2-one (1 g, crude) as an orange oil. MS (ESI): mass calcd. For $C_{11}H_{13}NO_2$ 191.09 m/z found 192.1 $[M+H]^+$.

[00458] ***Step 4***: To a solution of 1-benzyl-4-hydroxy-pyrrolidin-2-one (1 g, 5.23 mmol, 1 eq) in DCM (20 mL) was added BAST (1.74 g, 7.84 mmol, 1.72 mL, 1.5 eq) at 0 °C. The mixture was stirred at 20 °C for 1 hour. LC-MS showed 1-benzyl-4-hydroxy-pyrrolidin-2-one remained. Several new peaks were shown on LC-MS and the desired compound was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75*30mm*3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 10%-35% B over 8.0 min) to give the desired 1-benzyl-4-fluoro-pyrrolidin-2-one (420 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{11}H_{12}FNO$ 193.09 m/z found 194.1 $[M+H]^+$.

[00459] ***Step 5***: To a solution of 1-benzyl-4-fluoro-pyrrolidin-2-one (370 mg, 1.91 mmol, 1 eq) in THF (4 mL) were added $Ti(i\text{-}PrO)_4$ (544 mg, 1.91 mmol, 565 μL, 1 eq) and EtMgBr (3 M, 1.28 mL, 2 eq) at 0 °C. The mixture was stirred at 20 °C for 12 hours. LC-MS showed 1-benzyl-4-fluoro-pyrrolidin-2-one was consumed completely. Diethyloxonio(trifluoro)boranuide (544 mg, 3.83 mmol, 471 μL, 2 eq) was added to the mixture. The mixture was stirred at 20 °C for 4 hours. LC-MS showed the desired mass was detected. The reaction mixture was quenched by 3N hydrochloric acid (6 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:1%-25% B over 8.0 min) to give the desired 4-benzyl-6-fluoro-4-azaspiro[2.4]heptane (80 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{16}FN$ 205.13 m/z found 206.2 $[M+H]^+$.

[00460] ***Step 6***: A mixture of 4-benzyl-6-fluoro-4-azaspiro [2.4] heptane (70 mg, 341 μmol, 1 eq), $Pd(OH)_2$ (479 mg, 341 μmol, 10% purity) in MeOH (3 mL) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 20 °C for 1 hour under H_2(15 PSI) atmosphere. TLC (dichloromethane / methanol = 5/1) indicated 4-benzyl-6-fluoro-4-azaspiro [2.4] heptane was consumed completely and one new spot was formed. The reaction mixture was filtered, and concentrated under reduced pressure to give the desired 6-fluoro-4-azaspiro [2.4] heptane (40 mg, crude) as a yellow gum.

[00461] ***Step 7***: To a solution of 6-fluoro-4-azaspiro [2.4] heptane (40 mg, 347 μmol, 1 eq) in THF (1 mL) was added dropwise TEA (352 mg, 3.47 mmol, 484 μL, 10 eq) at 25 °C. After addition, the mixture was stirred at this temperature for 10 minutes, and the solution of (1Z)-2,6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (131 mg, 347 μmol, 1 eq) in THF (1 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 20 minutes. LC-MS showed 6-fluoro-4-azaspiro [2.4] heptane was consumed completely and one main peak with the desired mass was detected. Then it was separated between 20 mL of water and 40 mL of ethyl acetate. The organic phase was separated, washed with 30 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2,6-dichlorophenyl) -(6-fluoro-4-azaspiro [2.4] heptan-4-yl) methylene] amino]-4-methyl-benzenesulfonamide (150 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{20}H_{20}Cl_2FN_3O_2S$ 455.06 m/z found 456.0 $[M+H]^+$.

[00462] ***Step 8***: To a solution of N-[(E)-[(2, 6-dichlorophenyl)-(6-fluoro-4-azaspiro [2.4] heptan-4-yl) methylene] amino]-4-methyl-benzenesulfonamide (130 mg, 285 μmol, 1 eq) in DMF (3 mL) was added K_2CO_3 (197 mg, 1.42 mmol, 5 eq). The mixture was stirred at 100 °C for 2 hours. LC-MS showed N-[(E)-[(2, 6-dichlorophenyl)-(6-fluoro-4-azaspiro [2.4] heptan-4-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to water (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl)-1-(p-tolylsulfonyl) indazole (120 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{19}ClFN_3O_2S$ 419.09 m/z found 420.0 $[M+H]^+$.

[00463] ***Step 9***: To a solution of 4-chloro-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl)-1-(p-tolylsulfonyl) indazole (120 mg, 286 μmol, 1 eq) in MeOH (3 mL) was added K_2CO_3 (30.3 mg, 219 μmol, 5 eq). The mixture was stirred at 70 °C for 2 hours. LC-MS showed 4-chloro-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (5 mL) and extracted with EtOAc (3 mL X 3). The combined organic layers were washed with brine (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-

chloro-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl)-1H-indazole (20 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{13}ClFN_3$ 265.08 m/z found 266.1 $[M+H]^+$.

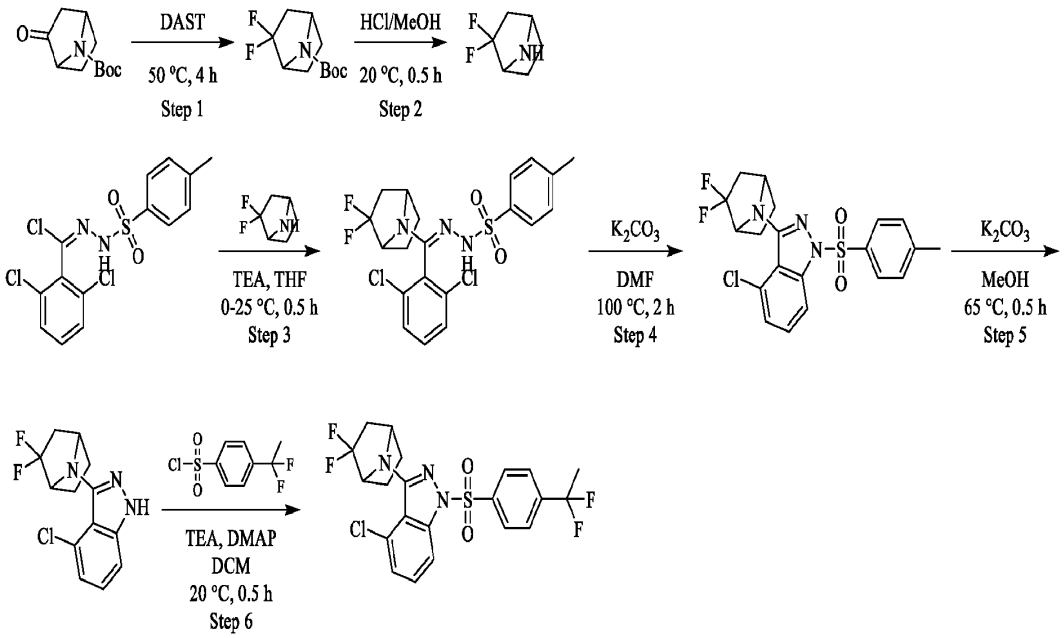
[00464] ***Step 10***: To a solution of 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (20.4 mg, 84.7 μmol, 1.5 eq) and 4-chloro-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl)-1H-indazole (15 mg, 56.5 μmol, 1 eq) in DCM (2 mL) were added TEA (28.6 mg, 282 μmol, 39.3 μL, 5 eq) and DMAP (690 μg, 5.65 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl)-1H-indazole was consumed completely and one main peak with the desired mass was detected. The reaction mixture was concentrated to give the crude product. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 50%-80% B over 8.0 min) to give the desired 4-chloro-1-[4-(1,1-difluoroethyl) phenyl] sulfonyl-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl) indazole (2 mg, 4.21 μmol, 7.46% yield, 98.88% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 7.63 (t, J = 8.1 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 5.51 - 5.32 (m, 1H), 3.83 - 3.58 (m, 2H), 2.43 - 2.29 (m, 1H), 2.25 - 2.06 (m, 1H), 1.99 - 1.87 (m, 3H), 0.94 - 0.83 (m, 1H), 0.78 - 0.71 (m, 1H), 0.70 - 0.63 (m, 1H), 0.54 - 0.46 (m, 1H). MS (ESI): mass calcd. For $C_{21}H_{19}ClF_3N_3O_2S$ 469.08 m/z found 470.1 $[M+H]^+$.

[00465] ***Step 11:*** 4-Chloro-1-[4-(1,1-difluoroethyl) phenyl] sulfonyl-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl) indazole (24 mg, 51.1 μmol, 1 eq) was separated by SFC (column: DAICEL CHIRALPAK IC (250 mm * 30 mm, 5 μm); mobile phase: [Heptane-IPA]; B%:2%, isocratic elution mode) to give two isomers. The structures were assigned arbitrarily. 4-Chloro-1-[4-(1,1-difluoroethyl) phenyl] sulfonyl-3-[(6R)-6-fluoro-4-azaspiro [2.4] heptan-4-yl] indazole (1.0 mg, 2.10 μmol, 4.11% yield, 98.59% purity, Rt = 4.491 minutes; E.E. by chiral HPLC (%) = 100.0%) was isolated as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 8.3 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H), 7.72 (t, J = 8.1 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 5.63 - 5.38 (m, 1H), 3.92 - 3.69 (m, 2H), 2.54 - 2.38 (m, 1H), 2.36 - 2.20 (m, 1H), 2.01 (t, J = 19.1 Hz, 3H), 1.02 - 0.94 (m, 1H), 0.89 - 0.80 (m, 1H), 0.78 - 0.71 (m, 1H), 0.58 (ddd, J = 4.8, 6.3, 10.6 Hz, 1H). HPLC: 98.59% (220 nm), 98.65% (215 nm), 99.10% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{19}ClF_3N_3O_2S$ 469.08 m/z found 470.1 $[M+H]^+$.

[00466] 4-Chloro-1-[4-(1,1-difluoroethyl) phenyl] sulfonyl-3-[(6S)-6-fluoro-4-azaspiro [2.4] heptan-4-yl] indazole (1.2 mg, 2.54 μmol, 4.96% yield, 99.28% purity, Rt = 5.223 minutes; E.E.

by chiral HPLC (%) = 98.40%) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 8.1 Hz, 1H), 7.99 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.6 Hz, 2H), 7.69 (t, J = 8.1 Hz, 1H), 7.52 (d, J = 7.4 Hz, 1H), 5.60 - 5.38 (m, 1H), 3.92 - 3.65 (m, 2H), 2.49 - 2.35 (m, 1H), 2.32 - 2.18 (m, 1H), 1.98 (t, J = 19.1 Hz, 3H), 1.00 - 0.91 (m, 1H), 0.87 - 0.78 (m, 1H), 0.74 - 0.67 (m, 1H), 0.60 - 0.51 (m, 1H). HPLC: 99.28% (220 nm), 84.33% (215 nm), 100.00% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{19}ClF_3N_3O_2S$ 469.08 m/z found 470.1 $[M+H]^+$.

Compound 62: 4-Chloro-3-(2, 2-difluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole



[00467] ***Step 1***: A mixture of tert-butyl 2-oxo-7-azabicyclo [2.2.1] heptane-7-carboxylate (300 mg, 1.42 mmol, 1 eq) in DAST (3 mL) was stirred at 50 °C for 4 hours. TLC (petroleum ether : ethyl acetate = 5:1) indicated tert-butyl 2-oxo-7-azabicyclo [2.2.1] heptane-7-carboxylate was consumed completely and one new spot was formed. The reaction mixture was added to sat. $NaHCO_3$ aq. (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether: ethyl acetate = 5:1) to give the desired tert-butyl 2, 2-difluoro-7-azabicyclo [2.2.1] heptane-7-carboxylate (210 mg, crude) as a white solid.

[00468] ***Step 2***: A mixture of tert-butyl 2, 2-difluoro-7-azabicyclo [2.2.1] heptane-7-carboxylate (210 mg, 900 μmol, 1 eq) in HCl/EtOAc (1 mL, 4M) was stirred at 20 °C for 0.5 hour. TLC (petroleum ether: ethyl acetate = 5:1) indicated tert-butyl 2, 2-difluoro-7-azabicyclo [2.2.1] heptane-7-carboxylate was consumed completely and one new spot was formed. The reaction mixture was concentrated to give the desired 2, 2-difluoro-7-azabicyclo [2.2.1] heptane (150 mg, crude, HCl) as a yellow solid.

[00469] ***Step 3***: To a solution of 2, 2-difluoro-7-azabicyclo [2.2.1] heptane (130 mg, 767 μmol, 1 eq, HCl) in THF (2 mL) was added dropwise TEA (388 mg, 3.83 mmol, 533 μL, 5 eq) at 25 °C. After addition, the mixture was stirred at this temperature for 10 minutes, and the solution of (1E)-2,6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (318 mg, 843 μmol, 1.1 eq) in THF (2 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 20 minutes. LC-MS showed 2, 2-difluoro-7-azabicyclo [2.2.1] heptane was consumed completely, and the desired mass was detected. The reaction mixture was added to water (5 mL) and extracted with EtOAc (3 mL X 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2, 6-dichlorophenyl)-(2, 2-difluoro-7-azabicyclo [2.2.1] heptan-7-yl) methylene] amino]-4-methyl-benzenesulfonamide (360 mg, crude) as a white solid. MS (ESI): mass calcd. For $C_{20}H_{19}Cl_2F_2N_3O_2S$ 473.05, m/z found 474.1 $[M+H]^+$.

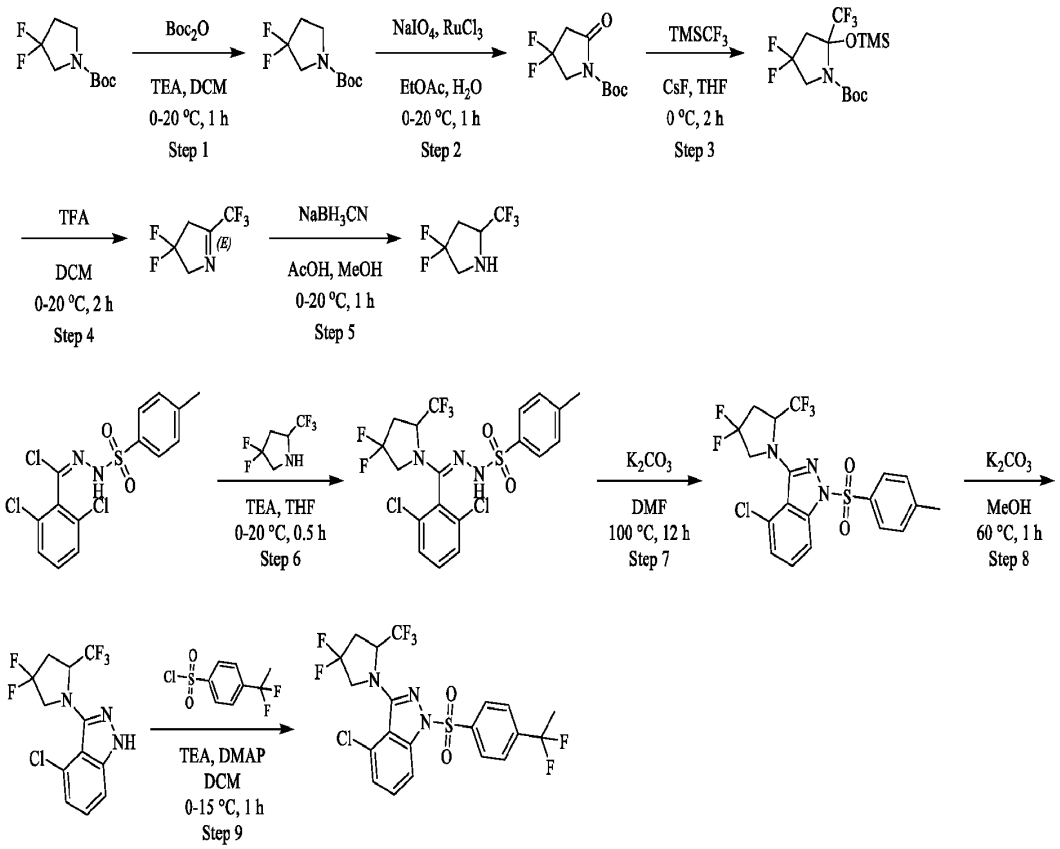
[00470] ***Step 4***: To a solution of N-[(E)-[(2, 6-dichlorophenyl)-(2, 2-difluoro-7-azabicyclo [2.2.1] heptan-7-yl) methylene] amino]-4-methyl-benzenesulfonamide (360 mg, 759 μmol, 1 eq) in DMF (2 mL) was added K_2CO_3 (524 mg, 3.79 mmol, 5 eq). The mixture was stirred at 100 °C for 2 hours. LC-MS showed a little N-[(E)-[(2, 6-dichlorophenyl)-(2, 2-difluoro-7-azabicyclo [2.2.1] heptan-7-yl) methylene] amino]-4-methyl-benzenesulfonamide remained. Several new peaks were shown on LC-MS and of the desired compound was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(2, 2-difluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1-(p-tolylsulfonyl) indazole (320 mg, crude) as yellow oil. MS (ESI): mass calcd. For $C_{20}H_{18}ClF_2N_3O_2S$ 437.08, m/z found 438.2 $[M+H]^+$.

[00471] ***Step 5***: To a solution of 4-chloro-3-(2, 2-difluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1-(p-tolylsulfonyl) indazole (320 mg, 731 μmol, 1 eq) in MeOH (5 mL) was added K_2CO_3 (505

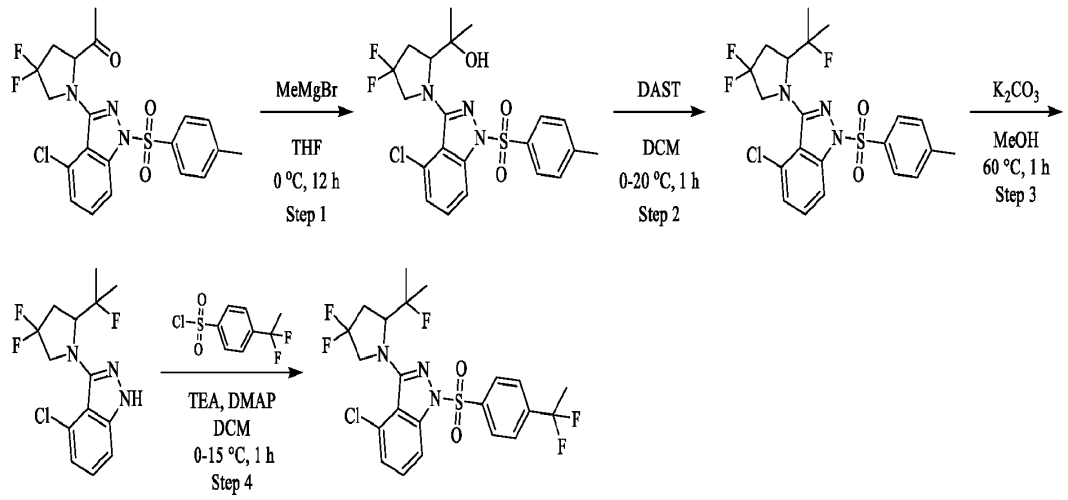
mg, 3.65 mmol, 5 eq). The mixture was stirred at 65 °C for 0.5 hour. LC-MS showed 4-chloro-3-(2, 2-difluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether: ethyl acetate = 3:1) to give the desired 4-chloro-3-(2, 2-difluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1H-indazole (130 mg, crude) as yellow oil. MS (ESI): mass calcd. For $C_{13}H_{12}ClF_2N_3$ 283.07, m/z found 284.2 $[M+H]^+$.

[00472] ***Step 6***: To a solution of 4-(1,1-difluoroethyl) benzenesulfonyl chloride (38.2 mg, 159 μmol, 1.5 eq) and 4-chloro-3-(2, 2-difluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1H-indazole (30.0 mg, 106 μmol, 1 eq) in DCM (2 mL) were added TEA (53.5 mg, 529 μmol, 73.6 μL, 5 eq) and DMAP (1.29 mg, 10.6 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(2, 2-difluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (2 mL) and extracted with EtOAc (1 mL X 3). The combined organic layers were washed with brine (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75*30mm*3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:60%-90% B over 8.0 min) to give the desired 4-chloro-3-(2, 2-difluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole (18.5 mg, 37.8 μmol, 35.8% yield, 99.78% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.6 Hz, 2H), 7.69 (t, J = 8.1 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 4.53 - 4.39 (m, 2H), 3.45 - 3.41 (m, 1H), 3.36 - 3.33 (m, 1H), 2.10 - 1.98 (m, 1H), 1.98 - 1.87 (m, 2H), 1.82 (br t, J = 6.2 Hz, 2H), 1.62 (br d, J = 7.3 Hz, 2H). HPLC: 99.78% (220 nm), 99.84% (215 nm), 100.00% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{18}ClF_4N_3O_2S$ 487.07, m/z found 488.1 $[M+H]^+$.

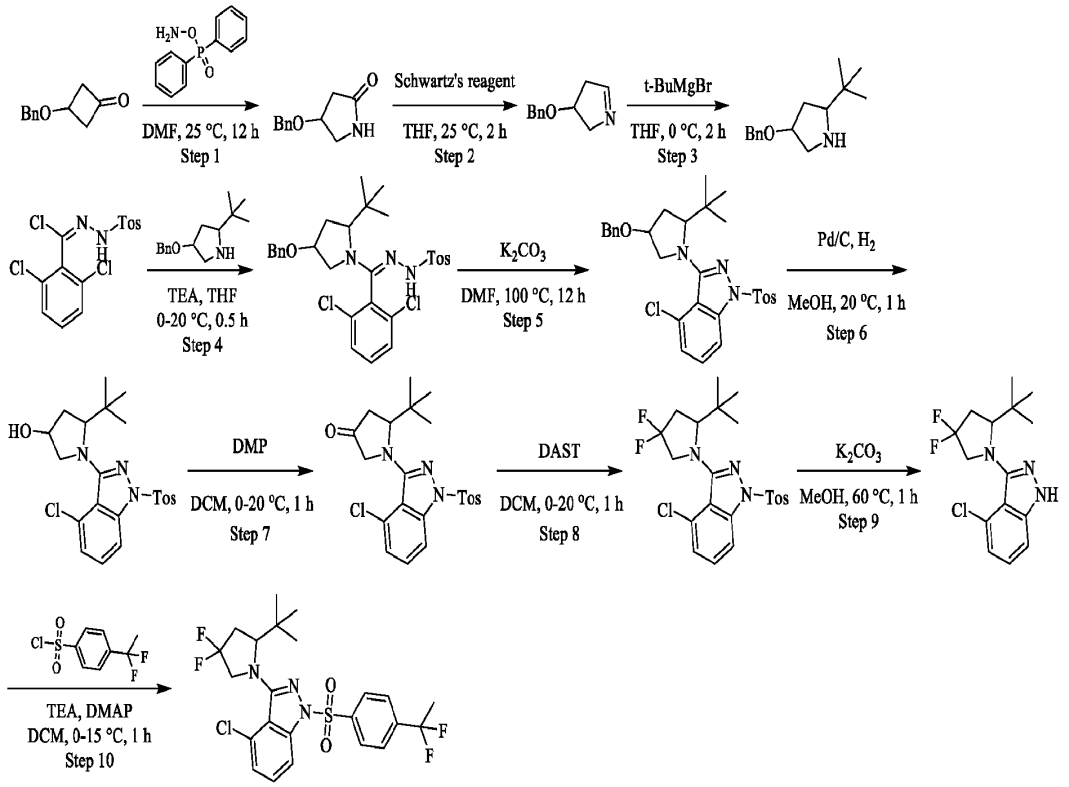
[00473] Compound 63: 4-Chloro-3-(4,4-difluoro-2-(trifluoromethyl) pyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl) phenyl) sulfonyl)-1H-indazole



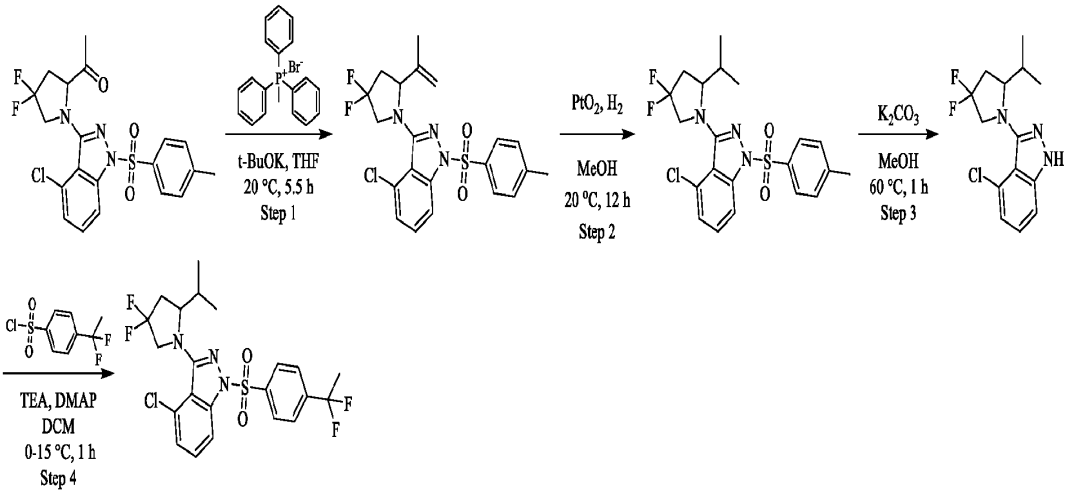
[00474] Compound 64: 4-Chloro-3-(4,4-difluoro-2-(2-fluoropropan-2-yl)pyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole



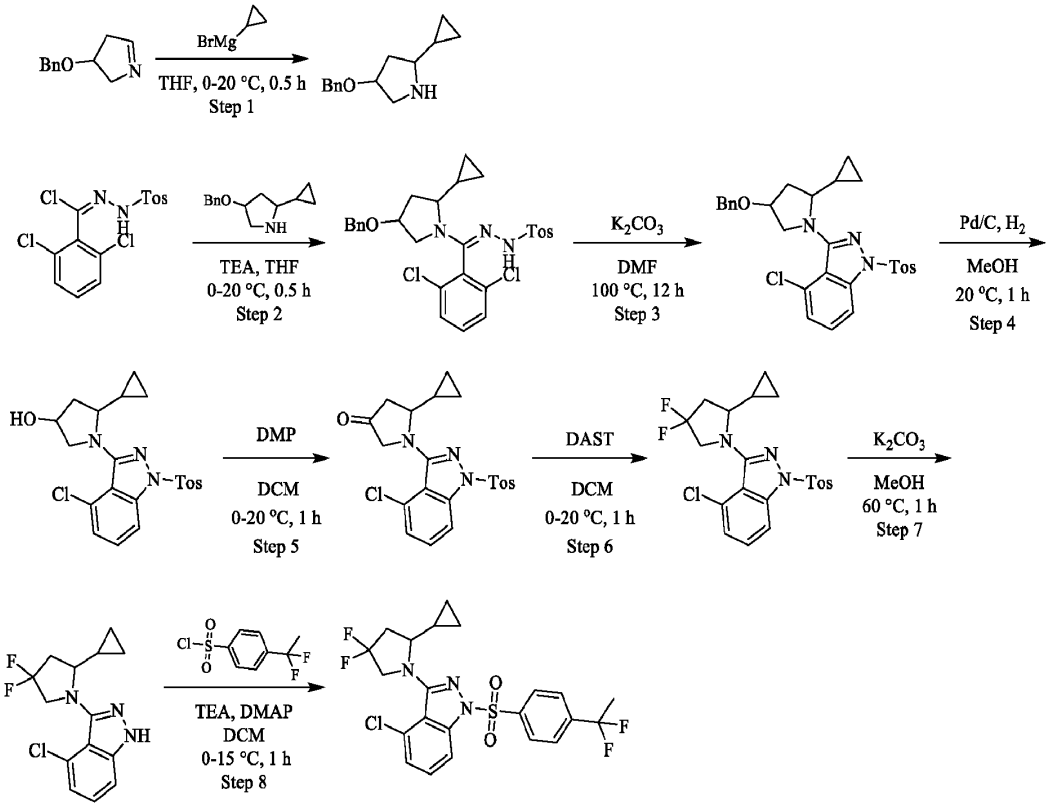
[00475] Compound 65: 3-(2-(Tert-butyl)-4,4-difluoropyrrolidin-1-yl)-4-chloro-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole



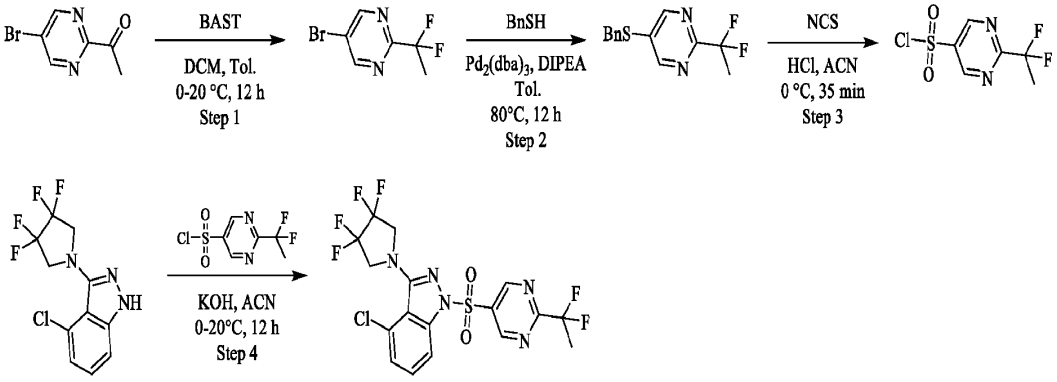
[00476] Compound 66: 4-Chloro-3-(4,4-difluoro-2-isopropylpyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole



[00477] Compound 67: 4-Chloro-3-(2-cyclopropyl-4,4-difluoropyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole



Compound 68: 4-Chloro-1- [2-(1, 1-difluoroethyl) pyrimidin-5-yl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole



[00478] ***Step 1***: To a solution of 1-(5-bromopyrimidin-2-yl) ethanone (2 g, 9.95 mmol, 1 eq) in DCM (120 mL) and toluene (10 mL) was added BAST (8.80 g, 39.8 mmol, 8.72 mL, 4 eq) at 0 °C under N_2. The mixture was stirred at 20 °C for 12 hours. LC-MS showed 1-(5-bromopyrimidin-2-yl) ethanone was consumed completely and one main peak with the desired

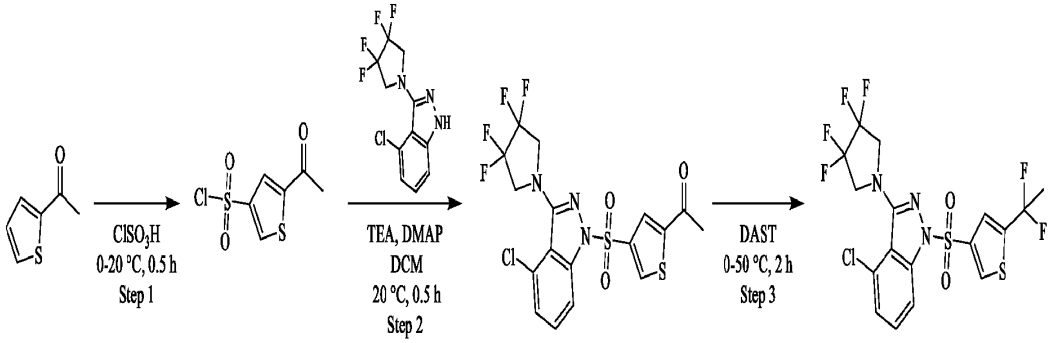
mass was detected. Then it was separated between 30 mL of $NaHCO_3$ solution and 60 mL of EtOAc. The organic phase was separated, washed with 30 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 2 g SepaFlash® Silica Flash Column, Eluent of 0~20% ethyl acetate/petroleum ether gradient @ 60 mL/min) to give the desired 5-bromo-2-(1, 1-difluoroethyl) pyrimidine (2.16 g, 9.69 mmol, 97.3% yield) as a yellow oil. MS (ESI): mass calcd. For $C_6H_5BrF_2N_2$ 221.96 m/z found 223.0 $[M+H]^+$.

[00479] ***Step 2***: A mixture of 5-bromo-2-(1, 1-difluoroethyl) pyrimidine (2 g, 8.97 mmol, 1 eq), phenylmethanethiol (1.67 g, 13.5 mmol, 1.58 mL, 1.5 eq), DIEA (2.32 g, 17.9 mmol, 3.12 mL, 2 eq), Xantphos (519 mg, 897 μmol, 0.1 eq) and $Pd_2(dba)_3$ (821 mg, 897 μmol, 0.1 eq) in dioxane (11 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 hours under N_2 atmosphere. LC-MS showed 5-bromo-2-(1, 1-difluoroethyl) pyrimidine was consumed completely and the desired mass was detected. The reaction mixture was partitioned between water (50 mL) and EtOAc (30 mL). The organic phase was separated, washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex luna C18 250 * 50 mm *10 μm; mobile phase: [H_2O (0.1% TFA)-ACN]; gradient:40%-70% B over 10.0 min) to give the desired 5-benzylsulfanyl-2-(1,1-difluoroethyl) pyrimidine (2.5 g, crude) was obtained as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{12}F_2N_2S$ 266.07 m/z found 267.1 $[M+H]^+$.

[00480] ***Step 3***: To a solution of HCl (0.3 mL) in ACN (3 mL) was added NCS (602 mg, 4.51 mmol, 4 eq) at 0 °C. The mixture was stirred at 0 °C for 5 min. The solution of 5-benzylsulfanyl-2-(1, 1-difluoroethyl) pyrimidine (300 mg, 1.13 mmol, 1 eq) in ACN (3 mL) was added dropwise to the reaction. The mixture was stirred at 0 °C for 30 min. LCMS showed 5-benzylsulfanyl-2-(1, 1-difluoroethyl) pyrimidine was consumed completely and one main peak with the desired mass was detected. The reaction mixture was concentrated to give the crude product. The reaction mixture was added to water (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 2-(1,1-difluoroethyl) pyrimidine-5-sulfonyl chloride (270 mg, crude) as a white solid. MS (ESI): mass calcd. For $C_6H_5ClF_2N_2O_2S$ 241.97 m/z found 292.1 $[M+H+49]^+$.

[00481] ***Step 4***: To a solution of 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (10 mg, 34.1 µmol, 1 eq) and 2-(1, 1-difluoroethyl) pyrimidine-5-sulfonyl chloride (66.1 mg, 272 µmol, 8 eq) in ACN (1 mL) was added KOH (22.5 mg, 341 µmol, 85% purity, 10 eq) at 0 °C. The mixture was stirred at 20 °C for 12 hours. LC-MS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and a little of the desired mass was detected. The reaction mixture was added to water (3 mL), extracted with EtOAc (6 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 µm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 55%-80% B over 8.0 minutes) to give the desired 4-chloro-1-[2-(1,1-difluoroethyl) pyrimidin-5-yl] sulfonyl-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl) indazole (1 mg, 1.91 µmol, 5.61% yield, 95.50% purity) as a white solid. ^{1}HNMR (400 MHz, DMSO-*d*$_6$) δ 9.46 (s, 2H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.71 (t, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 4.26 (br t, *J* = 12.2 Hz, 4H), 2.00 (t, *J* = 19.2 Hz, 3H). HPLC: 95.50% (220 nm), 95.14% (215 nm), 93.23% (254 nm). MS (ESI): mass calcd. For $C_{17}H_{12}ClF_6N_5O_2S$ 499.03, m/z found 500.0 $[M+H]^+$.

Compound 69: 4-Chloro-1- [[5-(1, 1-difluoroethyl) -3-thienyl] sulfonyl]-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole



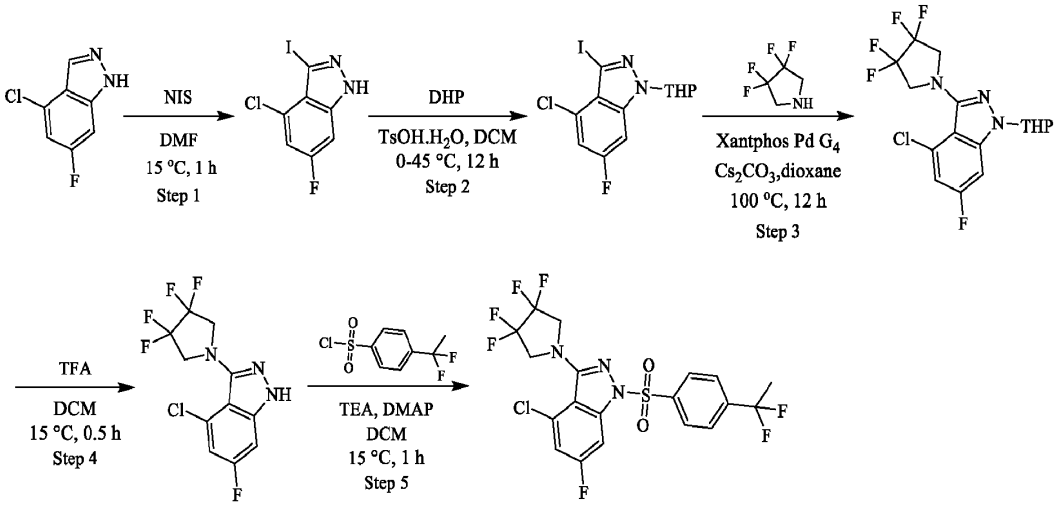
[00482] ***Step 1***: HSO_3Cl (3 mL) was added to 1-(2-thienyl) ethanone (600 mg, 4.76 mmol, 512 µL, 1 eq) slowly at 0 °C. The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 1-(2-thienyl) ethanone was consumed completely and the desired mass was detected. (The sample was quenched with piperidine). The reaction mixture was quenched by addition water (30 mL) at 0 °C and extracted with EtOAc (30 mL). The combined organic layers were washed with brine

(30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired 5-acetylthiophene-3-sulfonyl chloride (60 mg, 267 μmol, 5.62% yield) as a yellow solid. MS (ESI): mass calcd. For $C_6H_5ClO_3S_2$ 223.94 m/z found 274.1 $[M+H+49]^+$.

[00483] ***Step 2***: To a solution of 5-acetylthiophene-3-sulfonyl chloride (45.9 mg, 204 μmol, 2 eq) and 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (30 mg, 102 μmol, 1 eq) in DCM (2 mL) were added TEA (51.7 mg, 511 μmol, 71.1 μL, 5 eq) and DMAP (1.25 mg, 10.2 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LCMS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to water (10 mL), extracted with DCM (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ethyl acetate = 2/1) to give the desired 1- [4-[4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazol-1-yl] sulfonyl-2-thienyl] ethanone (35 mg, 72.6 μmol, 71.1% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{17}H_{12}ClF_4N_3O_3S_2$ 480.99 m/z found 482.0 $[M+H]^+$.

[00484] ***Step 3***: 1- [4- [4-Chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazol-1-yl] sulfonyl-2-thienyl] ethanone (30 mg, 62.3 μmol, 1 eq) was added into DAST (0.5 mL) at 0 °C. The mixture was stirred at 50 °C for 2 hours under N_2. LC-MS showed 1-[4-[4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazol-1-yl] sulfonyl-2-thienyl] ethanone remained and the desired compound was detected. The reaction mixture was quenched by addition sat. aq. $NaHCO_3$ (5 mL) and extracted with EtOAc (10 mL X 4). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:50%-80% B over 8.0 min) to give the desired 4-chloro-1- [[5-(1, 1-difluoroethyl) -3-thienyl] sulfonyl]-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole (2.8 mg, 5.53 μmol, 8.88% yield, 99.53% purity) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.76 (br d, J = 1.1 Hz, 1H), 7.69 (t, J = 8.1 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 4.26 (br t, J = 11.9 Hz, 4H), 2.08 (t, J = 18.9 Hz, 3H). HPLC: 99.53% (220 nm), 99.63% (215 nm), 100.00% (254 nm). MS (ESI): mass calcd. For $C_{17}H_{12}ClF_6N_3O_2S_2$ 503.00 m/z found 504.0 $[M+H]^+$.

Compound 70: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-6-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole



[00485] ***Step 1***: To a solution of 4-chloro-6-fluoro-1H-indazole (500 mg, 2.93 mmol, 1 eq) in DMF (5 mL) was added NIS (726 mg, 3.22 mmol, 1.1 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-chloro-6-fluoro-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-6-fluoro-3-iodo-1H-indazole (860 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_7H_3ClFIN_2$ 295.9, m/z found 297.0 $[M+H]^+$.

[00486] ***Step 2***: To the solution of 4-chloro-6-fluoro-3-iodo-1H-indazole (860 mg, 2.90 mmol, 1 eq) and TsOH.H_2O (55.2 mg, 290 μmol, 0.1 eq) in DCM (10 mL) was added 3, 4-dihydro-2H-pyran (366 mg, 4.35 mmol, 398 μL, 1.5 eq) at 0 °C. The solution was stirred at 45 °C for 12 hours. LC-MS showed 4-chloro-6-fluoro-3-iodo-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc = 3/1) to give the desired 4-chloro-6-fluoro-3-iodo-1-tetrahydropyran-2-yl-indazole (900 mg, 2.36 mmol, 81.5% yield) as a little yellow solid. MS (ESI): mass calcd. For $C_{12}H_{11}ClFIN_2O$ 380.0, m/z found 381.1 $[M+H]^+$.

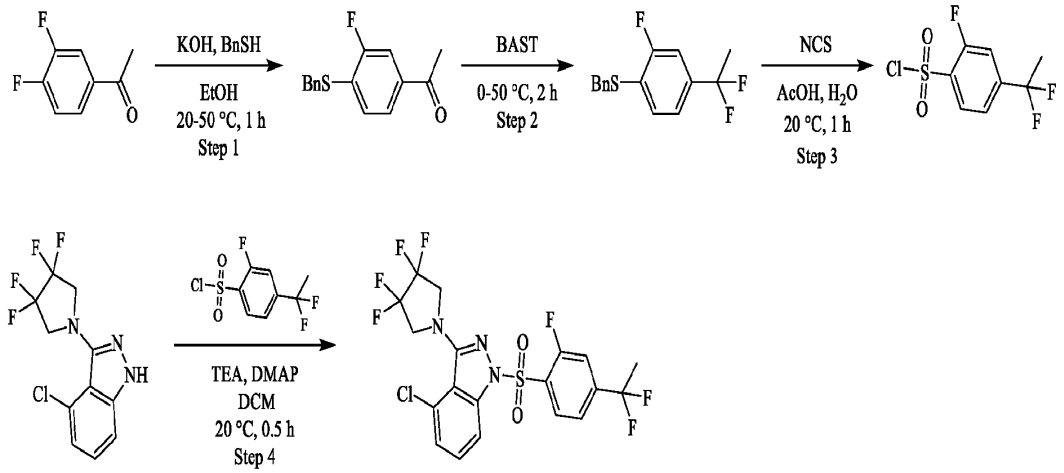
[00487] ***Step 3***: Two reactions were carried out in parallel. A mixture of 4-chloro-6-fluoro-3-iodo-1-tetrahydropyran-2-yl-indazole (200 mg, 526 μmol, 1 eq), 3, 3, 4, 4-tetrafluoropyrrolidine (113 mg, 631 μmol, 1.2 eq, HCl), Xantphos Pd G4 (50.6 mg, 52.6 μmol, 0.10 eq) and Cs_2CO_3 (342 mg, 1.05 mmol, 2 eq) in dioxane (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. LC-MS showed 4-chloro-6-fluoro-3-iodo-1-tetrahydropyran-2-yl-indazole was consumed completely and the desired mass was detected. Two reactions were combined. The reaction mixture was partitioned between 30 mL of H_2O and 40 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-6-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-2-yl-indazole (410 mg, crude) as a black solid. MS (ESI): mass calcd. For $C_{16}H_{15}ClF_5N_3O$ 395.1, m/z found 396.1 $[M+H]^+$.

[00488] ***Step 4***: To a solution of 4-chloro-6-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-2-yl-indazole (210 mg, 531 μmol, 1 eq) in DCM (5 mL) was added TFA (1.54 g, 13.5 mmol, 1 mL, 25.4 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 4-chloro-6-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-2-yl-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 20 mL of H_2O and 30 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc = 2/1) to give the desired 4-chloro-6-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (100 mg, 321 μmol, 60.5% yield) as a white solid. MS (ESI): mass calcd. For $C_{11}H_7ClF_5N_3$ 311.0, m/z found 312.0 $[M+H]^+$.

[00489] ***Step 5***: To a solution of 4-chloro-6-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (30 mg, 96.3 μmol, 1 eq) and 4-(1,1-difluoroethyl) benzenesulfonyl chloride (34.75 mg, 144 μmol, 1.5 eq) in DCM (2 mL) were added TEA (19.5 mg, 193 μmol, 26.8 μL, 2 eq) and DMAP (1.18 mg, 9.63 μmol, 0.1 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-chloro-6-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product.

The residue was purified by *prep*-HPLC (TFA condition; Method: column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 55%-75% B over 8.0 min) to give the desired 4-chloro-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-6-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole (18 mg, 34.0 μmol, 35.4% yield, 97.65% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J = 8.3 Hz, 2H), 7.87 (dd, J = 1.9, 8.8 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.61 (dd, J = 1.9, 9.0 Hz, 1H), 4.21 (br t, J = 12.3 Hz, 4H), 1.94 (t, J = 19.1 Hz, 3H). HPLC: 97.65% (220 nm), 97.56% (215 nm), 96.56% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{13}ClF_7N_3O_2S$ 515.0, m/z found 516.0 $[M+H]^+$.

Compound 71: 4-Chloro-1- [4-(1, 1-difluoroethyl)-2-fluoro-phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole



[00490] ***Step 1***: To a solution of 1-(3, 4-difluorophenyl) ethanone (2 g, 12.8 mmol, 1.61 mL, 1 eq) in EtOH (20 mL) were added BnSH (2.55 g, 20.5 mmol, 2.41 mL, 1.6 eq) and KOH (2.16 g, 38.4 mmol, 3 eq) at 20 °C. The mixture was stirred at 50 °C for 1 hour. LC-MS showed 1-(3, 4-difluorophenyl) ethanone was consumed completely and the desired compound was detected. The reaction mixture was filtered, and concentrated under reduced pressure to give a residue, and partitioned between water (40 mL) and EtOAc (30 mL). The organic phase was separated, washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% EtOAc/petroleum ether gradient @ 100 mL/min) to give the desired 1-(4-benzylsulfanyl-3-fluoro-phenyl) ethanone (3.05 g, 11.7 mmol,

91.5% yield) as an orange solid. MS (ESI): mass calcd. For $C_{15}H_{13}FOS$ 260.07 m/z found 261.1 $[M+H]^+$.

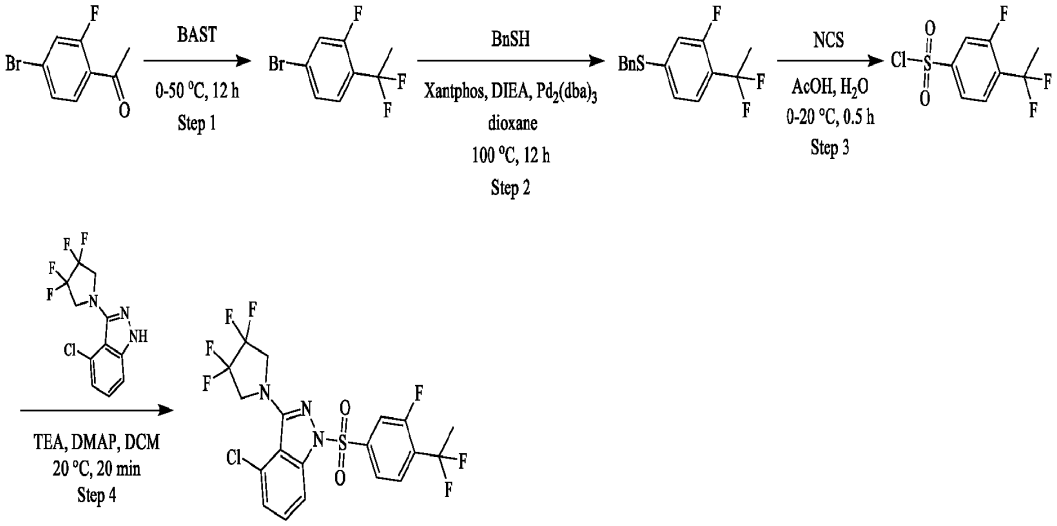
[00491] ***Step 2***: 1-(4-Benzylsulfanyl-3-fluoro-phenyl) ethanone (1 g, 3.84 mmol, 1 eq) was added into BAST (15 mL) at 0 °C. The mixture was stirred at 50 °C for 2 hours. TLC (petroleum ether / ethyl acetate = 5/1) showed 1-(4-benzylsulfanyl-3-fluoro-phenyl) ethanone was consumed completely and one new spot was formed. The reaction mixture was quenched by aq. $NaHCO_3$ (150 mL) at 0 °C, and then extracted with EtOAc (150 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~10% EtOAc/petroleum ether gradient @ 80 mL/min) to give the desired 1-benzylsulfanyl-4-(1, 1-difluoroethyl)-2-fluoro-benzene (720 mg, 2.55 mmol, 66.4% yield) as a white solid.

[00492] ***Step 3***: To a solution of 1-benzylsulfanyl-4-(1, 1-difluoroethyl)-2-fluoro-benzene (300 mg, 1.06 mmol, 1 eq) in AcOH (2 mL) and H_2O (0.4 mL) was added NCS (426 mg, 3.19 mmol, 3 eq). The mixture was stirred at 20 °C for 1 hour. LC-MS showed 1-benzylsulfanyl-4-(1, 1-difluoroethyl)-2-fluoro-benzene was consumed completely and the desired compound was detected. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 5/1) to give the desired 4-(1, 1-difluoroethyl)-2-fluoro-benzenesulfonyl chloride (170 mg, crude) as a colourless oil. MS (ESI): mass calcd. For $C_{14}H_{14}ClFO_2$ 257.97 m/z found 308.1 $[M+H+49]^+$.

[00493] ***Step 5***: To a solution of 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (30 mg, 102 μmol, 1 eq) and 4-(1, 1-difluoroethyl)-2-fluoro-benzenesulfonyl chloride (26.4 mg, 102 μmol, 1 eq) in DCM (2 mL) were added TEA (51.7 mg, 511 μmol, 71.1 μL, 5 eq) and DMAP (1.25 mg, 10.2 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to water (10 mL) and extracted with DCM (10 mL X 3). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna

C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:60%-85% B over 8.0 min) to give the desired 4-chloro-1- [4-(1, 1-difluoroethyl)-2-fluoro-phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole (10.0 mg, 19.2 μmol, 18.8% yield, 98.92% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 - 8.04 (m, 2H), 7.75 - 7.68 (m, 2H), 7.65 (br d, J = 8.4 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 4.19 (br t, J = 12.4 Hz, 4H), 1.95 (br t, J = 19.1 Hz, 3H). HPLC: 98.92% (220 nm), 98.99% (215 nm), 98.46% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{13}ClF_7N_3O_2S$ 515.03 m/z found 516.0 $[M+H]^+$.

Compound 72: 4-Chloro-1- [4-(1, 1-difluoroethyl)-3-fluoro-phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole



[00494] ***Step 1***: 1-(4-Bromo-2-fluoro-phenyl) ethanone (1 g, 4.61 mmol, 1 eq) was added in BAST (17 mL) at 0 °C. The mixture was stirred at 50 °C for 12 hours. TLC (petroleum ether / ethyl acetate = 1/0) showed 1-(4-bromo-2-fluoro-phenyl) ethanone was remained and one new spot was formed. The reaction mixture was quenched by aq. $NaHCO_3$ (30 mL) at 0 °C, and then extracted with EtOAc (50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~0% EtOAc/petroleum ether gradient @ 80 mL/min) to give the desired 4-bromo-1-(1, 1-difluoroethyl)-2-fluoro-benzene (540 mg, 2.26 mmol, 49.0% yield) as a colourless liquid.

[00495] ***Step 2***: A mixture of 4-bromo-1-(1,1-difluoroethyl)-2-fluoro-benzene (540 mg, 2.26 mmol, 1 eq), BnSH (0.44 g, 3.54 mmol, 416 μL, 1.57 eq), Xantphos (131 mg, 226 μmol, 0.1 eq), DIEA (584 mg, 4.52 mmol, 787 μL, 2 eq) and $Pd_2(dba)_3$ (207 mg, 226 μmol, 0.1 eq) in dioxane (6 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. TLC (petroleum ether / ethyl acetate = 1/0) showed 4-bromo-1-(1, 1-difluoroethyl)-2-fluoro-benzene remained and one new spot was formed. The reaction mixture was partitioned between water (20 mL) and EtOAc (15 mL). The organic phase was separated, washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (petroleum ether / acetate ethyl = 1/0) to give the desired 4-benzylsulfanyl-1-(1, 1-difluoroethyl)-2-fluoro-benzene (548 mg, 1.94 mmol, 85.9% yield) as a yellow oil.

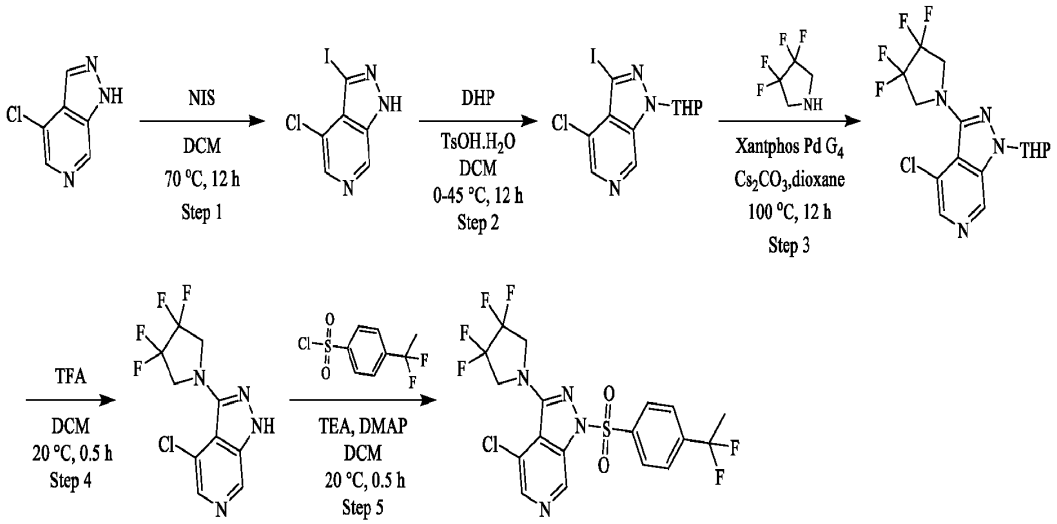
[00496] ***Step 3***: To a solution of 4-benzylsulfanyl-1-(1, 1-difluoroethyl)-2-fluoro-benzene (300 mg, 1.06 mmol, 1 eq) in AcOH (4 mL), H_2O (1 mL) was added NCS (568 mg, 4.25 mmol, 4 eq) at 0 °C. The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-benzylsulfanyl-1-(1, 1-difluoroethyl)-2-fluoro-benzene was consumed completely and the desired compound was detected (the sample was quenched by piperidine). The reaction mixture was concentrated under reduced pressure to remove AcOH. The residue was diluted with H_2O (15 mL) and extracted with EtOAc (10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (petroleum ether / acetate ethyl = 5/1) to give the desired 4-(1, 1-difluoroethyl)-3-fluoro-benzenesulfonyl chloride (113 mg, 437 μmol, 41.1% yield) as a yellow liquid. MS (ESI): mass calcd. For $C_{14}H_{14}ClFO_2$ 257.97 m/z found 308.1 $[M+H+49]^+$.

[00497] ***Step 4***: To a solution of 4-chloro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1H-indazole (30 mg, 102 μmol, 1 eq), 4-(1,1-difluoroethyl)-3-fluoro-benzenesulfonyl chloride (34.4 mg, 133 μmol, 1.3 eq) in DCM (2 mL) were added TEA (20.7 mg, 204 μmol, 28.4 μL, 2 eq) and DMAP (1.25 mg, 10.2 μmol, 0.1 eq). The mixture was stirred at 20 °C for 20 min. LC-MS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and the desired compound was detected. The reaction mixture was filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:65%-75% B over 10.0 min) to give the desired 4-chloro-1-[4-(1,1-difluoroethyl)-3-

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fluoro-phenyl] sulfonyl-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl) indazole (6.6 mg, 12.62 μmol, 98.66% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 8.5 Hz, 1H), 7.94 (br d, J = 10.0 Hz, 1H), 7.86 - 7.76 (m, 2H), 7.70 (t, J = 8.1 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 4.25 (br t, J = 12.2 Hz, 4H), 1.97 (t, J = 19.4 Hz, 3H). HPLC: 98.66% (220 nm), 98.62% (215 nm), 98.19% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{13}ClF_7N_3O_2S$ 515.03 m/z found 516.0 $[M+H]^+$.

Compound 73: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) pyrazolo [3, 4-c] pyridine



[00498] ***Step 1***: To a solution of 4-chloro-1H-pyrazolo [3, 4-c] pyridine (0.5 g, 3.26 mmol, 1 eq) in DMF (3 mL) was added NIS (806 mg, 3.58 mmol, 1.1 eq). The mixture was stirred at 70 °C for 12 hours. LC-MS showed 4-chloro-1H-pyrazolo [3, 4-c] pyridine remained and the desired mass was detected. The reaction mixture was added to water (50 mL) and extracted with EtOAc (50 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-iodo-1H-pyrazolo[3,4-c] pyridine (900 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_6H_3ClIN_3$ 278.91 m/z found 279.9 $[M+H]^+$.

[00499] ***Step 2***: To a solution of 4-chloro-3-iodo-1H-pyrazolo [3, 4-c] pyridine (0.9 g, 3.22 mmol, 1 eq) in DCM (30 mL) were added TsOH.H_2O (61.3 mg, 322 μmol, 0.1 eq) and 3,4-dihydro-2H-pyran (406 mg, 4.83 mmol, 442 μL, 1.5 eq) at 0 °C. The mixture was stirred at 45 °C for 12 hours. LC-MS showed 4-chloro-3-iodo-1H-pyrazolo [3, 4-c] pyridine remained, and the

desired compound was detected. The reaction mixture was added to water (200 mL) and extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-iodo-1-tetrahydropyran-3-yl-pyrazolo [3, 4-c] pyridine (400 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{11}H_{11}ClIN_3O$ 362.96 m/z found 364.0 $[M+H]^+$.

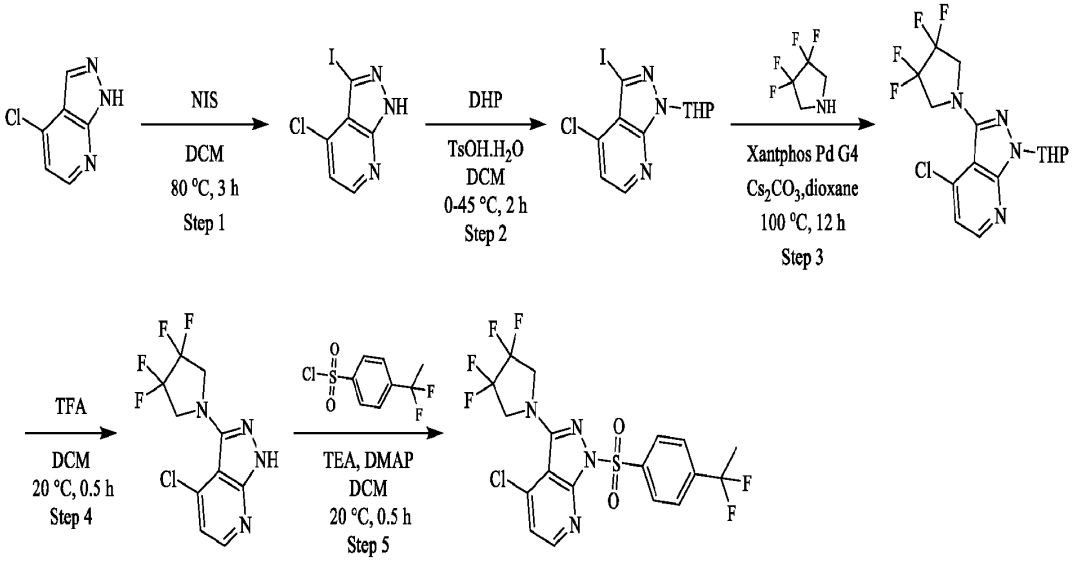
[00500] ***Step 3***: A mixture of 4-chloro-3-iodo-1-tetrahydropyran-3-yl-pyrazolo [3, 4-c] pyridine (380 mg, 1.05 mmol, 1 eq), 3, 3, 4, 4-tetrafluoropyrrolidine (225 mg, 1.25 mmol, 1.2 eq, HCl), Cs_2CO_3 (681 mg, 2.09 mmol, 2 eq) and Xantphos Pd G4 (101 mg, 105 μmol, 0.1 eq) in dioxane (4 mL) was degassed and purged with N_2 for 3 times. The mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. LC-MS showed 4-chloro-3-iodo-1-tetrahydropyran-3-yl-pyrazolo [3, 4-c] pyridine was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to water (40 mL) and extracted with EtOAc (20 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-3-yl-pyrazolo [3, 4-c] pyridine (390 mg, crude) as a black oil. MS (ESI): mass calcd. For $C_{15}H_{15}ClF_4N_4O$ 378.09 m/z found 379.1 $[M+H]^+$.

[00501] ***Step 4***: To a solution of 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-3-yl-pyrazolo [3, 4-c] pyridine (390 mg, 1.03 mmol, 1 eq) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-3-yl-pyrazolo[3,4-c] pyridine was consumed completely and the desired mass was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) , dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 1/1) to give the desired 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-pyrazolo [3, 4-c] pyridine (100 mg, 339 μmol, 33.0% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{10}H_7ClF_4N_4$ 294.03 m/z found 295.0 $[M+H]^+$.

[00502] ***Step 5***: To a solution of 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-pyrazolo [3, 4-c] pyridine (50 mg, 170 μmol, 1 eq) and 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (61.3 mg, 255 μmol, 1.5 eq) in DCM (2 mL) were added TEA (85.9 mg, 849 μmol, 118 μL, 5 eq)

and DMAP (2.07 mg, 17.0 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-pyrazolo [3, 4-c] pyridine was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to water (10 mL) and extracted with DCM (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:50%-80% B over 8.0 min) to give the desired 4-chloro-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) pyrazolo [3, 4-c] pyridine (19.4 mg, 38.4 μmol, 22.7% yield, 98.84% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 8.69 (s, 1H), 8.17 (br d, J = 8.3 Hz, 2H), 7.84 (br d, J = 8.4 Hz, 2H), 4.35 (br t, J = 11.7 Hz, 4H), 2.00 (br t, J = 19.1 Hz, 3H). HPLC: 98.84% (220 nm), 99.08% (215 nm), 98.98% (254 nm). MS (ESI): mass calcd. For $C_{18}H_{13}ClF_6N_4O_2S$ 498.04 m/z found 499.0 $[M+H]^+$.

Compound 74:4-Chloro-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) pyrazolo [3, 4-b] pyridine



[00503] ***Step 1***: To a solution of 4-chloro-1H-pyrazolo [3, 4-b] pyridine (500 mg, 3.26 mmol, 1 eq) in DMF (3 mL) was added NIS (952 mg, 4.23 mmol, 1.3 eq). The mixture was stirred at 80 °C for 3 hours. LC-MS showed 4-chloro-1H-pyrazolo [3, 4-b] pyridine was consumed

completely and the desired mass was detected. The reaction mixture was added to water (100 mL) and extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-iodo-1H-pyrazolo[3,4-b] pyridine (900 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_6H_3ClIN_3$ 278.91 m/z found 279.9 $[M+H]^+$.

[00504] ***Step 2***: To a solution of 4-chloro-3-iodo-1H-pyrazolo[3,4-b] pyridine (900 mg, 3.22 mmol, 1 eq) in DCM (10 mL) were added $TsOH.H_2O$ (61.3 mg, 322 μmol, 0.1 eq) and 3, 4-dihydro-2H-pyran (406 mg, 4.83 mmol, 442 μL, 1.5 eq) at 0 °C. The mixture was stirred at 45 °C for 2 hours. LC-MS showed 4-chloro-3-iodo-1H-pyrazolo [3, 4-b] pyridine remained, and the desired compound was detected. The reaction mixture was added to water (200 mL) and extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-iodo-1-tetrahydropyran-3-yl-pyrazolo [3, 4-b] pyridine (500 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{11}H_{11}ClIN_3O$ 362.96 m/z found 364.0 $[M+H]^+$.

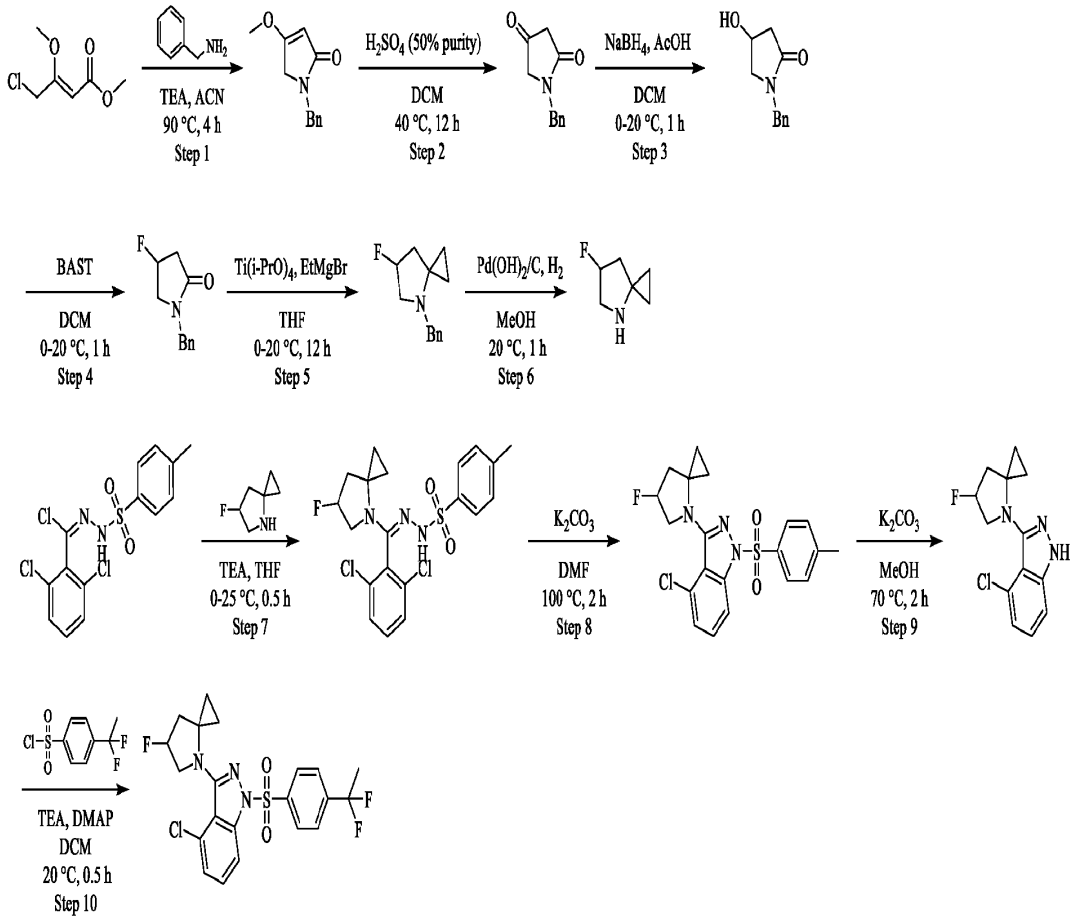
[00505] ***Step 3***: A mixture of 4-chloro-3-iodo-1-tetrahydropyran-3-yl-pyrazolo[3,4-b] pyridine (500 mg, 1.38 mmol, 1 eq), 3,3,4,4-tetrafluoropyrrolidine (296 mg, 1.65 mmol, 1.2 eq, HCl), Cs_2CO_3 (896 mg, 2.75 mmol, 2 eq), Xantphos Pd G4 (132 mg, 138 μmol, 0.1 eq) in dioxane (5 mL) was degassed and purged with N_2 for 3 times, and the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. LC-MS showed 4-chloro-3-iodo-1-tetrahydropyran-3-yl-pyrazolo [3, 4-b] pyridine was consumed completely and the desired mass was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-3-yl-pyrazolo [3, 4-b] pyridine (50 mg, crude) as a black solid. MS (ESI): mass calcd. For $C_{15}H_{15}ClF_4N_4O$ 378.09 m/z found 379.1 $[M+H]^+$.

[00506] ***Step 4***: To a solution of 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-3-yl-pyrazolo [3, 4-b] pyridine (50 mg, 132 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-3-yl-pyrazolo [3, 4-b] pyridine was

consumed completely and the desired mass was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-pyrazolo [3, 4-b] pyridine (20 mg, 67.9 μmol, 51.4% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{10}H_7ClF_4N_4$ 294.03 m/z found 295.0 $[M+H]^+$.

[00507] ***Step 5***: To a solution of 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-pyrazolo [3, 4-b] pyridine (20 mg, 67.9 μmol, 1 eq) and 4-(1,1-difluoroethyl) benzenesulfonyl chloride (24.5 mg, 102 μmol, 1.5 eq) in DCM (2 mL) were added TEA (34.4 mg, 339 μmol, 47.2 μL, 5 eq) and DMAP (829 μg, 6.79 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-pyrazolo [3, 4-b] pyridine was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to water (10 mL) and extracted with DCM (10 mL X 3). The combined organic layers were washed with brine (10 mL),dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:45%-75% B over 8.0 min) to give the desired 4-chloro-1-[4-(1,1-difluoroethyl) phenyl] sulfonyl-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl) pyrazolo[3,4-b] pyridine (9.3 mg, 18.3 μmol, 26.9% yield, 98.09% purity) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 5.1 Hz, 1H), 8.11 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 5.1 Hz, 1H), 4.37 - 4.23 (m, 4H), 1.94 (t, J = 19.1 Hz, 3H). HPLC: 98.09% (220 nm), 97.74% (215 nm), 99.16% (254 nm). MS (ESI): mass calcd. For $C_{18}H_{13}ClF_6N_4O_2S$ 498.04 m/z found 499.0 $[M+H]^+$.

Compound 75: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl) indazole



[00508] ***Step 1***: To a refluxing solution of phenylmethanamine (8.46 g, 79.0 mmol, 8.61 mL, 1.3 eq) in ACN (85 mL) were added methyl (E)-4-chloro-3-methoxy-but-2-enoate (10 g, 60.8 mmol, 1 eq) in ACN (100 mL) and a solution of TEA (7.99 g, 79.0 mmol, 11.0 mL, 1.3 eq) in ACN (100 mL) dropwise meanwhile. The mixture was stirred at 90 °C for 4 hours. LC-MS showed phenylmethanamine was consumed completely and one main peak with the desired mass was detected. The reaction mixture was partitioned between water (150 mL) and EtOAc (300 mL). The organic phase was separated, washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~100% ethyl acetate/petroleum ether gradient @ 80 mL/min) to give the desired 1-benzyl-3-methoxy-2H-pyrrol-5-one (8.5 g, 41.8 mmol, 65.4% yield) as a yellow solid. MS (ESI): mass calcd. For $C_{12}H_{13}NO_2$ 203.09 m/z found 204.1 $[M+H]^+$.

[00509] ***Step 2***: To a solution of 1-benzyl-3-methoxy-2H-pyrrol-5-one (4 g, 19.7 mmol, 1 eq) in DCM (40 mL) was added H_2SO_4 (20.0 g, 102 mmol, 10.9 mL, 50% purity, 5.18 eq). The mixture was stirred at 40 °C for 12 hours. LC-MS showed 1-benzyl-3-methoxy-2H-pyrrol-5-one remained. Several new peaks were shown on LC-MS and the desired compound was detected. The reaction mixture was added to water (200 mL), extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (0.1% TFA condition) to give the desired 1-benzylpyrrolidine-2, 4-dione (1.9 g, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{11}H_{11}NO_2$ 189.08 m/z found 190.1 $[M+H]^+$.

[00510] ***Step 3***: To a solution of 1-benzylpyrrolidine-2,4-dione (1 g, 5.29 mmol, 1 eq) and AcOH (3.17 g, 52.9 mmol, 3.03 mL, 10 eq) in DCM (20 mL) was added $NaBH_4$ (400 mg, 10.6 mmol, 2 eq) at 0 °C. The mixture was stirred at 20 °C for 1 hour. LCMS showed 1-benzylpyrrolidine-2, 4-dione was consumed completely and the desired mass was detected. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 1-benzyl-4-hydroxy-pyrrolidin-2-one (1 g, crude) as an orange oil. MS (ESI): mass calcd. For $C_{11}H_{13}NO_2$ 191.09 m/z found 192.1 $[M+H]^+$.

[00511] ***Step 4***: To a solution of 1-benzyl-4-hydroxy-pyrrolidin-2-one (1 g, 5.23 mmol, 1 eq) in DCM (20 mL) was added BAST (1.74 g, 7.84 mmol, 1.72 mL, 1.5 eq) at 0 °C. The mixture was stirred at 20 °C for 1 hour. LCMS showed 1-benzyl-4-hydroxy-pyrrolidin-2-one remained. Several new peaks were shown on LCMS and the desired compound was detected. The reaction mixture was added to water (100 mL), extracted with EtOAc (50 mL X 3). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:10%-35% B over 8.0 min) to give the desired 1-benzyl-4-fluoro-pyrrolidin-2-one (420 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{11}H_{12}FNO$ 193.09 m/z found 194.1 $[M+H]^+$.

[00512] ***Step 5***: To a solution of 1-benzyl-4-fluoro-pyrrolidin-2-one (370 mg, 1.91 mmol, 1 eq) in THF (4 mL) were added $Ti(i\text{-}PrO)_4$ (544 mg, 1.91 mmol, 565 μL, 1 eq) and EtMgBr (3 M, 1.28 mL, 2 eq) at 0 °C. The mixture was stirred at 20 °C for 12 hours. LC-MS showed 1-benzyl-4-fluoro-pyrrolidin-2-one was consumed completely. Diethyloxonio(trifluoro)boranuide (544 mg, 3.83 mmol, 471 μL, 2 eq) was added to the mixture. The mixture was stirred at 20 °C for 4 hours. LC-MS showed the desired mass was detected. The reaction mixture was quenched by 3N hydrochloric acid (6 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:1%-25% B over 8.0 min) to give the desired 4-benzyl-6-fluoro-4-azaspiro [2.4] heptane (80 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{16}FN$ 205.13 m/z found 206.2 $[M+H]^+$.

[00513] ***Step 6***: A mixture of 4-benzyl-6-fluoro-4-azaspiro [2.4] heptane (70 mg, 341 μmol, 1 eq), $Pd(OH)_2/C$ (479 mg, 341 μmol, 10% purity) in MeOH (3 mL) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 20 °C for 1 hour under H_2 (15 psi) atmosphere. TLC (DCM / methanol = 5/1) indicated 4-benzyl-6-fluoro-4-azaspiro [2.4] heptane was consumed completely and one new spot was formed. The reaction mixture was filtered, and concentrated under reduced pressure to give the desired 6-fluoro-4-azaspiro [2.4] heptane (40 mg, crude) as a yellow gum.

[00514] ***Step 7***: To a solution of 6-fluoro-4-azaspiro [2.4] heptane (40 mg, 347 μmol, 1 eq) in THF (1 mL) was added dropwise TEA (352 mg, 3.47 mmol, 484 μL, 10 eq) at 25 °C. After addition, the mixture was stirred at this temperature for 10 minutes, and then the solution of (1Z)-2,6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (131 mg, 347 μmol, 1 eq) in THF (1 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 20 minutes. LC-MS showed 6-fluoro-4-azaspiro [2.4] heptane was consumed completely and one main peak with the desired mass was detected. Then the solution was separated between 20 mL of water and 40 mL of ethyl acetate. The organic phase was separated, washed with 30 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2,6-dichlorophenyl) -(6-fluoro-4-azaspiro [2.4] heptan-4-yl) methylene] amino]-4-

methyl-benzenesulfonamide (150 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{20}H_{20}Cl_2FN_3O_2S$ 455.06 m/z found 456.0 $[M+H]^+$.

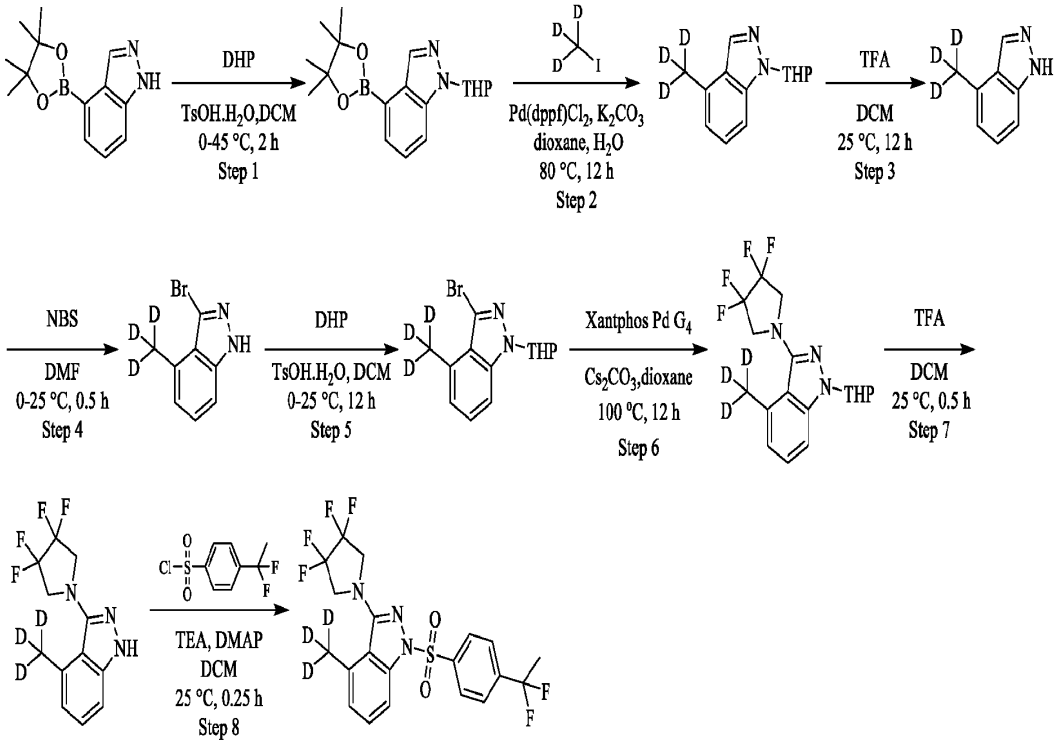
[00515] ***Step 8***: To a solution of N-[(E)- [(2, 6-dichlorophenyl) -(6-fluoro-4-azaspiro [2.4] heptan-4-yl) methylene] amino]-4-methyl-benzenesulfonamide (130 mg, 285 μmol, 1 eq) in DMF (3 mL) was added K_2CO_3 (197 mg, 1.42 mmol, 5 eq). The mixture was stirred at 100 °C for 2 hours. LC-MS showed N-[(E)- [(2, 6-dichlorophenyl) -(6-fluoro-4-azaspiro [2.4] heptan-4-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to water (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl)-1-(p-tolylsulfonyl) indazole (120 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{19}ClFN_3O_2S$ 419.09 m/z found 420.0 $[M+H]^+$.

[00516] ***Step 9***: To a solution of 4-chloro-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl)-1-(p-tolylsulfonyl) indazole (120 mg, 286 μmol, 1 eq) in MeOH (3 mL) was added K_2CO_3 (30.3 mg, 219 μmol, 5 eq). The mixture was stirred at 70 °C for 2 hours. LC-MS showed 4-chloro-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (5 mL) and extracted with EtOAc (3 mL X 3). The combined organic layers were washed with brine (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl)-1H-indazole (20 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{13}ClFN_3$ 265.08 m/z found 266.1 $[M+H]^+$.

[00517] ***Step 10***: To a solution of 4-(1,1-difluoroethyl) benzenesulfonyl chloride (20.4 mg, 84.7 μmol, 1.5 eq) and 4-chloro-3-(6-fluoro-4-azaspiro[2.4]heptan-4-yl)-1H-indazole (15 mg, 56.5 μmol, 1 eq) in DCM (2 mL) were added TEA (28.6 mg, 282 μmol, 39.3 μL, 5 eq) and DMAP (690 μg, 5.65 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LCMS showed 4-chloro-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl)-1H-indazole was consumed completely and one main peak with the desired mass was detected. The reaction mixture was concentrated to give the crude product. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:50%-80% B over 8.0 min) to give the desired 4-chloro-1-[4-(1,1-difluoroethyl) phenyl]

sulfonyl-3-(6-fluoro-4-azaspiro [2.4] heptan-4-yl) indazole (2 mg, 4.21 μmol, 7.46% yield, 98.88% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 7.63 (t, J = 8.1 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 5.51 - 5.32 (m, 1H), 3.83 - 3.58 (m, 2H), 2.43 - 2.29 (m, 1H), 2.25 - 2.06 (m, 1H), 1.99 - 1.87 (m, 3H), 0.94 - 0.83 (m, 1H), 0.78 - 0.71 (m, 1H), 0.70 - 0.63 (m, 1H), 0.54 - 0.46 (m, 1H). HPLC: 98.88% (220 nm), 99.10% (215 nm), 99.77% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{19}ClF_3N_3O_2S$ 469.08 m/z found 470.1 $[M+H]^+$.

Compound 76:1-[4-(1, 1-Difluoroethyl) phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-4-(trideuteriomethyl) indazole



[00518] ***Step 1***: To a solution of 4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1H-indazole (2 g, 8.19 mmol, 1 eq) in DCM (30 mL) were added TsOH.H$_2$O (156 mg, 819 μmol, 0.1 eq) and 3, 4-dihydro-2H-pyran (1.03 g, 12.3 mmol, 1.12 mL,1.5 eq) at 0 °C. The mixture was stirred at 45 °C for 2 hours. LC-MS showed 4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1H-indazole remained, and the desired compound was detected. The reaction mixture was added to water (200 mL), extracted with EtOAc (100 mL X 3). The combined organic layers were

washed with brine (200 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 1-tetrahydropyran-3-yl-4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) indazole (2.6 g, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{18}H_{25}BN_2O_3$ 328.20, m/z found 329.2 $[M+H]^+$.

[00519] ***Step 2***: A mixture of trideuterio(iodo)methane (2.12 g, 14.6 mmol, 910 µL, 3 eq), 1-tetrahydropyran-3-yl-4-(4, 4, 5, 5- tetramethyl-1, 3, 2-dioxaborolan-2-yl) indazole (1.6 g, 4.87 mmol, 1 eq), $Pd(dppf)Cl_2$ (357 mg, 488 µmol, 0.1eq), K_2CO_3 (2.02 g, 14.6 mmol, 3 eq) in H_2O (1 mL) and dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 hours under N_2 atmosphere. LC-MS showed 1-tetrahydropyran-3-yl-4-(4, 4, 5, 5- tetramethyl-1, 3, 2-dioxaborolan-2-yl) indazole was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to water (50 mL), extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 1-tetrahydropyran-3-yl-4-(trideuteriomethyl) indazole (1.2 g, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{13}H_{13}D_3N_2O$ 219.15, m/z found 220.1 $[M+H]^+$.

[00520] ***Step 3***: To a solution of 1-tetrahydropyran-2-yl-4-(trideuteriomethyl) indazole (1.2 g, 5.47 mmol, 1 eq) in DCM (15 mL) was added TFA (5.12 g, 44.9 mmol, 3.33 mL, 8.20 eq). The mixture was stirred at 25 °C for 12 hours. LC-MS showed 1-tetrahydropyran-2-yl-4-(trideuteriomethyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 30 mL of H_2O and 40 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 1/0 to 3/1) to give the desired 4-(trideuteriomethyl)-1H-indazole (137 mg, 811 µmol, 14.8% yield, 80% purity) as a brown solid. MS (ESI): mass calcd. For $C_8H_5D_3N_2$ 135.09, m/z found 136.1 $[M+H]^+$.

[00521] ***Step 4***: To a solution of 4-(trideuteriomethyl)-1H-indazole (30 mg, 222 µmol, 1 eq) in DMF (1 mL) was added NBS (35.6 mg, 200 µmol, 0.9 eq) at 0 °C. The mixture was stirred at 25 °C for 0.5 hour. LC-MS showed 4-(trideuteriomethyl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over

Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 3-bromo-4-(trideuteriomethyl)-1H-indazole (46 mg, 200 μmol, 89.8% yield, 92.7% purity) as a white solid. MS (ESI): mass calcd. For $C_8H_4D_3BrN_2$ 213.00, m/z found 214.0 $[M+H]^+$.

[00522] ***Step 5***: To the solution of 3-bromo-4-(trideuteriomethyl)-1H-indazole (46 mg, 215 μmol, 1 eq) and $TsOH.H_2O$ (4.09 mg, 21.5 μmol, 0.1 eq) in DCM (2 mL) was added 3, 4-dihydro-2H-pyran (27.1 mg, 322 μmol, 29.5 μL, 1.5 eq) at 0 °C. The solution was stirred at 25 °C for 12 hours. LC-MS showed -bromo-4-(trideuteriomethyl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 6/1) to give the desired 3-bromo-1-tetrahydropyran-2-yl-4-(trideuteriomethyl) indazole (18 mg, 60.4 μmol, 28.1% yield) as a little yellow solid. MS (ESI): mass calcd. For $C_{13}H_{12}D_3BrN_2O$ 297.06, m/z found 298.0 $[M+H]^+$.

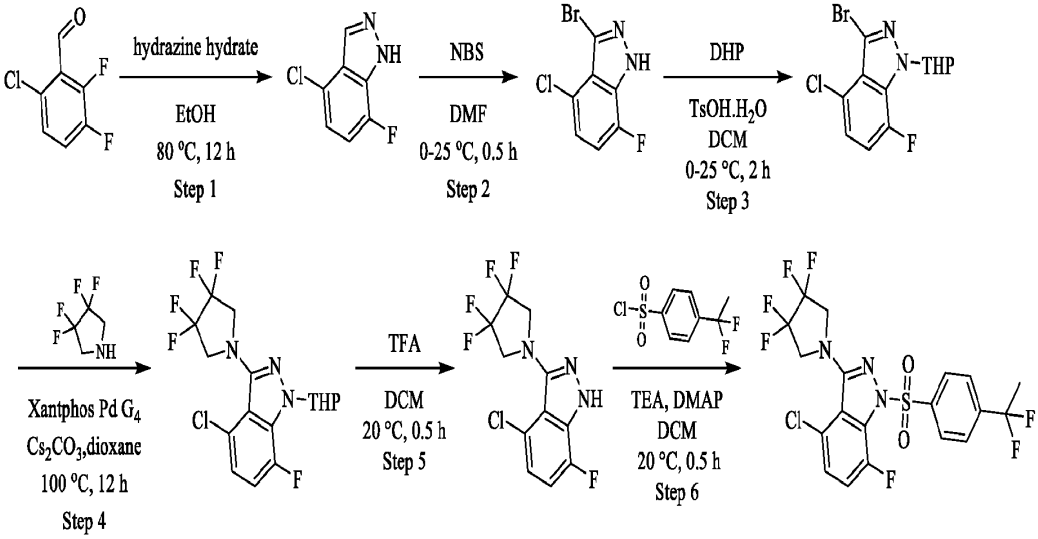
[00523] ***Step 6***: A mixture of 3-bromo-1-tetrahydropyran-2-yl-4-(trideuteriomethyl) indazole (18 mg, 60.4 μmol, 1 eq), 3, 3, 4, 4-tetrafluoropyrrolidine (16.3 mg, 90.6 μmol, 1.5 eq, HCl), Xantphos Pd G4 (5.81 mg, 6.04 μmol, 0.1 eq), Cs_2CO_3 (39.3 mg, 121 μmol, 2 eq) in dioxane (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. LC-MS showed 3-bromo-1-tetrahydropyran-2-yl-4-(trideuteriomethyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 5 mL of H_2O and 5 mL of EtOAc. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether: ethyl acetate = 5:1) to give the desired 3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-2-yl-4-(trideuteriomethyl) indazole (15 mg, 41.6 μmol, 69.0% yield) was obtained as a white solid. MS (ESI): mass calcd. For $C_{17}H_{16}D_3F_4N_3O$ 360.17, m/z found 361.2 $[M+H]^+$.

[00524] ***Step 7***: To a solution of 3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-2-yl-4-(trideuteriomethyl) indazole (15 mg, 41.6 μmol, 1 eq) in DCM (1 mL) was added TFA (461 mg, 4.04 mmol, 0.3 mL, 97.0 eq). The mixture was stirred at 25 °C for 0.5 hour. LC-MS showed

3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-2-yl-4-(trideuteriomethyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 5 mL of H_2O and 5 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired 3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-4-(trideuteriomethyl)-1H-indazole (10 mg, 36.2 μmol, 87.0% yield) as a little yellow solid. MS (ESI): mass calcd. For $C_{12}H_8D_3F_4N_3$ 276.11, m/z found 277.1 $[M+H]^+$.

[00525] ***Step 8***: To a solution of 3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-4-(trideuteriomethyl)-1H-indazole (9.5 mg, 34.4 μmol, 1 eq) and 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (12.4 mg, 51.6 μmol, 1.5 eq) in DCM (0.5 mL) were added TEA (6.96 mg, 68.8 μmol, 9.57 μL, 2 eq) and DMAP (420 μg, 3.44 μmol, 0.1 eq). The mixture was stirred at 25 °C for 0.25 hour. LC-MS showed 3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-4-(trideuteriomethyl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-HPLC (TFA condition; Method: column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 55%-80% B over 8.0 min) to give the desired 1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-4-(trideuteriomethyl) indazole (3 mg, 6.24 μmol, 18.2% yield, 93.77% purity) as a light-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 - 7.89 (m, 3H), 7.73 (br d, J = 8.3 Hz, 2H), 7.55 (t, J = 7.9 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H), 4.12 (br t, J = 12.8 Hz, 4H), 1.91 (t, J = 19.1 Hz, 3H). HPLC: 93.77% (220 nm), 93.50% (215 nm), 94.62% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{14}D_3F_6N_3O_2S$ 480.11, m/z found 481.0 $[M+H]^+$.

Compound 77:4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-7-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole



[00526] ***Step 1***: To a solution of 6-chloro-2, 3-difluoro-benzaldehyde (2 g, 11.3 mmol, 1 eq) in 1, 2-dimethoxyethane (6.13 g, 68.0 mmol, 7.07 mL, 6 eq) was added $N_2H_4.H_2O$ (9.48 g, 152 mmol, 9.19 mL, 80% purity, 13.4 eq). The mixture was stirred at 80 °C for 12 hours. LCMS showed 6-chloro-2, 3-difluoro-benzaldehyde was consumed completely and the desired mass was detected. The reaction mixture was concentrated to give the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% ethyl acetate / petroleum ether gradient @ 100mL/min) to give the desired 4-chloro-7-fluoro-1H-indazole (1.88 g, 11.0 mmol, 97.3% yield) as a white solid. MS (ESI): mass calcd. For $C_7H_4ClFN_2$ 170.00, m/z found 171.0 $[M+H]^+$.

[00527] ***Step 2***: To a solution of 4-chloro-7-fluoro-2H-indazole (1 g, 5.86 mmol, 1 eq) in DMF (10 mL) was added NBS (1.04 g, 5.86 mmol, 1 eq) at 0 °C. The mixture was stirred at 25 °C for 0.5 hour. LC-MS showed 4-chloro-7-fluoro-2H-indazole was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to water (100 mL) and extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 1/0 to 3/1) to give the desired 3-bromo-4-chloro-7-fluoro-2H-indazole (1.3 g, crude) as a white solid. MS (ESI): mass calcd. For $C_7H_3BrClFN_2$ 247.92, m/z found 249.0 $[M+H]^+$.

[00528] ***Step 3***: To a solution of 3-bromo-4-chloro-7-fluoro-1H-indazole (1.25 g, 5.01 mmol, 1 eq) in DCM (10 mL) were added $TsOH.H_2O$ (95.3 mg, 501 μmol, 0.1 eq) and 3,4-dihydro-2H-pyran (632 mg, 7.52 mmol, 687 μL, 1.5 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hours. TLC (petroleum ether / ethyl acetate = 3/1) indicated 3-bromo-4-chloro-7-fluoro-1H-indazole was consumed completely and one new spot formed. The reaction mixture was added to water (200 mL) and extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% ethyl acetate / petroleum ether gradient @ 80 mL/min) to give the desired 3-bromo-4-chloro-7-fluoro-1-tetrahydropyran-3-yl-indazole (1.44 g, crude) as a yellow solid.

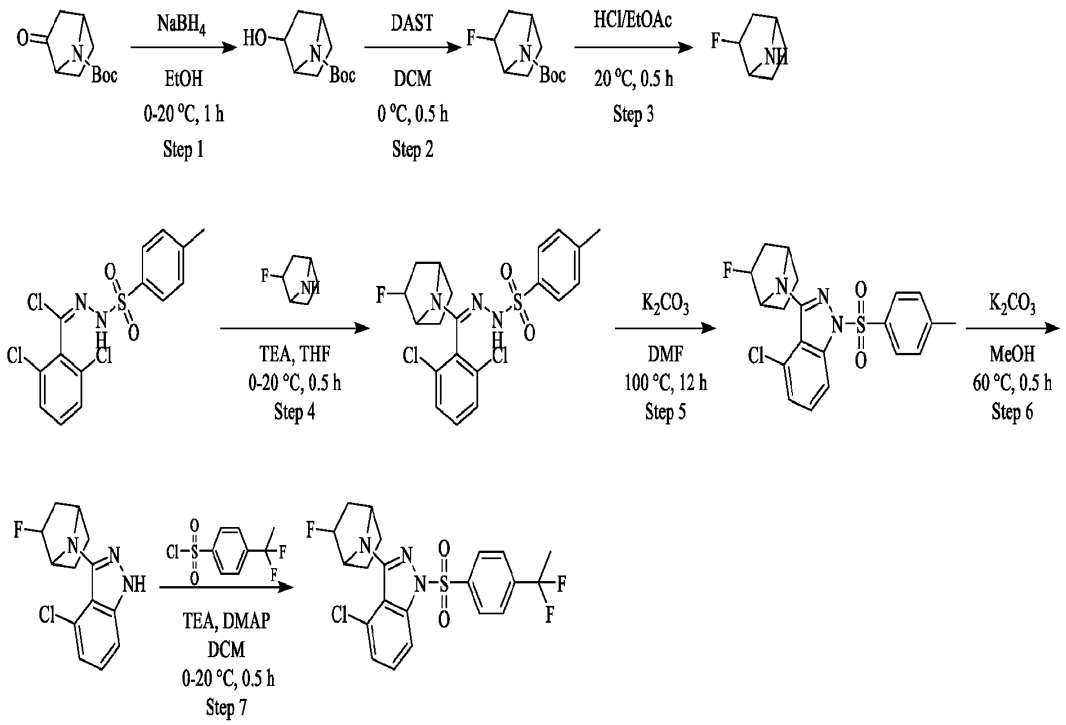
[00529] ***Step 4***: A mixture of 3-bromo-4-chloro-7-fluoro-1-tetrahydropyran-3-yl-indazole (600 mg, 1.80 mmol, 1 eq), 3,3,4,4-tetrafluoropyrrolidine (388 mg, 2.16 mmol, 1.2 eq, HCl), Cs_2CO_3 (1.17 g, 3.60 mmol, 2 eq), Xantphos Pd G4 (173 mg, 180 μmol, 0.1 eq) in dioxane (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. LC-MS showed 3-bromo-4-chloro-7-fluoro-1-tetrahydropyran-3-yl-indazole remained, and the desired compound was detected. The reaction mixture was added to water (100 mL), extracted with EtOAc (50 mL X 3). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-7-fluoro-3-(3,3,4,4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-3-yl-indazole (700 mg, crude) as a black solid. MS (ESI): mass calcd. For $C_{16}H_{15}ClF_5N_3O$ 395.08, m/z found 396.0 $[M+H]^+$.

[00530] ***Step 5***: To a solution of 4-chloro-7-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-3-yl-indazole (700 mg, 1.77 mmol, 1 eq) in DCM (10 mL) was added TFA (5 mL). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-7-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1-tetrahydropyran-3-yl-indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 4/1) to give the desired 4-chloro-7-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (400 mg, 1.28 mmol, 72.6%

yield) as a yellow solid. MS (ESI): mass calcd. For $C_{11}H_7ClF_5N_3$ 311.02, m/z found 312.0 $[M+H]^+$.

[00531] ***Step 6***: To a solution of 4-chloro-7-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole (20 mg, 64.2 μmol, 1 eq) and 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (30.9 mg, 128 μmol, 2 eq) in DCM (3 mL) were added TEA (32.5 mg, 321 μmol, 44.7 μL, 5 eq) and DMAP (784 μg, 6.42 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-7-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl)-1H-indazole was consumed completely and one main peak with the desired mass was detected. The reaction mixture was added to water (10 mL) and extracted with DCM (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:55%-80% B over 8.0 min) to give the desired 4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-7-fluoro-3-(3, 3, 4, 4-tetrafluoropyrrolidin-1-yl) indazole (9.7 mg, 18.61 μmol, 29.0% yield, 98.99% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 7.66 - 7.48 (m, 2H), 4.22 (br t, J = 12.1 Hz, 4H), 1.95 (t, J = 19.1 Hz, 3H). HPLC: 98.99% (220 nm), 99.10% (215 nm), 99.54% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{13}ClF_7N_3O_2S$ 515.03, m/z found 516.0 $[M+H]^-$.

Compound 78:4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(2-fluoro-7-azabicyclo [2.2.1] heptan-7-yl) indazole



[00532] ***Step 1:*** To a solution of tert-butyl 2-oxo-7-azabicyclo [2.2.1] heptane-7-carboxylate (400 mg, 1.89 mmol, 1 eq) in EtOH (10 mL) was added $NaBH_4$ (107 mg, 2.84 mmol, 1.5 eq) portionwise at 0 °C. The mixture was stirred at 20 °C for 1 hour. TLC indicated tert-butyl 2-oxo-7-azabicyclo [2.2.1] heptane-7-carboxylate was consumed completely and one new spot was formed. The residue was diluted with HCl (1 N, 5 mL) and the resulting mixture was allowed to return to room temperature. The EtOH was evaporated in vacuo. The reaction mixture was added to water (20 mL), extracted with DCM (20 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether/EtOAc = 5/1) to give the desired tert-butyl 2-hydroxy-7-azabicyclo [2.2.1] heptane-7-carboxylate (150 mg, 703 µmol, 50.0% yield) as a pale-yellow oil.

[00533] ***Step 2***: To a solution of tert-butyl 2-hydroxy-7-azabicyclo [2.2.1] heptane-7-carboxylate (95 mg, 445 µmol, 1 eq) in DCM (2 mL) was added DAST (108 mg, 668 µmol, 88.3 µL, 1.5 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 0.5 hour. TLC indicated tert-butyl 2-hydroxy-7-azabicyclo [2.2.1] heptane-7-carboxylate was consumed completely and one new spot was formed. The reaction mixture was added to water (1 mL), extracted with DCM (3 mL). The combined organic layers were washed with brine (1 mL) and dried over Na_2SO_4,

filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc=5/1) to give the desired tert-butyl 2-fluoro-7-azabicyclo [2.2.1] heptane-7-carboxylate (33 mg, 153 μmol, 34.4% yield) as a yellow oil.

[00534] ***Step 3***: A mixture of tert-butyl 2-fluoro-7-azabicyclo [2.2.1] heptane-7-carboxylate (33 mg, 153 μmol, 1 eq) in HCl/EtOAc (4M, 2 mL) was stirred at 20 °C for 0.5 hour. TLC (petroleum ether / EtOAc=5/1) indicated tert-butyl 2-fluoro-7-azabicyclo [2.2.1] heptane-7-carboxylate was consumed completely and one new spot was formed. The reaction mixture was concentrated to give the desired 2-fluoro-7-azabicyclo [2.2.1] heptane (20 mg, crude, HCl) as a yellow solid.

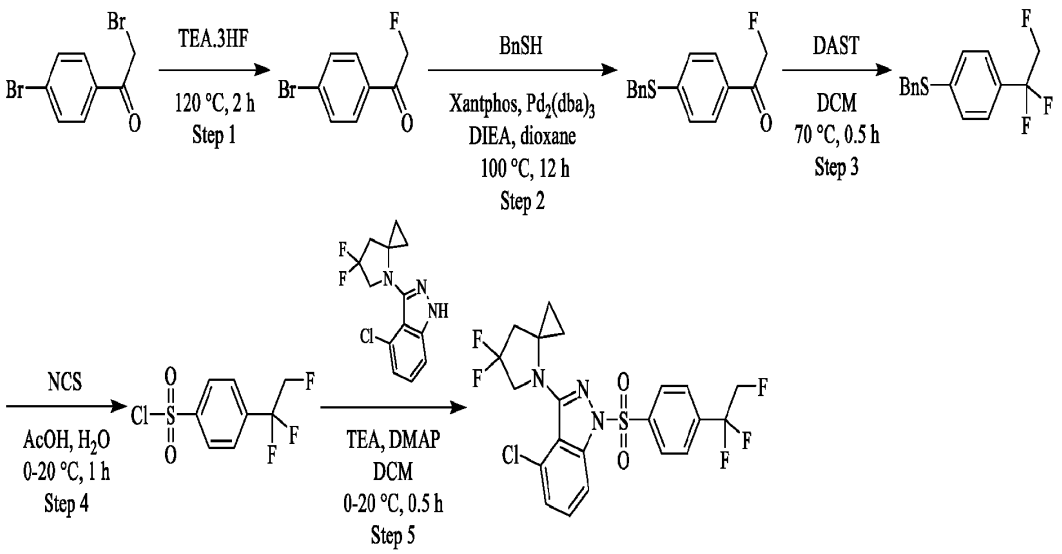
[00535] ***Step 4***: To a solution of 2-fluoro-7-azabicyclo [2.2.1] heptane (20 mg, 132 μmol, 1 eq, HCl) in THF (1 mL) was added TEA (133 mg, 1.32 mmol, 184 μL, 10 eq) dropwise at 0°C. After addition, the mixture was stirred at this temperature for 10 minutes, and then (1E)-2,6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (49.8 mg, 132 μmol, 1 eq) in THF (1 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 20 °C for 20 minutes. LC-MS showed 2-fluoro-7-azabicyclo [2.2.1] heptane was consumed completely and one main peak with the desired mass was detected. Then it was separated between water (1 mL) and EtOAc (3 mL). The organic phase was separated, washed with brine (1 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)- [(2, 6-dichlorophenyl) -(2-fluoro-7-azabicyclo [2.2.1] heptan-7-yl) methylene] amino]-4-methyl-benzenesulfonamide (70 mg, crude, HCl) as a yellow solid. MS (ESI): mass calcd. $C_{20}H_{20}C_{l2}FN_3O_2S$ 455.06, m/z found 456.0$[M+H]^+$.

[00536] ***Step 5***: To a solution of N-[(E)- [(2, 6-dichlorophenyl) -(2-fluoro-7-azabicyclo [2.2.1] heptan-7-yl) methylene] amino]-4-methyl-benzenesulfonamide (70 mg, 153 μmol, 1 eq) in DMF (3 mL) was added K_2CO_3 (106 mg, 767 μmol, 5 eq). The mixture was stirred at 100 °C for 12 hours. LC-MS showed N-[(E)- [(2, 6-dichlorophenyl) -(2-fluoro-7-azabicyclo [2.2.1] heptan-7-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. The reaction mixture was added to water (3 mL) and extracted with EtOAc (9 mL). The combined organic layers were washed with brine (3 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(2-fluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1-(p-tolylsulfonyl) indazole (70 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{19}ClFN_3O_2S$ 419.09, m/z found 420.2 $[M+H]^+$.

[00537] ***Step 6***: To a solution of 4-chloro-3-(2-fluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1-(p-tolylsulfonyl) indazole (70 mg, 167 μmol, 1 eq) in MeOH (2 mL) was added K_2CO_3 (115 mg, 834 μmol, 5 eq). The mixture was stirred at 60 °C for 0.5 hour. LC-MS showed 4-chloro-3-(2-fluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (3 mL) and extracted with EtOAc (9 mL). The combined organic layers were washed with brine (3 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc = 2/1) to give the desired 4-chloro-3-(2-fluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1H-indazole (24 mg, 90.3 μmol, 54.2% yield) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{13}ClFN_3$ 265.08, m/z found 266.2 $[M+H]^+$.

[00538] ***Step 7***: Two reactions were carried out in parallel. To a solution of 4-chloro-3-(2-fluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1H-indazole (10 mg, 37.6 μmol, 1 eq) and 4-(1,1-difluoroethyl) benzenesulfonyl chloride (13.6 mg, 56.5 μmol, 1.5 eq) in DCM (1 mL) were added TEA (11.4 mg, 113 μmol, 15.7 μL, 3 eq) and DMAP (460 μg, 3.76 μmol, 0.1 eq) at 0 °C. The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(2-fluoro-7-azabicyclo [2.2.1] heptan-7-yl)-1H-indazole remained and the desired mass was detected. Two reactions were combined for workup. The reaction mixture was added to water (3 mL) and extracted with DCM (9 mL). The combined organic layers were washed with brine (3 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 60%-90% B over 8.0 minutes) to give the desired 4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(2-fluoro-7-azabicyclo [2.2.1] heptan-7-yl) indazole (3.8 mg, 7.46 μmol, 8.76% yield, 92.19% purity) as a yellow solid. ^1H NMR (400 MHz, DMSO-*d_6*) δ 8.08 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.66 (t, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 5.36 - 5.10 (m, 1H), 4.48 - 4.19 (m, 2H), 2.29 - 2.16 (m, 1H), 1.92 (t, *J* = 19.1 Hz, 4H), 1.74 - 1.65 (m, 1H), 1.63 - 1.53 (m, 2H), 1.45 - 1.33 (m, 1H). HPLC: 92.19% (220 nm), 90.96% (215 nm), 88.81% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{19}ClF_3N_3O_2S$ 469.08, m/z found 470.1 $[M+H]^+$.

Compound 79:4-Chloro-3-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl)-1-[4-(1, 1, 2-trifluoroethyl) phenyl] sulfonyl-indazole



[00539] ***Step 1:*** To a solution of 2-bromo-1-(4-bromophenyl) ethanone (9 g, 32.4 mmol, 1 eq) was added 3HF.TEA (59.3 g, 368 mmol, 60.0 mL, 11.4 eq). The mixture was stirred at 120 °C for 2 hours. TLC indicated 2-bromo-1-(4-bromophenyl) ethanone was consumed completely and one new spot was formed. The reaction mixture was added to ice water (200 mL) and extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether / EtOAc=1/0 to 0/1) to give the desired 1-(4-bromophenyl)-2-fluoro-ethanone (3.5 g, 16.1 mmol, 50.0% yield) as a yellow oil.

[00540] ***Step 2***: A mixture of phenylmethanethiol (2.20 g, 17.7 mmol, 2.08 mL, 1.1 eq), 1-(4-bromophenyl)-2-fluoro-ethanone (3.5 g, 16.1 mmol, 1 eq), DIEA (4.17 g, 32.3 mmol, 5.62 mL, 2 eq), Xantphos (933 mg, 1.61 mmol, 0.1 eq) and $Pd_2(dba)_3$ (369 mg, 403 µmol, 0.025 eq) in dioxane (35 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. LC-MS showed 1-(4-bromophenyl)-2-fluoro-ethanone was consumed completely and the desired mass was detected. The reaction mixture was added to water (100 mL) and extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica

gel, petroleum ether / EtOAc =1/0 to 0/1) to give the desired 1-(4-benzylsulfanylphenyl)-2-fluoro-ethanone (2 g, 7.68 mmol, 50.0% yield) as a yellow solid.

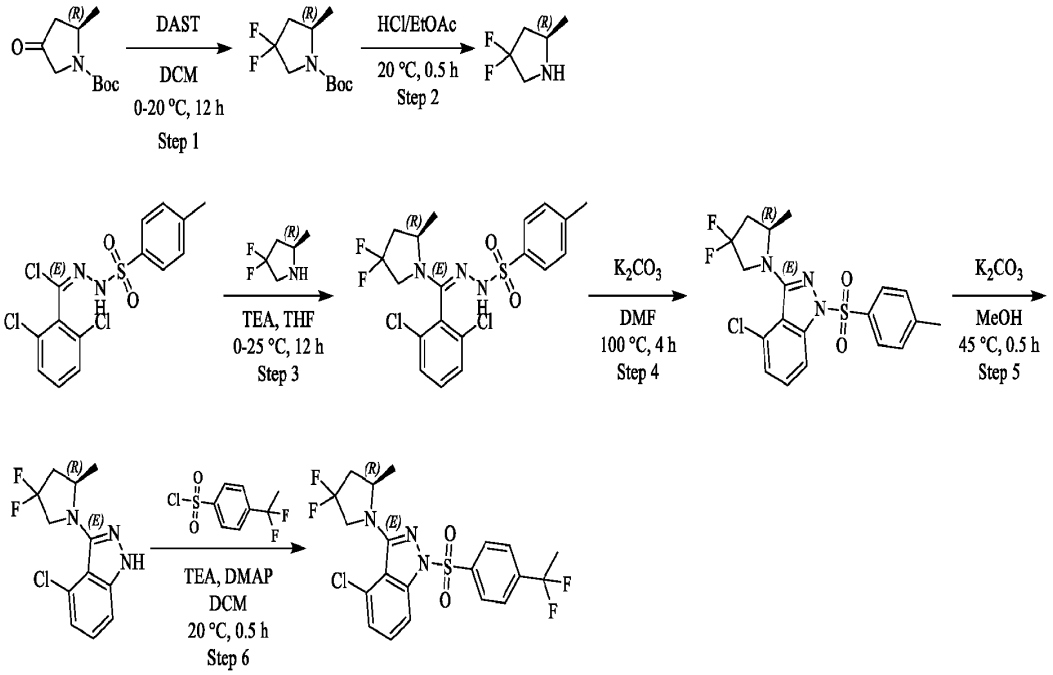
[00541] ***Step 3***: Four reactions were carried out in parallel. A mixture of 1-(4-benzylsulfanylphenyl)-2-fluoro-ethanone (300 mg, 1.15 mmol, 1 eq) and DAST (10 mL) was stirred at 70 °C for 0.5 hour. TLC indicated 1-(4-benzylsulfanylphenyl)-2-fluoro-ethanone remained and one new spot was formed. Four reactions were combined for workup. The reaction mixture was added to water (30 mL) and extracted with DCM (60 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc = 7/1) to give the desired 1-benzylsulfanyl-4-(1, 1, 2-trifluoroethyl) benzene (480 mg, 1.70 mmol, 36.9% yield) as a yellow oil.

[00542] ***Step 4***: Four reactions were carried out in parallel. To a solution of 1-benzylsulfanyl-4-(1, 1, 2-trifluoroethyl) benzene (115 mg, 407 μmol, 1 eq) in AcOH (1 mL) and H_2O (0.2 mL) was added NCS (163 mg, 1.22 mmol, 3 eq) at 0 °C. The mixture was stirred at 20 °C for 1 hour. LC-MS showed 1-benzylsulfanyl-4-(1, 1, 2-trifluoroethyl) benzene was consumed completely and the desired compound was detected. Four reactions were combined for workup. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (15 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc=5/1) to give the desired 4-(1, 1, 2-trifluoroethyl) benzenesulfonyl chloride (40 mg, 155 μmol, 9.49% yield) as a yellow oil. MS (ESI): mass calcd. $C_8H_6ClF_3O_2S$ 257.97, m/z found 308.2$[M+H+49]^+$.

[00543] ***Step 5***: Two reactions were carried out in parallel. To a solution of 4-(1,1,2-trifluoroethyl) benzenesulfonyl chloride (18.2 mg, 70.5 μmol, 4 eq) and 4-chloro-3-(6,6-difluoro-4-azaspiro [2.4] heptan-4-yl)-1H-indazole (5 mg, 17.6 μmol, 1 eq) in DCM (2 mL) were added TEA (364 mg, 3.59 mmol, 0.5 mL, 204 eq) and DMAP (215 μg, 1.76 μmol, 0.1 eq) at 0 °C. The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl)-1H-indazole was consumed completely and the desired compound was detected. Two reactions were combined for workup. The reaction mixture was added to water (3 mL) and extracted with DCM (9 mL). The combined organic layers were washed with brine (3 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue.

The residue was purified by *prep*-HPLC (column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 45%-75% B over 8.0 minutes) to give the desired 4-chloro-3-(6, 6-difluoro-4-azaspiro [2.4] heptan-4-yl)-1- [4-(1, 1, 2-trifluoroethyl) phenyl] sulfonyl-indazole (2 mg, 3.95 μmol, 11.22% yield, 100.00% purity) as a gray gum. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.08 (br d, *J* = 8.0 Hz, 1H), 8.00 (br d, *J* = 8.0 Hz, 2H), 7.82 (br d, *J* = 8.3 Hz, 2H), 7.70 - 7.62 (m, 1H), 7.48 (br d, *J* = 7.4 Hz, 1H), 5.07 - 4.80 (m, 2H), 3.85 (br t, *J* = 12.7 Hz, 2H), 1.26 - 1.20 (m, 2H), 0.90 (br s, 2H), 0.61 (br s, 2H). HPLC: 100.00% (220 nm), 99.14% (215 nm), 94.70% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{17}ClF_5N_3O_2S$ 505.07, m/z found 506.1 $[M+H]^+$.

Compound 80:4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2R)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl] indazole



[00544] ***Step 1:*** To a solution of tert-butyl (2R)-2-methyl-4-oxo-pyrrolidine-1-carboxylate (250 mg, 1.25 mmol, 1 eq) in DCM (4 mL) was added DAST (425 mg, 2.63 mmol, 348 μL, 2.1 eq) at 0 °C. The mixture was stirred at 20 °C for 12 hours. TLC indicated tert-butyl (2R)-2-methyl-4-oxo-pyrrolidine-1-carboxylate was consumed completely and one new spot was formed. The reaction mixture was added to water (15 mL), extracted with DCM (30 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4, filtered, and

concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / EtOAc = 5/1) to give the desired tert-butyl (2R)-4,4-difluoro-2-methyl-pyrrolidine-1-carboxylate (160 mg, 723 μmol, 57.6% yield) as a yellow oil.

[00545] ***Step 2:*** A mixture of tert-butyl (2R)-4, 4-difluoro-2-methyl-pyrrolidine-1-carboxylate (150 mg, 678 μmol, 1 eq) in HCl/EtOAc (2 mL) was stirred at 20 °C for 0.5 hour. TLC indicated tert-butyl (2R)-4, 4-difluoro-2-methyl-pyrrolidine-1-carboxylate was consumed completely and one new spot formed. The reaction mixture was concentrated to give the desired (2R)-4, 4-difluoro-2-methyl-pyrrolidine (80 mg, crude) as a yellow oil.

[00546] ***Step 3***: To a solution of 2, 6-dichloro-N'-(p-tolylsulfonyl) benzohydrazide (237 mg, 660 μmol, 1 eq) in THF (2 mL) was added dropwise TEA (200 mg, 1.98 mmol, 276 μL, 3 eq) at 25 °C. After addition, the mixture was stirred at this temperature for 0.5 hour, and then (2R)-4, 4-difluoro-2-methyl-pyrrolidine (80.0 mg, 660 μmol, 1 eq) in THF (2 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 11.5 hours. LC-MS showed 2, 6-dichloro-N'-(p-tolylsulfonyl) benzohydrazide was consumed completely and the desired mass was detected. Then it was separated between water (10 mL) and EtOAc (10 mL). The organic phase was separated, washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)- [(2, 6-dichlorophenyl)-[(2R)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl] methylene] amino]-4-methyl-benzenesulfonamide (300 mg, crude) as a yellow solid. MS (ESI): mass calcd. $C_{19}H_{19}Cl_2F_2N_3O_2S$ 461.05, m/z found 462.1 $[M+H]^+$.

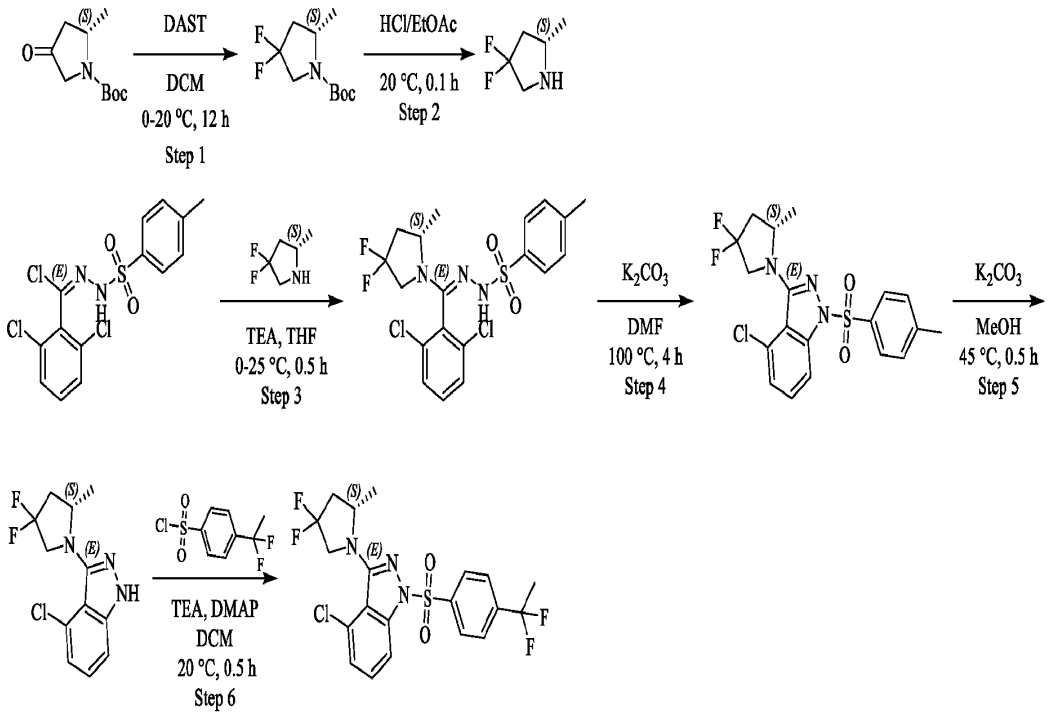
[00547] ***Step 4***: To a solution of N-[(E)- [(2, 6-dichlorophenyl)-[(2R)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl] methylene] amino]-4-methyl-benzenesulfonamide (300 mg, 649 μmol, 1 eq) in DMF (6 mL) was added K_2CO_3 (269 mg, 1.95 mmol, 3 eq). The mixture was stirred at 100 °C for 4 hours. LC-MS showed N-[(E)- [(2, 6-dichlorophenyl)-[(2R)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl] methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. The reaction mixture was added to water (15 mL), extracted with EtOAc (30 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-[(2R)-4,4-difluoro-2-methyl-pyrrolidin-1-yl]-1-(p-tolylsulfonyl) indazole (350 mg, crude) as a yellow oil. MS (ESI): mass calcd. $C_{19}H_{18}ClF_2N_3O_2S$ 425.08, m/z found 426.2 $[M+H]^+$.

[00548] ***Step 5***: To a solution of 4-chloro-3-[(2R)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl]-1-(p-tolylsulfonyl) indazole (350 mg, 822 μmol, 1 eq) in MeOH (10 mL) was added K_2CO_3 (568

mg, 4.11 mmol, 5 eq). The mixture was stirred at 45 °C for 0.5 hour. LCMS showed 4-chloro-3-[(2R)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl]-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (50 mL), extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-[(2R)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl]-1H-indazole (30 mg, crude) as a yellow oil. MS (ESI): mass calcd. $C_{12}H_{12}ClF_2N_3$ 271.07, m/z found 272.1$[M+H]^+$.

[00549] ***Step 6***: To a solution of 4-(1,1-difluoroethyl) benzenesulfonyl chloride (79.7 mg, 331 μmol, 3 eq) and 4-chloro-3-[(2R)-4,4-difluoro-2-methyl-pyrrolidin-1-yl]-1H-indazole (30 mg, 110 μmol, 1 eq) in DCM (2 mL) were added TEA (55.9 mg, 552 μmol, 76.9 μL, 5 eq) and DMAP (1.35 mg, 11.0 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-[(2R)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl]-1H-indazole was consumed completely, and the desired mass was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:60%-85% B over 8.0 min) to give the desired 4-chloro-1-[4-(1,1-difluoroethyl) phenyl] sulfonyl-3-[(2R)-4,4-difluoro-2-methyl-pyrrolidin-1-yl] indazole (5.3 mg, 10.6 μmol, 9.64% yield, 95.53% purity) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.6 Hz, 2H), 7.67 (t, J = 8.1 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 4.46 - 4.36 (m, 1H), 4.32 - 4.17 (m, 1H), 3.58 (ddd, J = 4.8, 11.9, 16.4 Hz, 1H), 2.73 - 2.59 (m, 1H), 2.29 - 2.11 (m, 1H), 1.92 (t, J = 19.1 Hz, 3H), 1.00 (d, J = 6.1 Hz, 3H). HPLC: 95.53% (220 nm), 94.11% (215 nm), 97.93% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{18}ClF_4N_3O_2S$ 475.07, m/z found 476.0 $[M+H]^+$.

Compound 81:4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2S)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl] indazole



[00550] ***Step 1:*** To a solution of tert-butyl (2S)-2-methyl-4-oxo-pyrrolidine-1-carboxylate (190 mg, 956 μmol, 1 eq) in DCM (3 mL) was added DAST (461 mg, 2.86 mmol, 378 μL, 3 eq) at 0 °C. The mixture was stirred at 20 °C for 12 hours. TLC (petroleum ether / ethyl acetate = 5/1) indicated tert-butyl (2S)-2-methyl-4-oxo-pyrrolidine-1-carboxylate was consumed completely and one new spot was formed. The reaction mixture was added to sat. $NaHCO_3$ aq. (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 5/1) to give the desired tert-butyl (2S)-4, 4-difluoro-2-methyl-pyrrolidine-1-carboxylate (120 mg, crude) as a white solid.

[00551] ***Step 2:*** A mixture of tert-butyl (2S)-4, 4-difluoro-2-methyl-pyrrolidine-1-carboxylate (120 mg, 542 μmol, 1 eq) in HCl/EtOAc (5 mL) was stirred at 20 °C for 0.1 hour. TLC (petroleum ether / ethyl acetate = 5/1) indicated tert-butyl (2S)-4, 4-difluoro-2-methyl-pyrrolidine-1-carboxylate was consumed completely and one new spot was formed. The reaction mixture was concentrated to give the desired (2S)-4, 4-difluoro-2-methyl-pyrrolidine (80 mg, crude, HCl) as a yellow solid.

[00552] ***Step 3***: To a solution of (2S)-4, 4-difluoro-2-methyl-pyrrolidine (80 mg, 508 μmol, 1 eq, HCl) in THF (2 mL) was added TEA (514 mg, 5.08 mmol, 707 μL, 10 eq) dropwise at 25 °C. After addition, the mixture was stirred at this temperature for 10 minutes, and then (1Z)-2,6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (288 mg, 761 μmol, 1.5 eq) in THF (2 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 20 minutes. LC-MS showed (2S)-4, 4-difluoro-2-methyl-pyrrolidine was consumed completely and the desired mass was detected. Then it was separated between 10 mL of water and 10 mL of ethyl acetate. The organic phase was separated, washed with 10 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2,6-dichlorophenyl)-[(2S)-4,4-difluoro-2-methyl-pyrrolidin-1-yl] methylene] amino]-4-methyl-benzenesulfonamide (230 mg, crude) as a yellow solid. MS (ESI): mass calcd. $C_{19}H_{19}Cl_2F_2N_3O_2S$ 461.05, m/z found 462.1 $[M+H]^+$.

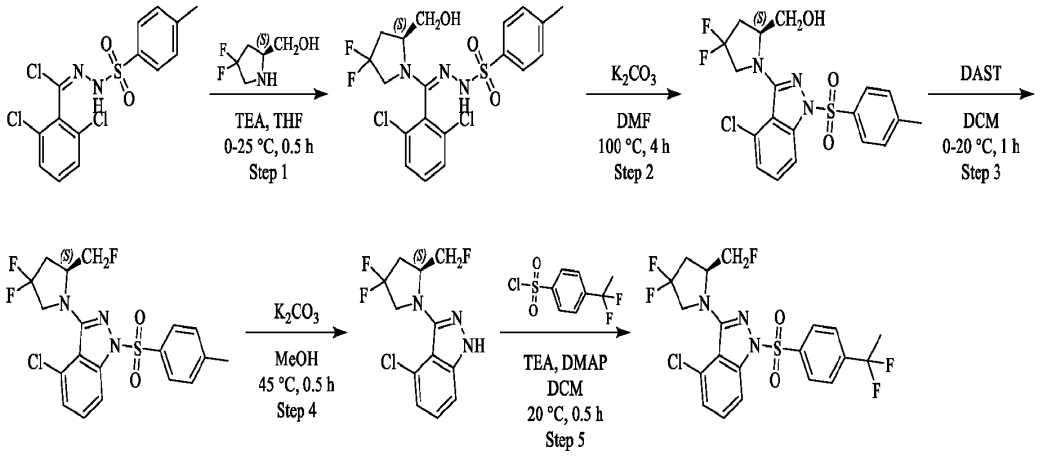
[00553] ***Step 4***: To a solution of N-[(E)- [(2, 6-dichlorophenyl)-[(2S)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl] methylene] amino]-4-methyl-benzenesulfonamide (230 mg, 497 μmol, 1 eq) in DMF (10 mL) was added K_2CO_3 (344 mg, 2.49 mmol, 5 eq). The mixture was stirred at 100 °C for 4 hours. LC-MS showed N-[(E)- [(2, 6-dichlorophenyl)-[(2S)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl] methylene] amino]-4-methyl-benzenesulfonamide was consumed completely and the desired mass was detected. Then it was separated between 10 mL of water and 10 mL of ethyl acetate. The organic phase was separated, washed with 10 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-[(2S)-4,4-difluoro-2-methyl-pyrrolidin-1-yl]-1-(p-tolylsulfonyl) indazole (210 mg, crude) as a yellow solid. MS (ESI): mass calcd. $C_{19}H_{18}ClF_2N_3O_2S$ 425.08, m/z found 426.2$[M+H]^+$.

[00554] ***Step 5***: To a solution of 4-chloro-3-[(2S)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl]-1-(p-tolylsulfonyl) indazole (210 mg, 493 μmol, 1 eq) in MeOH (10 mL) was added K_2CO_3 (341 mg, 2.47 mmol, 5 eq). The mixture was stirred at 45 °C for 0.5 hour. LC-MS showed 4-chloro-3-[(2S)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl]-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (50 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1)

to give the desired 4-chloro-3-[(2S)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl]-1H-indazole (50 mg, crude) as a yellow oil. MS (ESI): mass calcd. $C_{12}H_{12}ClF_2N_3$ 271.07, m/z found 272.1[M+H]$^+$.

[00555] ***Step 6***: To a solution of 4-(1,1-difluoroethyl) benzenesulfonyl chloride (79.7 mg, 331 μmol, 3 eq) and 4-chloro-3-[(2S)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl]-1H-indazole (30 mg, 110 μmol, 1 eq) in DCM (2 mL) were added TEA (55.9 mg, 552 μmol, 76.9 μL, 5 eq) and DMAP (1.35 mg, 11. μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-[(2S)-4, 4-difluoro-2-methyl-pyrrolidin-1-yl]-1H-indazole was consumed completely, and the desired mass was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:55%-85% B over 8.0 min) to give the desired 4-chloro-1-[4-(1,1-difluoroethyl) phenyl] sulfonyl-3-[(2S)-4,4-difluoro-2-methyl-pyrrolidin-1-yl] indazole (6.8 mg, 13. μmol, 12.6% yield, 97.59% purity) as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.67 (t, J = 8.1 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 4.45 - 4.36 (m, 1H), 4.31 - 4.16 (m, 1H), 3.64 - 3.52 (m, 1H), 2.74 - 2.60 (m, 1H), 2.29 - 2.11 (m, 1H), 1.92 (t, J = 19.1 Hz, 3H), 1.00 (d, J = 6.0 Hz, 3H). HPLC: 97.59% (220 nm), 98.08% (215 nm), 93.88% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{18}ClF_4N_3O_2S$ 475.07, m/z found 476.0 [M+H]$^+$.

Compound 82:4-Chloro-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2S)-4, 4-difluoro-2-(fluoromethyl) pyrrolidin-1-yl] indazole



[00556] ***Step 1***: To a solution of [(2S)-4,4-difluoropyrrolidin-2-yl] methanol (125 mg, 722 μmol, 1 eq, HCl) in THF (10 mL) was added dropwise TEA (731 mg, 7.22 mmol, 1.01 mL, 10 eq) at 25 °C. After addition, the mixture was stirred at this temperature for 10 minutes, and then (1Z)-2,6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (300 mg, 794.34 μmol, 1.1 eq) in THF (10 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 20 minutes. LCMS showed [(2S)-4, 4-difluoropyrrolidin-2-yl] methanol was consumed completely and the desired mass was detected. Then it was separated between 10 mL of water and 10 mL of ethyl acetate. The organic phase was separated, washed with 10 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2,6-dichlorophenyl)-[(2S)-4,4-difluoro-2-(hydroxymethyl) pyrrolidin-1-yl] methylene] amino]-4-methyl-benzenesulfonamide (340 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{19}H_{19}SN_3O_3F_2Cl_2$ 477.05, m/z found 478.0 $[M+H]^+$.

[00557] ***Step 2***: To a solution of [(2S)-1-[5-chloro-2-(p-tolylsulfonyl)-1, 2, 3-benzochloradiazin-4-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol (340 mg, 711 μmol, 1 eq) in DMF (10 mL) was added K_2CO_3 (491 mg, 3.55 mmol, 5 eq). The mixture was stirred at 100 °C for 4 hours. LCMS showed [(2S)-1-[5-chloro-2-(p-tolylsulfonyl)-1, 2, 3-benzochloradiazin-4-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol was consumed completely and the desired mass was detected. Then it was separated between 10 mL of water and 10 mL of ethyl acetate. The organic phase was separated, washed with 10 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 1/0 to 0/1) to give the desired [(2S)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol (50 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{19}H_{18}SN_3O_3F_2Cl$ 441.07, m/z found 442.0 $[M+H]^+$.

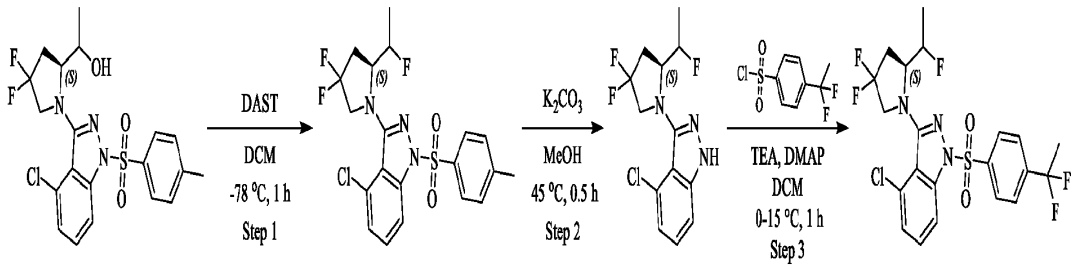
[00558] ***Step 3***: To a solution of [(2S)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4,4-difluoro-pyrrolidin-2-yl] methanol (50 mg, 113 μmol, 1 eq) in DCM (1 mL) was added DAST (73.0 mg, 453 μmol, 59.8 μL, 4 eq) at 0 °C. The mixture was stirred at 20 °C for 1 hour. LC-MS showed [(2S)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol was consumed completely and the desired mass was detected. The reaction mixture was added to saturated $NaHCO_3$ solution (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and

concentrated under reduced pressure to give the desired 4-chloro-1-(p-tolylsulfonyl)-3-[(2S)-4,4-difluoro-2-(fluoromethyl) pyrrolidin-1-yl] indazole (50 mg, crude) as a white solid. MS (ESI): mass calcd. For $C_{19}H_{17}ClF_3N_3O_2S$ 443.07, m/z found 444.1 $[M+H]^+$.

[00559] ***Step 4***: To a solution of 4-chloro-1-(p-tolylsulfonyl)-3-[(2S)-4, 4-difluoro-2-(fluoromethyl) pyrrolidin-1-yl] indazole (50 mg, 113 μmol, 1 eq) in MeOH (2 mL) was added K_2CO_3 (77.8 mg, 563 μmol, 5 eq). The mixture was stirred at 45 °C for 0.5 hour. LC-MS showed 4-chloro-1-(p-tolylsulfonyl)-3-[(2S)-4, 4-difluoro-2-(fluoromethyl) pyrrolidin-1-yl] indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (50 mL), extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 1/1) to give the desired 4-chloro-3-[(2S)-4, 4-difluoro-2-(fluoromethyl) pyrrolidin-1-yl]-1H-indazole (14 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{12}H_{11}ClF_3N_3$ 289.06, m/z found 290.1 $[M+H]^+$.

[00560] ***Step 5***: To a solution of 4-(1,1-difluoroethyl) benzenesulfonyl chloride (23.3 mg, 96.7 μmol, 2 eq) and 4-chloro-3-[(2S)-4,4-difluoro-2-(fluoromethyl) pyrrolidin-1-yl]-1H-indazole (14 mg, 48.3 μmol, 1 eq) in DCM (2 mL) were added TEA (24.5 mg, 242 μmol, 33.6 μL, 5 eq) and DMAP (590 μg, 4.83 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-[(2S)-4, 4-difluoro-2-(fluoromethyl) pyrrolidin-1-yl]-1H-indazole was consumed completely, and the desired mass was detected. The reaction mixture was added to water (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:55%-75% B over 8.0 min) to give the desired 4-chloro-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2S)-4, 4-difluoro-2-(fluoromethyl) pyrrolidin-1-yl] indazole (2.1 mg, 4.22 μmol, 8.73% yield, 99.25% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.67 (t, J = 8.1 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 5.24 - 5.04 (m, 1H), 3.81 - 3.66 (m, 1H), 3.60 - 3.44 (m, 3H), 2.70 - 2.55 (m, 1H), 2.49 - 2.35 (m, 1H), 1.93 (t, J = 19.1 Hz, 3H). HPLC: 99.25% (220 nm), 99.11% (215 nm), 98.51% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{17}ClF_5N_3O_2S$ 493.07, m/z found 494.0 $[M+H]^+$.

Compound 83: 4-chloro-3-((2S)-4,4-difluoro-2-(1-fluoroethyl)pyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole



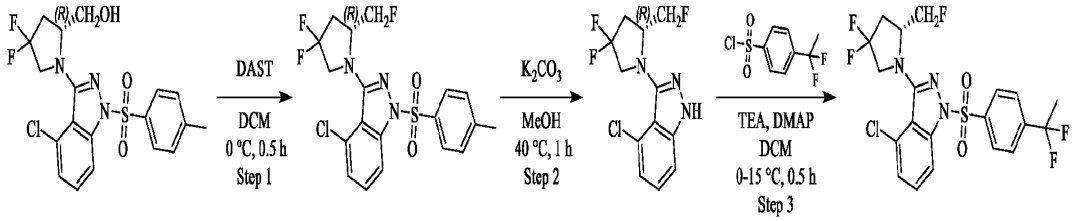
[00561] ***Step 1***: To a solution of 1-((S)-1-(4-chloro-1-tosyl-1H-indazol-3-yl)-4,4-difluoropyrrolidin-2-yl)ethan-1-ol (40 mg, 87.7 μmol, 1 eq) in DCM (2 mL) was added DAST (42.4 mg, 263 μmol, 34.8 μL, 3 eq). The mixture was stirred at -78 °C for 1 hour. TLC indicated 1-((S)-1-(4-chloro-1-tosyl-1H-indazol-3-yl)-4,4-difluoropyrrolidin-2-yl)ethan-1-ol was consumed completely and one new spot formed. The reaction mixture was quenched by aq.$NaHCO_3$.sat (10 mL), then reaction mixture was added H_2O (10 mL) and extracted with EtOAc (10 mL X 3). The combined organic phase was washed with brine (10 mL X 2), dried over Na_2SO_4, filtered, and concentrated in vacuum to give the desired 4-chloro-3-((2S)-4,4-difluoro-2-(1-fluoroethyl)pyrrolidin-1-yl)-1-tosyl-1H-indazole (40 mg, crude) as a pale-yellow solid.

[00562] ***Step 2***: To a solution of 4-chloro-3-((2S)-4,4-difluoro-2-(1-fluoroethyl)pyrrolidin-1-yl)-1-tosyl-1H-indazole (40 mg, 87.4 μmol, 1 eq) in MeOH (2 mL) was added K_2CO_3 (36.2 mg, 262 μmol, 3 eq). The mixture was stirred at 45 °C for 0.5 hour. LC-MS showed 4-chloro-3-((2S)-4,4-difluoro-2-(1-fluoroethyl)pyrrolidin-1-yl)-1-tosyl-1H-indazole was consumed completely and one main peak with the desired mass was detected. The reaction mixture was filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:35%-65% B over 8.0 min) to give the desired 4-chloro-3-((2S)-4,4-difluoro-2-(1-fluoroethyl)pyrrolidin-1-yl)-1H-indazole (10 mg, 29.6 μmol, 33.92% yield, 90% purity) as a pale-yellow solid. MS (ESI): mass calcd. For $C_{13}H_{13}ClF_3N_3$ 303.08, m/z found 304.0 $[M+H]^+$.

[00563] ***Step 3***: To a solution of 4-chloro-3-((2S)-4,4-difluoro-2-(1-fluoroethyl)pyrrolidin-1-yl)-1H-indazole (10 mg, 32.9 μmol, 1 eq) and 4-(1, 1-difluoroethyl) benzenesulfonyl chloride

(9.51 mg, 39.5 μmol, 1.2 eq) in DCM (2 mL) were added TEA (10 mg, 98.8 μmol, 13.8 μL, 3 eq) and DMAP (40.2 μg, 3.29^{e-1} μmol, 0.01 eq) at 0 °C. The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-chloro-3-((2S)-4,4-difluoro-2-(1-fluoroethyl)pyrrolidin-1-yl)-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1% TFA)-ACN]; gradient:55%-85% B over 8.0 min) to give the desired 4-chloro-3-((2S)-4,4-difluoro-2-(1-fluoroethyl)pyrrolidin-1-yl)-1-((4-(1,1-difluoroethyl)phenyl)sulfonyl)-1H-indazole (1 mg, 1.97 μmol, 5.98% yield, 100.00% purity) as a white solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.68 (t, J = 8.1 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 4.69 - 4.56 (m, 1H), 4.53 - 4.32 (m, 2H), 4.16 (br dd, J = 6.1, 11.7 Hz, 1H), 1.92 (t, J = 19.1 Hz, 3H), 1.52 - 1.38 (m, 2H), 1.21 - 1.09 (m, 3H). HPLC: 98.50% (220 nm), 98.15% (215 nm), 100.00% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{19}ClF_5N_3O_2S$ 507.08, m/z found 508.0 $[M+H]^+$.

Compound 84:4-Chloro-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2R)-4, 4-difluoro-2-(fluoromethyl) pyrrolidin-1-yl] indazole



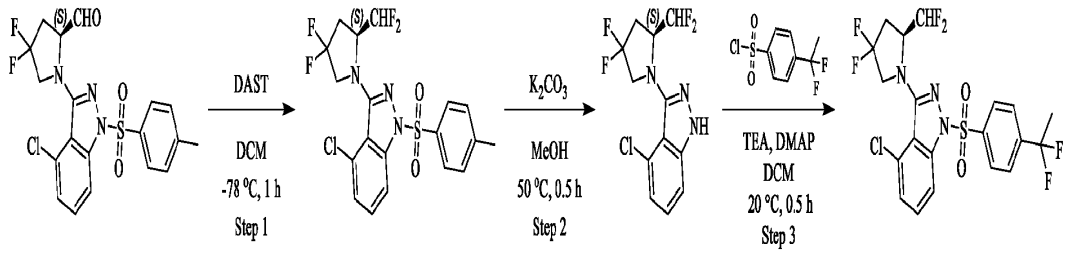
[00564] ***Step 1***: To a solution of [(2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol (34 mg, 76.9 μmol, 1 eq) in DCM (3 mL) was added DAST (49.6 mg, 308 μmol, 40.7 μL, 4 eq). The mixture was stirred at 0 °C for 0.5 hour. LCMS showed [(2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 5 mL of H_2O and 5 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-1-(p-tolylsulfonyl)-3-[(2R)-4,4-difluoro-2-(fluoromethyl) pyrrolidin-1-yl] indazole (68

mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{19}H_{17}ClF_3N_3O_2S$ 443.1, m/z found 444.1 $[M+H]^+$.

[00565] ***Step 2***: To a solution of 4-chloro-1-(p-tolylsulfonyl)-3-[(2R)-4, 4-difluoro-2-(fluoromethyl) pyrrolidin-1-yl] indazole (60 mg, 135 µmol, 1 eq) in MeOH (2 mL) was added K_2CO_3 (93.4 mg, 676 µmol, 5 eq). The mixture was stirred at 40 °C for 1 hour. LC-MS showed 4-chloro-1-(p-tolylsulfonyl)-3-[(2R)-4, 4-difluoro-2- (fluoromethyl) pyrrolidin-1-yl] indazole was consumed completely and the desired mass was detected. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 µm; mobile phase: [H_2O (0.1% TFA)-ACN]; gradient: 35%-65% B over 8.0 min) to give the desired 4-chloro-3-[(2R)-4, 4-difluoro-2- (fluoromethyl) pyrrolidin-1-yl]-1H-indazole (3 mg, 10.4 µmol, 7.66% yield) as a white solid. MS (ESI): mass calcd. For $C_{12}H_{11}ClF_3N_3$ 289.1, m/z found 290.1 $[M+H]^+$.

[00566] ***Step 3***: To a solution of 4-chloro-3-[(2R)-4, 4-difluoro-2- (fluoromethyl) pyrrolidin-1-yl]-1H-indazole (2.5 mg, 8.63 µmol, 1 eq) and 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (4.15 mg, 17.3 µmol, 2 eq) in DCM (0.5 mL) were added TEA (1.75 mg, 17.3 µmol, 2.40 µL, 2 eq) and DMAP (106 µg, 8.63e-1 µmol, 0.1 eq) at 0 °C. The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 4-chloro-3-[(2R)-4, 4-difluoro-2- (fluoromethyl) pyrrolidin-1-yl]-1H-indazole was consumed completely and the desired mass was detected. The reaction mixture was partitioned between 5 mL of H_2O and 5 mL of DCM. The organic phase was separated, washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-HPLC (TFA condition; Method: column: Waters Xbridge BEH C18 100 * 30mm * 10 µm; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient:50%-80% B over 8.0 min) to give the desired 4-chloro-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2R)-4, 4-difluoro-2-(fluoromethyl) pyrrolidin-1-yl] indazole (1 mg, 2.02 µmol, 23.5% yield, 99.70% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.66 (t, J = 8.1 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 5.22 - 5.02 (m, 1H), 3.81 - 3.67 (m, 1H), 3.60 - 3.39 (m, 5H), 1.92 (t, J = 19.1 Hz, 3H). HPLC: 99.70% (220 nm), 100.00% (215 nm), 100.00% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{17}ClF_5N_3O_2S$ 493.1, m/z found 494.1 $[M+H]^+$.

Compound 85:4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2S)-2-(difluoromethyl)-4, 4-difluoro-pyrrolidin-1-yl] indazole



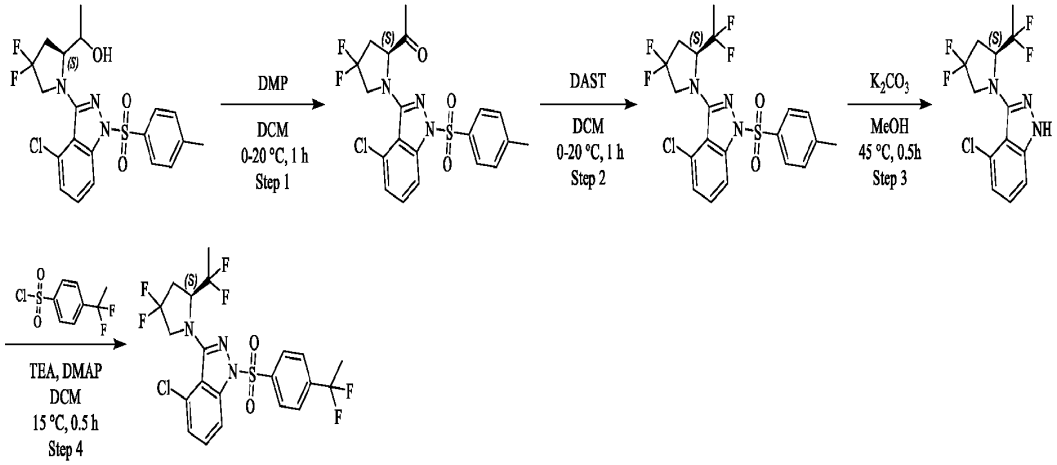
[00567] ***Step 1***: To a solution of (2S)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidine-2-carbaldehyde (200 mg, 455 μmol, 1 eq) in DCM (2 mL) was added DAST (147 mg, 909 μmol, 120 μL, 2 eq). The mixture was stirred at -78 °C for 1 hour. LC-MS showed (2S)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidine-2-carbaldehyde was consumed completely and one main peak with the desired mass was detected. The reaction mixture was quenched by aq. $NaHCO_3$ (20 ml), then added H_2O (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic phase was washed with brine (10 mL X 2), dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by *prep*-HPLC (column: Waters Xbridge 150 * 25 mm 10 μm; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient:55%-85% B over 8.0 min) to give the desired 4-chloro-1-(p-tolylsulfonyl)-3-[(2S)-2-(difluoromethyl)-4,4-difluoro-pyrrolidin-1-yl] indazole (22 mg, 41.44 μmol, 9.11% yield, 87% purity) as a pale-yellow oil. MS (ESI): mass calcd. For $C_{19}H_{16}ClF_4N_3O_2S$ 461.06, m/z found 462.0 $[M+H]^+$.

[00568] ***Step 2***: To a solution of 4-chloro-1-(p-tolylsulfonyl)-3-[(2S)-2-(difluoromethyl)-4, 4-difluoro-pyrrolidin-1-yl] indazole (22 mg, 47.6 μmol, 1 eq) in MeOH (2 mL) was added K_2CO_3 (19.8 mg, 143 μmol, 3 eq). The mixture was stirred at 50 °C for 0.5 hour. LC-MS showed 4-chloro-1-(p-tolylsulfonyl)-3-[(2S)-2-(difluoromethyl)-4, 4-difluoro-pyrrolidin-1-yl] indazole was consumed completely and one main peak with the desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-[(2S)-2-(difluoromethyl)-4, 4-difluoro-pyrrolidin-1-yl]-1H-indazole (10 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{12}H_{10}ClF_4N_3$ 307.05, m/z found 307.9 $[M+H]^+$.

[00569] ***Step 3***: To a solution of 4-(1,1-difluoroethyl) benzenesulfonyl chloride (12.5 mg, 52.0 μmol, 2 eq) and 4-chloro-3-[(2S)-2-(difluoromethyl)-4,4-difluoro-pyrrolidin-1-yl]-1H-indazole

(8 mg, 26.0 μmol, 1 eq) in DCM (2 mL) were added TEA (13.2 mg, 130 μmol, 18.1 μL, 5 eq) and DMAP (318 μg, 2.60 μmol, 0.1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-[(2S)-2-(difluoromethyl)-4, 4-difluoro-pyrrolidin-1-yl]-1H-indazole was consumed completely, and the desired mass was detected. The reaction mixture was added to water (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient: 60%-85% B over 8.0 min) to give the desired 4-chloro-1-[4-(1,1-difluoroethyl) phenyl]sulfonyl-3-[(2S)-2-(difluoromethyl)-4,4-difluoro-pyrrolidin-1-yl]indazole (6.5 mg, 12. μmol, 48.5% yield, 99.20% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 8.6 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.69 (t, J = 8.1 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 6.07 (dt, J = 3.7, 55.4 Hz, 1H), 5.06 (dt, J = 3.8, 8.0 Hz, 1H), 4.14 (ddd, J = 5.9, 12.2, 25.9 Hz, 1H), 3.82 (br t, J = 13.4 Hz, 1H), 2.95 - 2.80 (m, 1H), 2.65 - 2.55 (m, 1H), 1.93 (t, J = 19.1 Hz, 3H). HPLC: 99.20% (220 nm), 98.57% (215 nm), 100.00% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{16}ClF_6N_3O_2S$ 511.06, m/z found 512.0 $[M+H]^+$.

Compound 86: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2S)-2-(1, 1-difluoroethyl)-4, 4-difluoro-pyrrolidin-1-yl] indazole



[00570] ***Step 1***: To a solution of 1-((S)-1-(4-chloro-1-tosyl-1H-indazol-3-yl)-4,4-difluoropyrrolidin-2-yl)ethan-1-ol (30 mg, 65.8 μmol, 1 eq) in DCM (3 mL) was added DMP (55.8 mg, 132 μmol, 40.8 μL, 2 eq) at 0 °C. The mixture was stirred at 20 °C for 1 hour. LC-MS

showed 1-((S)-1-(4-chloro-1-tosyl-1H-indazol-3-yl)-4,4-difluoropyrrolidin-2-yl)ethan-1-ol was consumed completely and one main peak with the desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove DCM. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) give the desired 1-[(2S)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] ethanone (29 mg, 63.9 μmol) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{18}ClF_2N_3O_3S$ 453.07, m/z found 454.2 $[M+H]^+$.

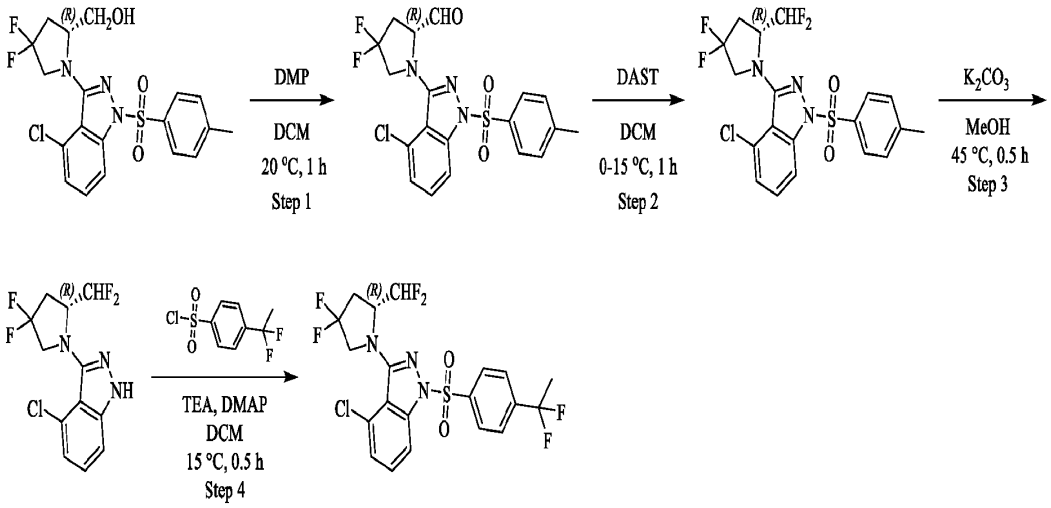
[00571] ***Step 2***: To a solution of 1-[(2S)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4,4-difluoro-pyrrolidin-2-yl] ethanone (25 mg, 55.1 μmol, 1 eq) in DCM (3 mL) was added DAST (35.5 mg, 220 μmol, 29.1 μL, 4 eq) at 0 °C. The mixture was stirred at 20 °C for 1 hour. LC-MS showed 1-[(2S)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] ethanone remained and the desired mass was detected. Then it was separated between 10 mL of water and 10 mL of ethyl acetate. The organic phase was separated, washed with 10 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-1-(p-tolylsulfonyl)-3-[(2S)-2-(1,1-difluoroethyl)-4,4-difluoro-pyrrolidin-1-yl] indazole (26 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{20}H_{18}ClF_4N_3O_2S$ 475.07, m/z found 476.1 $[M+H]^+$.

[00572] ***Step 2***: To a solution of 4-chloro-1-(p-tolylsulfonyl)-3-[(2S)-2-(1, 1-difluoroethyl)-4, 4-difluoro-pyrrolidin-1-yl] indazole (26 mg, 54.6 μmol, 1 eq) in MeOH (3 mL) was added K_2CO_3 (37.8 mg, 273 μmol, 5 eq). The mixture was stirred at 45 °C for 0.5 hour. LC-MS showed 4-chloro-1-(p-tolylsulfonyl)-3-[(2S)-2-(1, 1-difluoroethyl)-4, 4-difluoro-pyrrolidin-1-yl] indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (50 mL), extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-[(2S)-2-(1, 1-difluoroethyl)-4, 4-difluoro-pyrrolidin-1-yl]-1H-indazole (10 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{12}ClF_4N_3$ 321.07, m/z found 321.9 $[M+H]^+$.

[00573] ***Step 3***: To a solution of 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (12.0 mg, 49.7 μmol, 2 eq) and 4-chloro-3-[(2S)-2-(1, 1-difluoroethyl)-4, 4-difluoro-pyrrolidin-1-yl]-1H-indazole (8 mg, 24.9 μmol, 1 eq) in DCM (2 mL) were added TEA (12.6 mg, 124 μmol, 17.3 μL, 5 eq) and DMAP (304 μg, 2.49 μmol, 0.1 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-

MS showed 4-chloro-3-[(2S)-2-(1, 1-difluoroethyl)-4, 4-difluoro-pyrrolidin-1-yl]-1H-indazole was consumed completely, and the desired mass was detected. The reaction mixture was added to water (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:60%-85% B over 8.0 min) to give the desired 4-chloro-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2S)-2-(1, 1-difluoroethyl)-4, 4-difluoro-pyrrolidin-1-yl] indazole (7.3 mg, 13.9 μmol, 55.8% yield, 99.87% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H), 7.68 (t, J = 8.1 Hz, 1H), 7.52 (d, J = 7.4 Hz, 1H), 5.21 - 5.09 (m, 1H), 4.09 - 3.93 (m, 1H), 3.87 - 3.75 (m, 1H), 2.98 - 2.83 (m, 1H), 2.65 - 2.52 (m, 1H), 1.91 (t, J = 19.1 Hz, 3H), 1.43 (t, J = 19.2 Hz, 3H). HPLC: 99.87% (220 nm), 100.00% (215 nm), 100.00% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{18}ClF_6N_3O_2S$ 525.07, m/z found 526.1 $[M+H]^+$.

Compound 87: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2R)-2-(difluoromethyl)-4, 4-difluoro-pyrrolidin-1-yl] indazole



[00574] ***Step 1***: To a solution of [(2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol (55 mg, 124 μmol, 1 eq) in DCM (2 mL) was added DMP (106 mg, 249 μmol, 77.1 μL, 2 eq). The mixture was stirred at 20 °C for 1 hour. LC-MS showed [(2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol was

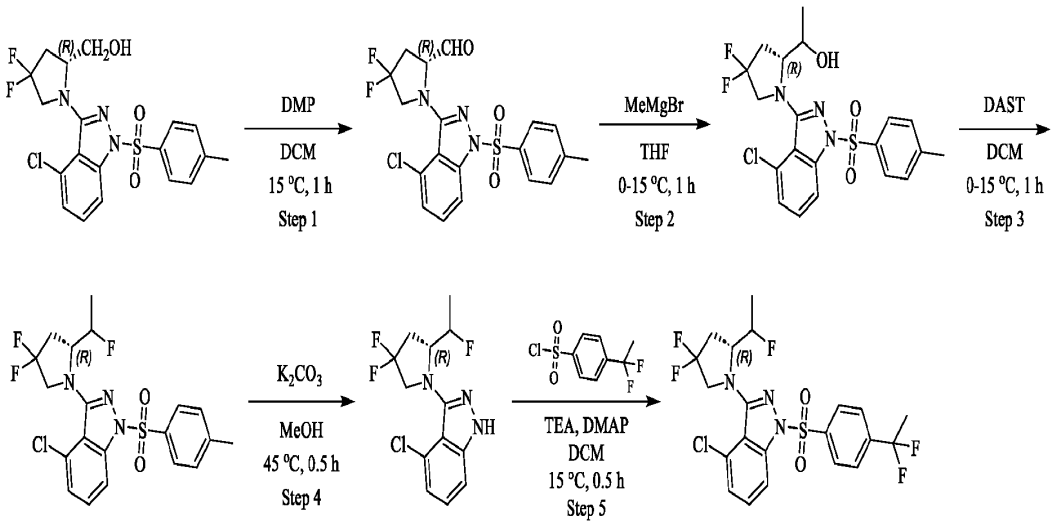
consumed completely and the desired mass was detected. The reaction was quenched by the addition of sat. Na_2SO_3 aq. (2 mL) at room temperature. The reaction was added Na_2CO_3 (sat.) to adjust pH to 7~8. The resulting mixture was extracted with DCM (3 X 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by *prep*-TLC (silica gel, petroleum ether/ethyl acetate = 2/1) to give the desired (2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidine-2-carbaldehyde (9 mg, crude) as a white solid. MS (ESI): mass calcd. For $C_{19}H_{16}ClF_4N_3O_2S$ 461.06, m/z found 462.0 $[M+H]^+$.

[00575] ***Step 2***: To a solution of (2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidine-2-carbaldehyde (9 mg, 20.5 μmol, 1 eq) in DCM (1 mL) was added DAST (13.2 mg, 81.8 μmol, 10.8 μL, 4 eq) at 0 °C. The mixture was stirred at 15 °C for 1 hour. LC-MS showed (2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidine-2-carbaldehyde was consumed completely and the desired mass was detected. Then it was separated between 10 mL of sat. aq. Na_2CO_3 and 10 mL of DCM. The organic phase was separated, washed with 10 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-1-(p-tolylsulfonyl)-3-[(2R)-2-(difluoromethyl)-4, 4-difluoro-pyrrolidin-1-yl] indazole (7 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{19}H_{16}ClF_4N_3O_2S$ 461.06, m/z found 462.0 $[M+H]^+$.

[00576] ***Step 3***: To a solution of 4-chloro-1-(p-tolylsulfonyl)-3-[(2R)-2-(difluoromethyl)-4, 4-difluoro-pyrrolidin-1-yl] indazole (6 mg, 13.0 μmol, 1 eq) in MeOH (1 mL) was added K_2CO_3 (8.98 mg, 65.0 μmol, 5 eq). The mixture was stirred at 45 °C for 0.5 hour. LC-MS showed 4-chloro-1-(p-tolylsulfonyl)-3-[(2R)-2-(difluoromethyl)-4, 4-difluoro-pyrrolidin-1-yl] indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (50 mL), extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:40%-65% B over 8.0 min) to give the desired 4-chloro-3-[(2R)-2-(difluoromethyl)-4,4-difluoro-pyrrolidin-1-yl]-1H-indazole (1 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{12}H_{10}ClF_4N_3$ 307.05, m/z found 307.9 $[M+H]^+$.

[00577] ***Step 4***: To a solution of 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (1.56 mg, 6.50 μmol, 2 eq) and 4-chloro-3-[(2R)-2-(difluoromethyl)-4, 4-difluoro-pyrrolidin-1-yl]-1H-indazole (1 mg, 3.25 μmol, 1 eq) in DCM (0.5 mL) were added TEA (1.64 mg, 16.3 μmol, 2.26 μL, 5 eq) and DMAP (39.7 μg, $3.25e^{-1}$ μmol, 0.1 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 4-chloro-3-[(2R)-2-(difluoromethyl)-4, 4-difluoro-pyrrolidin-1-yl]-1H-indazole was consumed completely, and the desired mass was detected. The reaction mixture was added to water (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm *3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:50%-80% B over 8.0 min) to give the desired 4-chloro-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2R)-2-(difluoromethyl)-4, 4-difluoro-pyrrolidin-1-yl] indazole (1.0 mg, 1.90 μmol, 58.3% yield, 97.03% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.6 Hz, 2H), 7.67 (t, J = 8.1 Hz, 1H), 7.52 (s, 1H), 6.27 - 5.79 (m, 1H), 5.13 - 4.98 (m, 1H), 4.21 - 4.05 (m, 1H), 3.86 - 3.74 (m, 1H), 2.91 - 2.80 (m, 1H), 2.62 - 2.59 (m, 1H), 1.92 (t, J = 19.1 Hz, 3H). HPLC: 97.03% (220 nm), 97.90% (215 nm), 96.43% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{16}ClF_6N_3O_2S$ 511.06, m/z found 512.0 $[M+H]^+$.

Compound 88: 4-Chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2R)-4, 4-difluoro-2-(1-fluoroethyl) pyrrolidin-1-yl] indazole



[00578] ***Step 1***: To a solution of [(2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol (100 mg, 226 μmol, 1 eq) in DCM (3 mL) was added DMP (192 mg, 453 μmol, 140 μL, 2 eq). The mixture was stirred at 15 °C for 1 hour. LC-MS showed [(2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] methanol remained. Several new peaks were shown on LC-MS and the desired compound was detected. The reaction was quenched by the addition of saturated Na_2SO_3 solution (2 mL) at room temperature. The pH value of the reaction was adjusted pH to 7~8 with saturated $NaHCO_3$ solution. The resulting mixture was extracted with DCM (3 X 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired (2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidine-2-carbaldehyde (40 mg, crude) as a white solid. MS (ESI): mass calcd. For $C_{19}H_{16}ClF_2N_3O_3S$ 439.06, m/z found 440.2 $[M+H]^+$.

[00579] ***Step 2***: To a solution of (2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidine-2-carbaldehyde (40 mg, 90.9 μmol, 1 eq) in THF (2 mL) was added MeMgBr (3 M, 60.6 μL, 2 eq) at 0 °C under N_2. The mixture was stirred at 15 °C for 1 hour. LC-MS showed (2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidine-2-carbaldehyde was consumed completely and the desired compound was detected. The reaction mixture was added to HCl (10 mL, 1 M) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 1-[(2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4,4-difluoro-pyrrolidin-2-yl] ethanol (30 mg, crude) as a white solid. MS (ESI): mass calcd. For $C_{20}H_{20}ClF_2N_3O_3S$ 455.09, m/z found 456.2 $[M+H]^+$.

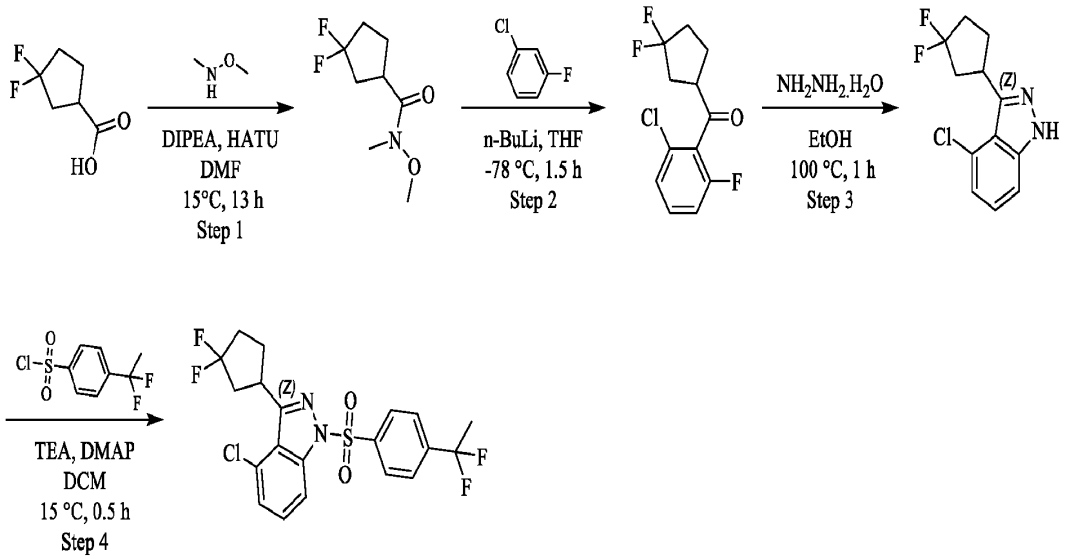
[00580] ***Step 3***: To a solution of 1-[(2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4,4-difluoro-pyrrolidin-2-yl] ethanol (27 mg, 59.2 μmol, 1 eq) in DCM (2 mL) was added DAST (38.2 mg, 237 μmol, 31.3 μL, 4 eq) at 0 °C under N_2. The mixture was stirred at 15 °C for 1 hour. LC-MS showed 1-[(2R)-1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-4, 4-difluoro-pyrrolidin-2-yl] ethanol was consumed completely and the desired compound was detected. The reaction mixture was added to sat. aq. $NaHCO_3$ (10 mL) and extracted with DCM (10 mL X 3). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-[(2R)-4, 4-difluoro-2-(1-

fluoroethyl) pyrrolidin-1-yl]-1-(p-tolylsulfonyl) indazole (20 mg, crude) as a white solid. MS (ESI): mass calcd. For $C_{20}H_{19}ClF_3N_3O_2S$ 457.08, m/z found 458.2 $[M+H]^+$.

[00581] ***Step 4***: To a solution of 4-chloro-3-[(2R)-4, 4-difluoro-2-(1-fluoroethyl) pyrrolidin-1-yl]-1-(p-tolylsulfonyl) indazole (17.0 mg, 37.1 μmol, 1 eq) in MeOH (1 mL) was added K_2CO_3 (25.7 mg, 186 μmol, 5 eq). The mixture was stirred at 45 °C for 0.5 hour. LC-MS showed 4-chloro-3-[(2R)-4, 4-difluoro-2-(1-fluoroethyl) pyrrolidin-1-yl]-1-(p-tolylsulfonyl) indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (50 mL) and extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-[(2R)-4, 4-difluoro-2-(1-fluoroethyl) pyrrolidin-1-yl]-1H-indazole (10 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{13}ClF_3N_3$ 303.08, m/z found 304.2 $[M+H]^+$.

[00582] ***Step 5***: To a solution of 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (14.3 mg, 59.3 μmol, 2 eq) and 4-chloro-3-[(2R)-4, 4-difluoro-2-(1-fluoroethyl) pyrrolidin-1-yl]-1H-indazole (9.00 mg, 29.6 μmol, 1 eq) in DCM (1 mL) were added TEA (15.0 mg, 148 μmol, 20.6 μL, 5 eq) and DMAP (362 μg, 2.96 μmol, 0.1 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 4-chloro-3-[(2R)-4, 4-difluoro-2-(1-fluoroethyl) pyrrolidin-1-yl]-1H-indazole was consumed completely, and the desired mass was detected. The reaction mixture was added to water (20 mL) and extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:55%-85% B over 8.0 min) to give the desired 4-chloro-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-[(2R)-4, 4-difluoro-2-(1-fluoroethyl) pyrrolidin-1-yl] indazole (1.0 mg, 1.75 μmol, 5.89% yield, 88.69% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.6 Hz, 2H), 7.68 (dd, J = 7.8, 8.4 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 5.04 - 4.81 (m, 1H), 4.25 - 4.15 (m, 1H), 3.68 - 3.49 (m, 2H), 2.48 - 2.40 (m, 2H), 1.92 (t, J = 19.1 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H). HPLC: 88.69% (220 nm), 88.46% (215 nm), 82.95% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{19}ClF_5N_3O_2S$ 507.08, m/z found 508.0 $[M+H]^+$.

Compound 89: 4-Chloro-3-(3, 3-difluorocyclopentyl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole



[00583] ***Step 1***: To a solution of 3, 3-difluorocyclopentanecarboxylic acid (1 g, 6.66 mmol, 1 eq) in DMF (10 mL) were added DIPEA (3.44 g, 26.6 mmol, 4.64 mL, 4 eq) and HATU (3.80 g, 9.99 mmol, 1.5 eq) at 15 °C under N_2. The mixture was stirred at 15 °C for 1 hour. N-methoxymethanamine; hydrochloride (975 mg, 9.99 mmol, 1.5 eq) was added to the mixture. The mixture was stirred at 15 °C for 12 hours. LC-MS showed 3, 3-difluorocyclopentanecarboxylic acid was consumed completely and the desired mass was detected. The reaction mixture was added to water (50 mL), extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% ethyl acetate / petroleum ether gradient @ 80 mL/min) to give the desired 3, 3-difluoro-N-methoxy-N-methyl-cyclopentanecarboxamide (1.15 g, crude) as a yellow oil. MS (ESI): mass calcd. For $C_8H_{13}F_2NO_2$ 193.09, m/z found 194.2 $[M+H]^+$.

[00584] ***Step 2***: To a solution of 1-chloro-3-fluoro-benzene (541 mg, 4.14 mmol, 443 µL, 1.6 eq) in THF (10 mL) was added *n*-BuLi (2.5 M, 1.66 mL, 1.6 eq) at -78 °C under N_2. The mixture was stirred at -78 °C for 0.5 hour. 3, 3-Difluoro-N-methoxy-N-methyl-cyclopentanecarboxamide (0.5 g, 2.59 mmol, 1 eq) in THF (3 mL) was added to the mixture at -78 °C. The mixture was

stirred at -78 °C for 1 hour. TLC (petroleum ether / ethyl acetate = 3/1) indicated 3, 3-difluoro-N-methoxy-N-methyl-cyclopentanecarboxamide was consumed completely and one new spot was formed. The reaction mixture was quenched by addition saturated aqueous NH_4Cl (20 mL) at 0 °C, and extracted with EtOAc (20 mL X 3). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired (2-chloro-6-fluoro-phenyl) -(3, 3-difluorocyclopentyl) methanone (170 mg, crude) as a yellow oil.

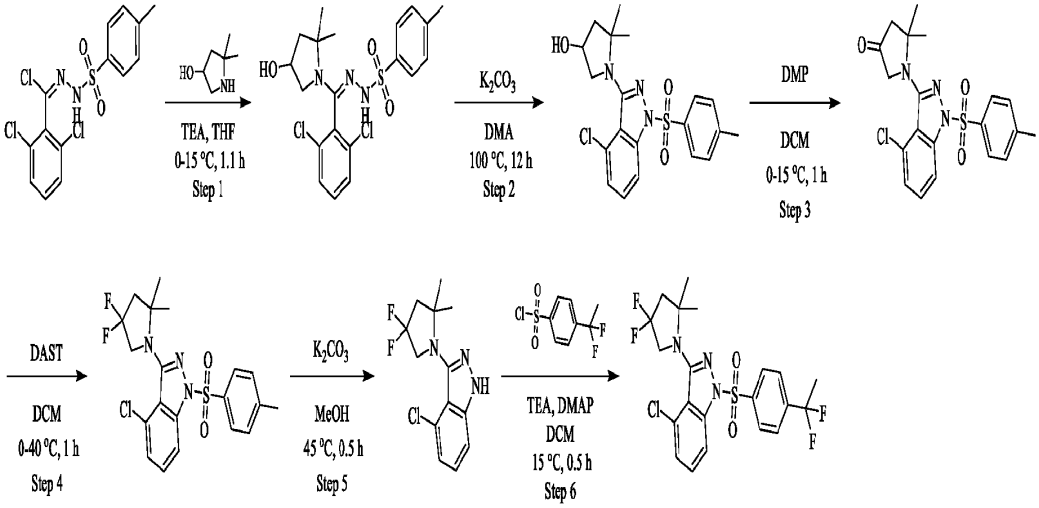
[00585] ***Step 3***: To a solution of (2-chloro-6-fluoro-phenyl) -(3, 3-difluorocyclopentyl) methanone (150 mg, 571 μmol, 1 eq) in EtOH (1 mL) was added $NH_2NH_2.H_2O$ (0.82 mL). The mixture was stirred at 100 °C for 1 hour. LC-MS showed (2-chloro-6-fluoro-phenyl) -(3, 3-difluorocyclopentyl) methanone was consumed completely and the desired mass was detected. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (20 mL X 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired 4-chloro-3-(3, 3-difluorocyclopentyl)-1H-indazole (40 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{12}H_{11}ClF_2N_2$ 256.06, m/z found 257.2 $[M+H]^+$.

[00586] ***Step 4***: To a solution of 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (37.5 mg, 156 μmol, 2 eq) and 4-chloro-3-(3, 3-difluorocyclopentyl)-1H-indazole (20 mg, 77.9 μmol, 1 eq) in DCM (1 mL) were added TEA (39.4 mg, 390 μmol, 54.2 μL, 5 eq) and DMAP (952 μg, 7.79 μmol, 0.1 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 4-chloro-3-(3, 3-difluorocyclopentyl)-1H-indazole was consumed completely, and the desired mass was detected. The reaction mixture was added to water (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:55%-85% B over 8.0 min) to give the desired 4-chloro-3-(3, 3-difluorocyclopentyl)-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole (8.2 mg, 17.7 μmol, 22.8% yield, 99.73% purity) as a pale-yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 7.68 (t, J = 8.1 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 4.16 - 4.05 (m, 1H), 2.69 - 2.52 (m, 2H), 2.37 - 2.16 (m, 3H), 2.07 - 1.99 (m,

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1H), 1.93 (t, J = 19.1 Hz, 3H). HPLC: 99.73% (220 nm), 99.88% (215 nm), 99.82% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{17}ClF_4N_2O_2S$ 460.06, m/z found 461.0 $[M+H]^+$.

Compound 90:4-Chloro-3-(4, 4-difluoro-2, 2-dimethyl-pyrrolidin-1-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole



[00587] ***Step 1***: To a solution of 5, 5-dimethylpyrrolidin-3-ol (554 mg, 4.81 mmol, 1 eq) in THF (10 mL) was added dropwise TEA (4.87 g, 48.1 mmol, 6.70 mL, 10 eq) at 15 °C. After addition, the mixture was stirred at this temperature for 0.1 hour, and then (1Z)-2,6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (2 g, 5.30 mmol, 1.1 eq) in THF (10 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 15 °C for 1 hour. LC-MS showed 5, 5-dimethylpyrrolidin-3-ol was consumed completely and the desired mass was detected. Then it was separated between 100 mL of water and 100 mL of ethyl acetate. The organic phase was separated, washed with 100 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired N-[(E)-[(2,6-dichlorophenyl) -(4-hydroxy-2,2-dimethyl-pyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (2.2 g, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{20}H_{23}Cl_2N_3O_3S$ 455.08, m/z found 456.1 $[M+H]^+$.

[00588] ***Step 2***: To a solution of N-[(E)- [(2, 6-dichlorophenyl) -(4-hydroxy-2, 2-dimethyl-pyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (2.2 g, 4.82 mmol, 1 eq) in DMA (20 mL) was added K_2CO_3 (3.33 g, 24.1 mmol, 5 eq). The mixture was stirred at 100 °C for 12 hours. LC-MS showed N-[(E)- [(2, 6-dichlorophenyl) -(4-hydroxy-2, 2-dimethyl-pyrrolidin-1-yl) methylene] amino]-4-methyl-benzenesulfonamide was consumed completely,

the desired mass was detected. Then it was separated between 100 mL of water and 100 mL of ethyl acetate. The organic phase was separated, washed with 100 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-5, 5-dimethyl-pyrrolidin-3-ol (1 g, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{22}ClN_3O_3S$ 419.11, m/z found 420.3 $[M+H]^+$.

[00589] ***Step 3***: To a solution of 1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-5, 5-dimethyl-pyrrolidin-3-ol (500 mg, 1.19 mmol, 1 eq) in DCM (10 mL) was added DMP (1.01 g, 2.38 mmol, 738 μL, 2 eq) at 0 °C. The mixture was stirred at 15 °C for 1 hour. LC-MS showed 1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-5, 5-dimethyl-pyrrolidin-3-ol was consumed completely and the desired mass was detected. The reaction was quenched by the addition of sat. Na_2SO_3 aq. (20 mL) at room temperature. The pH value of reaction was adjusted to 7~8 with saturated Na_2CO_3 solution. The resulting mixture was extracted with DCM (3 X 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-5, 5-dimethyl-pyrrolidin-3-one (330 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{20}ClN_3O_3S$ 417.09, m/z found 418.0 $[M+H]^+$.

[00590] ***Step 4***: To a solution of 1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-5, 5-dimethyl-pyrrolidin-3-one (100 mg, 239 μmol, 1 eq) in DCM (2 mL) was added DAST (1 mL) at 0 °C. The mixture was stirred at 40 °C for 1 hour. LC-MS showed 1-[4-chloro-1-(p-tolylsulfonyl) indazol-3-yl]-5, 5-dimethyl-pyrrolidin-3-one remained and the desired mass was detected. The reaction mixture was added to saturated $NaHCO_3$ solution (10 mL), extracted with DCM (10 mL X 3). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 4-chloro-3-(4, 4-difluoro-2, 2-dimethyl-pyrrolidin-1-yl)-1-(p-tolylsulfonyl) indazole (100 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{20}ClF_2N_3O_2S$ 439.09, m/z found 440.0 $[M+H]^+$.

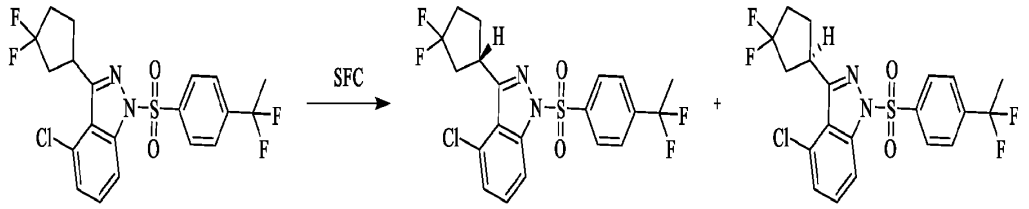
[00591] ***Step 5***: To a solution of 4-chloro-3-(4, 4-difluoro-2, 2-dimethyl-pyrrolidin-1-yl)-1-(p-tolylsulfonyl) indazole (100 mg, 227 μmol, 1 eq) in MeOH (1 mL) was added K_2CO_3 (157 mg, 1.14 mmol, 5 eq). The mixture was stirred at 45 °C for 0.5 hour. LC-MS showed 4-chloro-3-(4, 4-difluoro-2, 2-dimethyl-pyrrolidin-1-yl)-1-(p-tolylsulfonyl) indazole was consumed completely

and the desired mass was detected. The reaction mixture was added to H_2O (10 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired 4-chloro-3-(4, 4-difluoro-2, 2-dimethyl-pyrrolidin-1-yl)-1H-indazole (20 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{14}ClF_2N_3$ 285.08, m/z found 286.1 $[M+H]^+$.

[00592] ***Step 6***: To a solution of 4-(1,1-difluoroethyl) benzenesulfonyl chloride (30.3 mg, 126 μmol, 2 eq) and 4-chloro-3-(4,4-difluoro-2,2-dimethyl-pyrrolidin-1-yl)-1H-indazole (18 mg, 63 μmol, 1 eq) in DCM (2 mL) were added TEA (31.9 mg, 315 μmol, 43.8 μL, 5 eq) and DMAP (770 μg, 6.30 μmol, 0.1 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 4-chloro-3-(4, 4-difluoro-2, 2-dimethyl-pyrrolidin-1-yl)-1H-indazole was consumed completely, and the desired mass was detected. The reaction mixture was added to water (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:55%-85% B over 8.0 min) to give the desired 4-chloro-3-(4, 4-difluoro-2, 2-dimethyl-pyrrolidin-1-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole (8.3 mg, 16.9 μmol, 26.9% yield, 99.83% purity) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.79 (br d, J = 8.2 Hz, 2H), 7.66 (t, J = 8.0 Hz, 1H), 7.49 (d, J = 7.7 Hz, 1H), 3.99 (br t, J = 13.6 Hz, 2H), 2.32 (br t, J = 15.4 Hz, 2H), 1.92 (t, J = 19.1 Hz, 3H), 1.30 (s, 6H). HPLC: 99.83% (220 nm), 99.88% (215 nm), 99.77% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{20}ClF_4N_3O_2S$ 489.09, m/z found 490.0 $[M+H]^+$.

Compound 91:4-Chloro-3-[(1S)-3, 3-difluorocyclopentyl]-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole

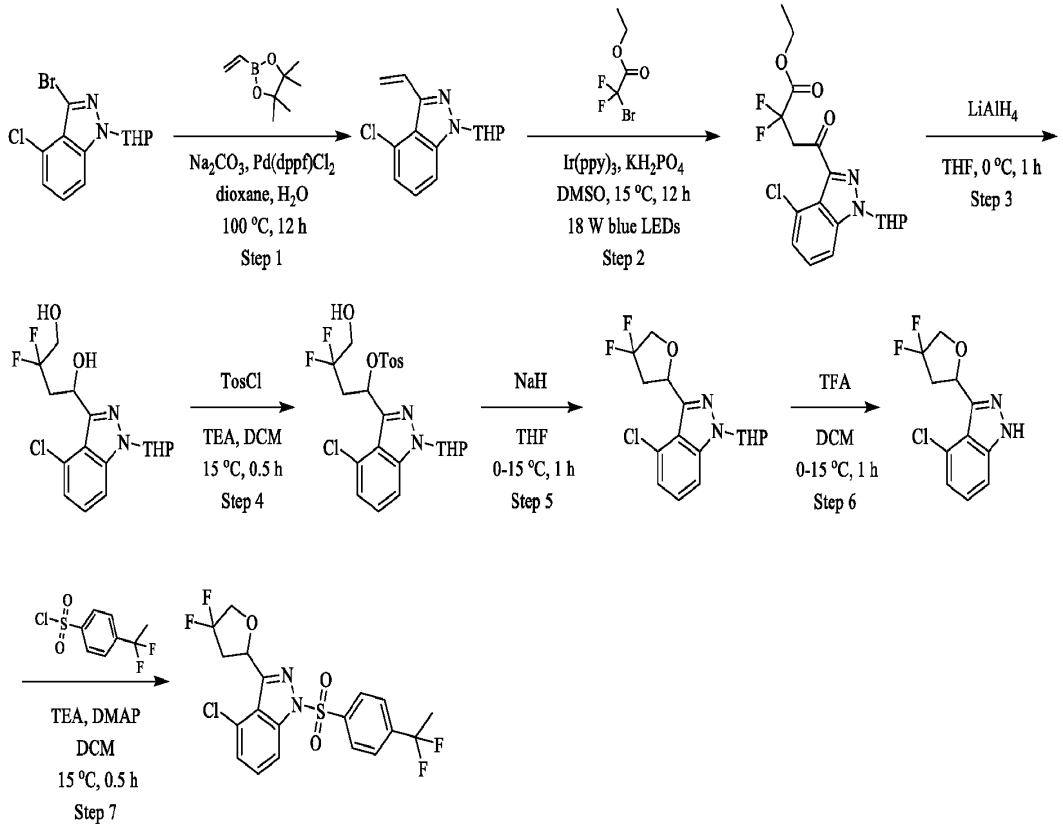
Compound 92:4-Chloro-3-[(1R)-3, 3-difluorocyclopentyl]-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole



[00593] ***Step 1:*** 4-Chloro-3-(3, 3-difluorocyclopentyl)-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole (16 mg, 34.7 μmol) was separated by SFC (column: DAICEL CHIRALPAK IG (250mm*30mm, 10 um); mobile phase: [CO_2-IPA (0.1% NH_3H_2O)]; B%:20%, isocratic elution mode) to give two isomers. The structures were assigned arbitrarily. 4-Chloro-3-[(1S)-3, 3-difluorocyclopentyl]-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole (5.3 mg, 11.3 μmol, 32.5% yield, 98.07% purity, Rt = 0.839 minutes; E.E. by chiral HPLC (%) = 99.52%) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 8.3 Hz, 1H), 8.04 (d, J = 8.6 Hz, 2H), 7.79 (d, J = 8.5 Hz, 2H), 7.67 (t, J = 8.1 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 4.15 - 4.05 (m, 1H), 2.68 - 2.52 (m, 2H), 2.34 (br s, 3H), 2.06 - 1.98 (m, 1H), 1.93 (t, J = 19.1 Hz, 3H). HPLC: 98.07% (220 nm), 98.04% (215 nm), 98.77% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{17}ClF_4N_2O_2S$ 460.06 m/z found 461.0 $[M+H]^+$.

[00594] 4-Chloro-3-[(1R)-3, 3-difluorocyclopentyl]-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole (4.0 mg, 8.67 μmol, 24.98% yield, 99.91% purity, Rt = 1.034 minutes; E.E. by chiral HPLC (%) = 99.44%) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 8.3 Hz, 1H), 8.04 (d, J = 8.3 Hz, 2H), 7.79 (d, J = 8.5 Hz, 2H), 7.68 (t, J = 8.1 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 4.15 - 4.04 (m, 1H), 2.71 - 2.53 (m, 2H), 2.34 (br s, 3H), 2.09 - 1.99 (m, 1H), 1.93 (t, J = 19.1 Hz, 3H). HPLC: 99.91% (220 nm), 100.00% (215 nm), 100.00% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{17}ClF_4N_2O_2S$ 460.06 m/z found 461.0 $[M+H]^+$.

Compound 93:4-Chloro-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(4, 4-difluorotetrahydrofuran-2-yl) indazole



[00595] ***Step 1***: Two reactions were carried out in parallel. The mixture of 3-bromo-4-chloro-1-tetrahydropyran-2-yl-indazole (0.5 g, 1.58 mmol, 1 eq), 4, 4, 5, 5-tetramethyl-2-vinyl-1, 3, 2-dioxaborolane (293 mg, 1.90 mmol, 322 μL, 1.2 eq), Na_2CO_3 (504 mg, 4.75 mmol, 3 eq), $Pd(dppf)Cl_2$ (116 mg, 158 μmol, 0.1 eq) in dioxane (10 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. LC-MS showed 3-bromo-4-chloro-1-tetrahydropyran-2-yl-indazole was consumed completely and the desired mass was detected. Two reactions were combined for workup. The reaction mixture was added to water (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 5/1) to give the desired 4-chloro-1-tetrahydropyran-2-yl-3-vinyl-indazole (490 mg, crude) as a white solid. MS (ESI): mass calcd. For $C_{14}H_{15}ClN_2O$ 262.09, m/z found 263.1 $[M+H]^+$.

[00596] ***Step 2***: Eight reactions were carried out in parallel. A mixture of 4-chloro-1-tetrahydropyran-2-yl-3-vinyl-indazole (50 mg, 190 μmol, 1 eq), ethyl 2-bromo-2,2-difluoro-

acetate (77.3 mg, 381 μmol, 49.1 μL, 2 eq), KH_2PO_4 (51.8 mg, 381 μmol, 22.2 μL, 2 eq), $Ir(ppy)_3$ (2.49 mg, 3.81 μmol, 0.02 eq) in DMSO (2 mL) was degassed and purged with N_2 for 3 times. The mixture was then irradiated by 18 W blue LEDs. Then the mixture was stirred at 15 °C for 12 hours under N_2 atmosphere. LC-MS showed 4-chloro-1-tetrahydropyran-2-yl-3-vinyl-indazole was consumed completely and the desired mass was detected. Eight reactions were combined for workup. The reaction mixture was added to water (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (ssilica gel, petroleum ether / ethyl acetate = 3/1) to give the desired ethyl 4-(4-chloro-1-tetrahydropyran-2-yl-indazol-3-yl)-2, 2-difluoro-4-oxo-butanoate (110 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{18}H_{19}ClF_2N_2O_4$ 400.10, m/z found 401.1 $[M+H]^+$.

[00597] ***Step 3***: To a solution of ethyl 4-(4-chloro-1-tetrahydropyran-2-yl-indazol-3-yl)-2, 2-difluoro-4-oxo-butanoate (110 mg, 274 μmol, 1 eq) in THF (3 mL) was added $LiAlH_4$ (2.5 M, 329 μL, 3 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 1 hour. LC-MS showed ethyl 4-(4-chloro-1-tetrahydropyran-2-yl-indazol-3-yl)-2, 2-difluoro-4-oxo-butanoate was consumed completely, the desired mass was detected. The reaction mixture was quenched by addition of 0.1 mL of H_2O at 0 °C, followed by 0.1 mL of 15% aqueous NaOH and 0.3 mL of H_2O at 0 °C under N_2. After being stirred at room temperature for 0.1 hour, the solid was removed by filtration. The filtrate was concentrated to dryness to give crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 1/1) to give the desired 1-(4-chloro-1-tetrahydropyran-2-yl-indazol-3-yl)-3, 3-difluoro-butane-1, 4-diol (40 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{16}H_{19}ClF_2N_2O_3$ 360.11, m/z found 361.1 $[M+H]^+$.

[00598] ***Step 4***: To a solution of 1-(4-chloro-1-tetrahydropyran-2-yl-indazol-3-yl)-3, 3-difluoro-butane-1, 4-diol (35 mg, 97.01 μmol, 1 eq) in DCM (1 mL) was added 4-methylbenzenesulfonyl chloride (TosCl) (19.4 mg, 102 μmol, 1.05 eq) and TEA (29. 5 mg, 291 μmol, 40.5 μL, 3 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 1-(4-chloro-1-tetrahydropyran-2-yl-indazol-3-yl)-3, 3-difluoro-butane-1, 4-diol was consumed completely and the desired mass was detected. The reaction mixture was added to water (20 mL), extracted with DCM (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired [1-(4-chloro-1-tetrahydropyran-2-yl-indazol-3-yl)-3,3-difluoro-4-hydroxy-butyl] 4-

methylbenzenesulfonate (49 mg, crude) as a yellow solid. MS (ESI): mass calcd. For $C_{23}H_{25}ClF_2N_2O_5S$ 514.11, m/z found 515.1 $[M+H]^+$.

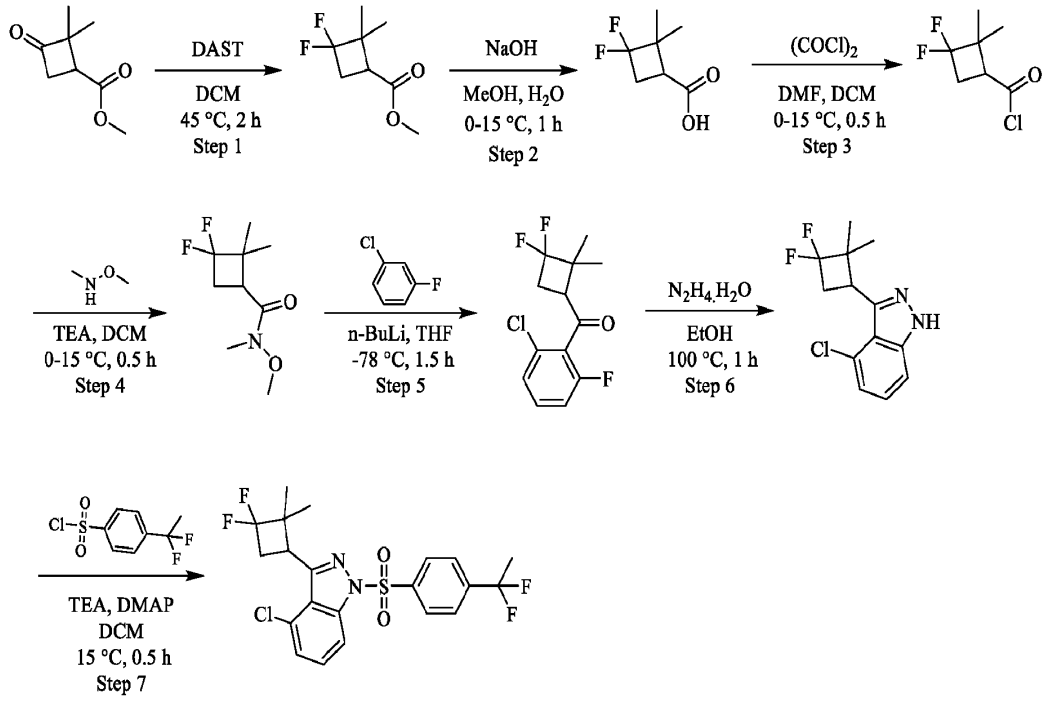
[00599] ***Step 5***: To a solution of [1-(4-chloro-1-tetrahydropyran-2-yl-indazol-3-yl)-3, 3-difluoro-4-hydroxy-butyl] 4-methylbenzenesulfonate (49 mg, 95.2 μmol, 1 eq) in THF (1 mL) was added NaH (9.13 mg, 228 μmol, 60% purity, 2.4 eq) at 0 °C. The mixture was stirred at 15 °C for 1 hour. LC-MS showed [1-(4-chloro-1-tetrahydropyran-2-yl-indazol-3-yl)-3, 3-difluoro-4-hydroxy-butyl] 4-methylbenzenesulfonate was consumed completely and the desired mass was detected. The mixture was cooled to room temperature, poured into HCl (2 mL), and extracted with EtOAc (40 mL). The combined organic layers were washed with brine (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 4-chloro-3-(4, 4-difluorotetrahydrofuran-2-yl)-1-tetrahydropyran-2-yl-indazole (32 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{16}H_{17}ClF_2N_2O_2$ 342.09, m/z found 343.1 $[M+H]^+$.

[00600] ***Step 6***: To a solution of 4-chloro-3-(4, 4-difluorotetrahydrofuran-2-yl)-1-tetrahydropyran-2-yl-indazole (32 mg, 93.4 μmol, 1 eq) in DCM (3 mL) was added TFA (0.3 mL) at 0 °C. The mixture was stirred at 15 °C for 1 hour. LC-MS showed 4-chloro-3-(4, 4-difluorotetrahydrofuran-2-yl)-1-tetrahydropyran-2-yl-indazole was consumed completely and the desired mass was detected. The reaction mixture was added to water (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-(4, 4-difluorotetrahydrofuran-2-yl)-1H-indazole (15 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{11}H_9ClF_2N_2O$ 258.04, m/z found 259.1 $[M+H]^+$.

[00601] ***Step 7***: To a solution of 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (27.9 mg, 116 μmol, 2 eq) and 4-chloro-3-(4, 4-difluorotetrahydrofuran-2-yl)-1H-indazole (15 mg, 58.0 μmol, 1 eq) in DCM (1 mL) were added TEA (29.3 mg, 290 μmol, 40.4 μL, 5 eq) and DMAP (709 μg, 5.80 μmol, 0.1 eq). The mixture was stirred at 15 °C for 0.5 hr. LC-MS showed 4-chloro-3-(4, 4-difluorotetrahydrofuran-2-yl)-1H-indazole was consumed completely, and the desired mass was detected. The reaction mixture was added to water (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase:

[H_2O (0.1%TFA)-ACN]; gradient:50%-80% B over 8.0 min) to give the desired 4-chloro-1- [4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(4, 4-difluorotetrahydrofuran-2-yl) indazole (10.3 mg, 22.1 μmol, 38.1% yield, 99.21% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.72 (t, J = 8.1 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 5.95 (t, J = 7.2 Hz, 1H), 4.14 - 3.90 (m, 2H), 3.15 - 2.87 (m, 2H), 1.95 (t, J = 19.1 Hz, 3H); HPLC: 99.21% (220 nm), 99.48% (215 nm), 99.49% (254 nm). MS (ESI): mass calcd. For $C_{19}H_{15}ClF_4N_2O_3S$ 462.04, m/z found 463.0 $[M+H]^+$.

Compound 94:4-Chloro-3-(3, 3-difluoro-2, 2-dimethyl-cyclobutyl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole



[00602] ***Step 1***: The mixture of methyl 2, 2-dimethyl-3-oxo-cyclobutanecarboxylate (0.5 g, 3.20 mmol, 1 eq) in DAST (4 mL) was stirred at 45 °C for 2 hours. TLC (petroleum ether / ethyl acetate = 3/1) indicated methyl 2, 2-dimethyl-3-oxo-cyclobutanecarboxylate was consumed completely and one new spot was formed. The reaction mixture was added to sat. $NaHCO_3$ aq. (20 mL), extracted with DCM (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give

the desired methyl 3, 3-difluoro-2, 2-dimethyl-cyclobutanecarboxylate (0.5 g, crude) as a yellow oil.

[00603] ***Step 2***: To a solution of methyl 3, 3-difluoro-2, 2-dimethyl-cyclobutanecarboxylate (0.5 g, 2.81 mmol, 1 eq) in MeOH (4 mL) and H_2O (1 mL) was added NaOH (337 mg, 8.42 mmol, 3 eq) at 0 °C. The mixture was stirred at 15 °C for 1 hour. TLC (petroleum ether / ethyl acetate = 3/1) indicated 3, 3-difluoro-2, 2-dimethyl-cyclobutanecarboxylate was consumed completely and one new spot was formed. The reaction mixture was added to HCl (50 mL, 1 M), extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 3, 3-difluoro-2, 2-dimethyl-cyclobutanecarboxylic acid (0.4 g, crude) as a yellow oil.

[00604] ***Step 3***: To a solution of 3, 3-difluoro-2, 2-dimethyl-cyclobutanecarboxylic acid (370 mg, 2.25 mmol, 1 eq) in DCM (4 mL) and DMF (16.5 mg, 225 μmol, 17.3 μL, 0.1 eq) was added $(COCl)_2$ (315 mg, 2.48 mmol, 217 μL, 1.1 eq) at 0 °C. The mixture was stirred at 15 °C for 0.5 hour. TLC (petroleum ether / ethyl acetate = 3/1) indicated 3, 3-difluoro-2, 2-dimethyl-cyclobutanecarboxylic acid was consumed completely and one new spot was formed. The reaction mixture was concentrated to give the desired 3, 3-difluoro-2, 2-dimethyl-cyclobutanecarbonyl chloride (410 mg, crude) as a yellow oil.

[00605] ***Step 4***: To a solution of 3, 3-difluoro-2, 2-dimethyl-cyclobutanecarbonyl chloride (410 mg, 2.25 mmol, 1 eq) in DCM (5 mL) were added TEA (1.14 g, 11.2 mmol, 1.56 mL, 5 eq) and N-methoxymethanamine hydrochloride (602 mg, 4.49 mmol, 2 eq, HCl) at 0 °C. The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 3, 3-difluoro-2, 2-dimethyl-cyclobutanecarbonyl chloride was consumed completely and the desired mass was detected. The reaction mixture was added to water (50 mL), extracted with DCM (30 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% ethyl acetate / petroleum ether gradient @ 80 mL/min) to give the desired 3, 3-difluoro-N-methoxy-N, 2, 2-trimethyl-cyclobutanecarboxamide (320 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_9H_{15}F_2NO_2$ 207.11, m/z found 208.2 $[M+H]^+$.

[00606] ***Step 5***: To a solution of 3, 3-difluoro-N-methoxy-N, 2, 2-trimethyl-cyclobutanecarboxamide (270 mg, 1.30 mmol, 1 eq) in THF (5 mL) was added *n*-BuLi (2.5 M,

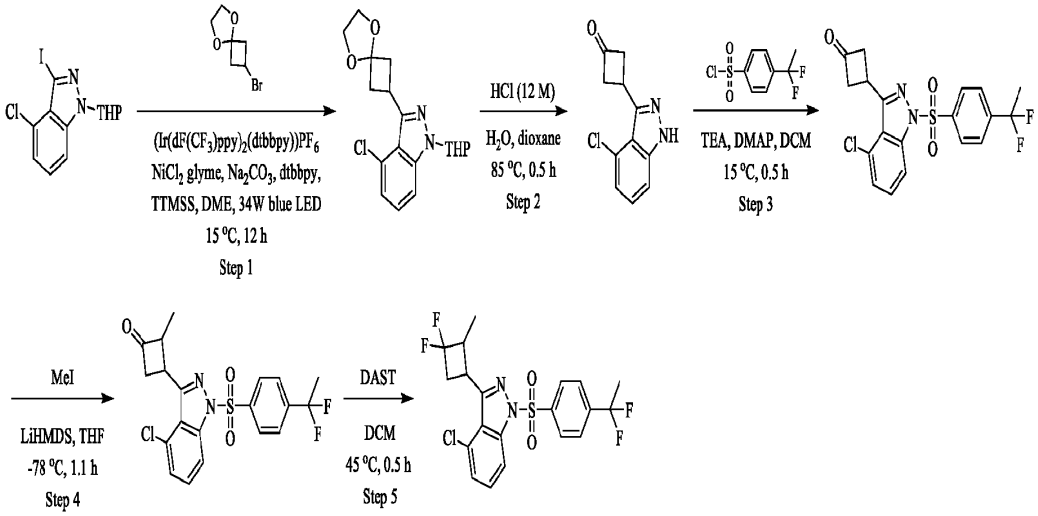
834 μL, 1.6 eq) at -78 °C under N_2. The mixture was stirred at -78 °C for 0.5 hour. 1-chloro-3-fluoro-benzene (272 mg, 2.08 mmol, 223 μL, 1.6 eq) in THF (5 mL) was added to the mixture at -78 °C. The mixture was stirred at -78 °C for 1 hour. TLC (petroleum ether / ethyl acetate = 10/1) indicated 3, 3-difluoro-N-methoxy-N, 2, 2-trimethyl-cyclobutanecarboxamide was consumed completely and one new spot formed. The reaction mixture was quenched by addition HCl (20 mL, 1 M) at 0 °C, and extracted with EtOAc (30 mL X 3). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by *prep*-TLC (silica gel, petroleum ether/Ethyl acetate = 10/1) to give the desired (2-chloro-6-fluoro-phenyl) -(3, 3-difluoro-2, 2-dimethyl-cyclobutyl) methanone (110 mg, crude) as a yellow oil.

[00607] ***Step 6***: To a solution of (2-chloro-6-fluoro-phenyl) -(3, 3-difluoro-2, 2-dimethyl-cyclobutyl) methanone (110 mg, 398 μmol, 1 eq) in EtOH (2 mL) was added $NH_2NH_2.H_2O$ (1.08 g, 21.6 mmol, 1.05 mL, 54.3 eq). The mixture was stirred at 100 °C for 1 hour. LC-MS showed (2-chloro-6-fluoro-phenyl) -(3, 3-difluoro-2, 2-dimethyl-cyclobutyl) methanone was consumed completely and the desired mass was detected. The reaction mixture was diluted with H_2O (30 ml) and extracted with EtOAc (20 mL X 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired 4-chloro-3-(3, 3-difluoro-2, 2-dimethyl-cyclobutyl)-1H-indazole (20 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{13}ClF_2N_2$ 270.07, m/z found 271.1 $[M+H]^+$.

[00608] ***Step 7***: To a solution of 4-(1,1-difluoroethyl) benzenesulfonyl chloride (35.6 mg, 148 μmol, 2 eq) and 4-chloro-3-(3,3-difluoro-2,2-dimethyl-cyclobutyl)-1H-indazole (20 mg, 73.9 μmol, 1 eq) in DCM (1 mL) were added TEA (37.4 mg, 369 μmol, 51.4 μL, 5 eq) and DMAP (903 μg, 7.39 μmol, 0.1 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 4-chloro-3-(3, 3-difluoro-2, 2-dimethyl-cyclobutyl)-1H-indazole was consumed completely, and the desired mass was detected. The reaction mixture was added to water (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm * 3 μm; mobile phase: [H_2O(0.1%TFA)-ACN]; gradient:60%-90% B over 8.0 min) to give the desired 4-chloro-3-(3, 3-difluoro-2, 2-dimethyl-cyclobutyl)-1-[4-(1, 1-difluoroethyl) phenyl]

sulfonyl-indazole (9.0 mg, 18.2 μmol, 24.6% yield, 95.99% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 8.5 Hz, 1H), 8.03 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 7.70 (t, J = 8.1 Hz, 1H), 7.53 (d, J = 7.3 Hz, 1H), 3.97 - 3.87 (m, 1H), 3.30 (br d, J = 7.4 Hz, 1H), 3.00 - 2.85 (m, 1H), 1.91 (t, J = 19.1 Hz, 3H), 1.33 (d, J = 1.1 Hz, 3H), 0.33 (s, 3H). HPLC: 95.99% (220 nm), 96.99% (215 nm), 96.87% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{19}ClF_4N_2O_2S$ 474.08, m/z found 475.0 $[M+H]^+$.

Compound 95: 4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-3-(3, 3-difluoro-2-methyl-cyclobutyl) indazole



[00609] ***Step 1***: Nine reactions were carried out in parallel. A mixture of 4-chloro-3-iodo-1-tetrahydropyran-2-yl-indazole (200 mg, 552 μmol, 1 eq), 2-bromo-5,8-dioxaspiro[3.4]octane (106 mg, 552 μmol, 1 eq), bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridyl]phenyl]iridium(1+);4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine;hexafluorophosphate (6.19 mg, 5.52 μmol, 0.01 eq), dibromonickel;1,2-dimethoxyethane (851 μg, 2.76 μmol, 0.005 eq) and 4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine (740 μg, 2.76 μmol, 0.005 eq) Na_2CO_3 (117 mg, 1.10 mmol, 2 eq) bis(trimethylsilyl)silyl-trimethyl-silane (137 mg, 552 μmol, 170 μL, 1 eq) in DME (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 15 °C for 12 hours under N_2 atmosphere. The mixture was then irradiated by 34 W blue LEDs. Then the mixture was stirred at 15 °C for 12 hours under N_2 atmosphere. LC-MS showed 4-chloro-3-iodo-1-tetrahydropyran-2-yl-indazole was consumed completely and the desired mass was detected. Nine reactions were combined for workup. The reaction mixture was added to

water (500 mL), extracted with EtOAc (100 mL X 3). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 4-chloro-3-(5, 8-dioxaspiro [3.4] octan-2-yl)-1-tetrahydropyran-2-yl-indazole (140 mg, crude) as a white solid. MS (ESI): mass calcd. For $C_{18}H_{21}ClN_2O_3$ 348.12, m/z found 349.1 $[M+H]^+$.

[00610] ***Step 2***: To a solution of 4-chloro-3-(5, 8-dioxaspiro [3.4] octan-2-yl)-1-tetrahydropyran-2-yl-indazole (140 mg, 401 μmol, 1 eq) in dioxane (2 mL) and H_2O (0.5 mL) was added HCl (12 M, 418 μL, 12.5 eq). The mixture was stirred at 85 °C for 0.5 hour. LC-MS showed 4-chloro-3-(5, 8-dioxaspiro [3.4] octan-2-yl)-1-tetrahydropyran-2-yl-indazole was consumed completely and the desired mass was detected. The reaction mixture was added to NaOH (2 M) until pH~7, extracted with DCM (5 mL X 3). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired 3-(4-chloro-1H-indazol-3-yl) cyclobutanone (110 mg, crude) as a pink solid. MS (ESI): mass calcd. For $C_{11}H_9ClN_2O$ 220.04, m/z found 221.0 $[M+H]^+$.

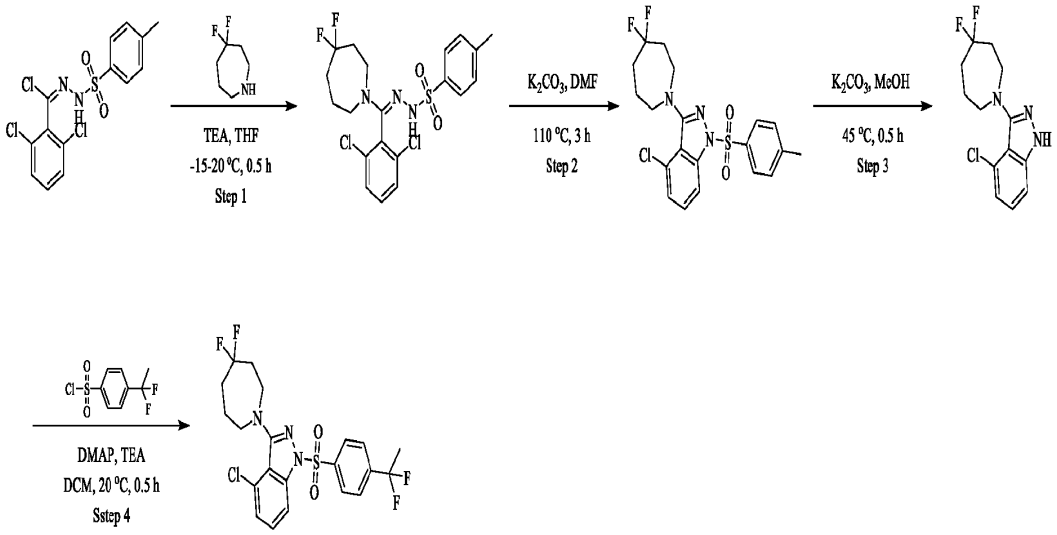
[00611] ***Step 3***: To a solution of 4-(1,1-difluoroethyl) benzenesulfonyl chloride (240 mg, 997 μmol, 2 eq) and 3-(4-chloro-1H-indazol-3-yl) cyclobutanone (110 mg, 499 μmol, 1 eq) in DCM (3 mL) were added TEA (252 mg, 2.49 mmol, 347 μL, 5 eq) and DMAP (6.09 mg, 49.9 μmol, 0.1 eq). The mixture was stirred at 15 °C for 0.5 hour. LC-MS showed 3-(4-chloro-1H-indazol-3-yl) cyclobutanone was consumed completely, and the desired mass was detected. The reaction mixture was added to water (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1) to give the desired 3-[4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazol-3-yl] cyclobutanone (90 mg, crude) as a white solid. MS (ESI): mass calcd. For $C_{19}H_{15}ClF_2N_2O_3S$ 424.05, m/z found 425.2 $[M+H]^+$.

[00612] ***Step 4***: Two reactions were carried out in parallel. To a solution of 3-[4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazol-3-yl] cyclobutanone (60 mg, 141 μmol, 1 eq) in THF (3 mL) was added LiHMDS (1 M, 169 μL, 1.2 eq) at -78 °C under N_2. The mixture was stirred at -78 °C for 0.5 hour. TMEDA (19.7 mg, 169 μmol, 25.6 μL, 1.2 eq) was added to the mixture at -78 °C. The mixture was stirred at -78 °C for 0.1 hour. Then MeI (80.2 mg, 565 μmol,

35.2 μL, 4 eq) was added to the mixture at -78 °C. The mixture was stirred at -78 °C for 0.5 hour. LC-MS showed 3-[4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazol-3-yl] cyclobutanone was consumed completely and the desired mass was detected. Two reactions were combined for workup. The reaction mixture was quenched by addition saturated aqueous HCl (5 mL, 1 M) at 0 °C slowly under N_2 and stirred at 25 °C for 5 minutes. Then THF was removed under vacuum. The resulting solution was extracted with EtOAc (10 mL X 3). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 2/1). Then the residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75*30mm*3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:50%-70% B over 8.0 min) to give the desired 3-[4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazol-3-yl]-2-methyl-cyclobutanone (40 mg, 91.1 μmol, 32.3% yield) as a white solid. MS (ESI): mass calcd. For $C_{20}H_{17}ClF_2N_2O_3S$ 438.06, m/z found 439.1 $[M+H]^+$.

[00613] ***Step 5:*** To a solution of 3-[4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazol-3-yl]-2-methyl-cyclobutanone (10 mg, 22.8 μmol, 1 eq) in DCM (0.5 mL) was added DAST (184 mg, 1.14 mmol, 151 μL, 50 eq). The mixture was stirred at 45 °C for 0.5 hour. LC-MS showed 3-[4-chloro-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazol-3-yl]-2-methyl-cyclobutanone was consumed completely, and the desired mass was detected. The reaction mixture was added to water (20 mL), extracted with EtOAc (10 mL X 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (TFA condition; column: Phenomenex Luna C18 75 * 30 mm *3 μm; mobile phase: [H_2O (0.1%TFA)-ACN]; gradient:65%-90% B over 8.0 min) to give the desired 4-chloro-1-[4-(1,1-difluoroethyl) phenyl] sulfonyl-3-(3,3-difluoro-2-methyl-cyclobutyl) indazole (3.0 mg, 6.49 μmol, 28.5% yield, 99.75% purity) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.6 Hz, 2H), 7.74 (t, J = 8.1 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 3.65 (q, J = 8.6 Hz, 1H), 3.39 - 3.30 (m, 1H), 3.15 - 3.03 (m, 1H), 2.93 - 2.79 (m, 1H), 1.99 (t, J = 19.2 Hz, 3H), 1.25 (d, J = 7.0 Hz, 3H). HPLC: 99.75% (220 nm), 99.83% (215 nm), 99.91% (254 nm). MS (ESI): mass calcd. For $C_{20}H_{17}ClF_4N_2O_2S$ 460.06, m/z found 461.0 $[M+H]^+$.

Compound 96: 4-chloro-3-(4, 4-difluoroazepan-1-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole



[00614] ***Step 1***: To the solution of (1E)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride (330 mg, 874 μmol, 1.5 eq) and TEA (590 mg, 5.83 mmol, 811 μL, 10 eq) in THF (1 mL) was added 4, 4-difluoroazepane (100 mg, 583 μmol, 1 eq, HCl) at -15 °C and the solution was stirred at 20 °C for 0.5 hour. LCMS showed (1E)-2, 6-dichloro-N-(p-tolylsulfonyl) benzohydrazonoyl chloride was consumed completely and the desired mass was detected. The reaction was concentrated under reduced pressure to give the desired N-[(E)-[(2, 6-dichlorophenyl)-(4, 4-difluoroazepan-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (270 mg, crude) as a yellow oil. MS (ESI): mass calcd. For $C_{20}H_{21}N_3SO_2Cl_2F_2$ 475.07 m/z found 476.1$[M+H]^+$.

[00615] ***Step 2:*** To a solution of N-[(E)-[(2, 6-dichlorophenyl)-(4, 4-difluoroazepan-1-yl) methylene] amino]-4-methyl-benzenesulfonamide (270 mg, 567 μmol, 1 eq) in DMF (5 mL) was added K_2CO_3 (1.57 g, 11.3 mmol, 20 eq). The mixture was stirred at 110 °C for 3 hours. LC-MS showed N-[(E)-[(2, 6-dichlorophenyl)-(4, 4-difluoroazepan-1-yl) methylene] amino]-4-methyl-benzenesulfonamide remained. Several new peaks were shown on LC-MS and the desired compound was detected. The reaction was cooled to 25 °C and poured in ice-water (30 mL). The mixture was extracted with MTBE (3 X 10 mL). The combined organics were concentrated to give the desired 4-chloro-3-(4, 4-difluoroazepan-1-yl)-1-(p-tolylsulfonyl) indazole (250 mg,

crude) as a brown oil. MS (ESI): mass calcd. For $C_{20}H_{20}N_3SO_2ClF_2$ 439.09 m/z found 440.1$[M+H]^+$.

[00616] ***Step 3:*** To a solution of 4-chloro-3-(4, 4-difluoroazepan-1-yl)-1-(p-tolylsulfonyl) indazole (250 mg, 568 μmol, 1 eq) in MeOH (5 mL) was added K_2CO_3 (393 mg, 2.84 mmol, 5 eq). The mixture was stirred at 45 °C for 0.5 hour. LC-MS showed 4-chloro-3-(4, 4-difluoroazepan-1-yl)-1-(p-tolylsulfonyl) indazole was consumed completely and one main peak with the desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. Then it was partitioned between 5 mL of water and 15 mL of ethyl acetate. The organic phase was separated, washed with 5 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired 4-chloro-3-(4, 4-difluoroazepan-1-yl)-1H-indazole (77 mg, 269 μmol, 47.4% yield) as a yellow oil. MS (ESI): mass calcd. For $C_{13}H_{14}N_3ClF_2$ 285.08 m/z found 286.1$[M+H]^+$.

[00617] ***Step 4:*** To a solution of 4-chloro-3-(4, 4-difluoroazepan-1-yl)-1H-indazole (67 mg, 235 μmol, 1 eq), 4-(1, 1-difluoroethyl) benzenesulfonyl chloride (84.7 mg, 352 μmol, 1.5 eq) and TEA (71.2 mg, 703 μmol, 97.9 μL, 3 eq) in DCM (2 mL) was added DMAP (28.7 mg, 235 μmol, 1 eq). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed 4-chloro-3-(4, 4-difluoroazepan-1-yl)-1H-indazole remained and one main peak with the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (silica gel, petroleum ether / ethyl acetate = 3/1) to give the desired 4-chloro-3-(4, 4-difluoroazepan-1-yl)-1-[4-(1, 1-difluoroethyl) phenyl] sulfonyl-indazole (44 mg, 84.4 μmol, 36.0% yield, 93.98% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.5 Hz, 2H), 7.63 (t, J = 8.1 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 3.45 (br d, J = 6.6 Hz, 4H), 2.38 - 2.13 (m, 4H), 1.92 (t, J = 19.1 Hz, 3H), 1.84 - 1.77 (m, 2H). HPLC: 94.37% (220 nm), 94.59% (215 nm), 93.98% (254 nm). MS (ESI): mass calcd. For $C_{21}H_{20}N_3F_4SO_2Cl$ 489.09 m/z found 490.1$[M+H]^+$.

Biological Assays

Lysosomal Ca^{2+} imaging

[00618] GCaMP3-ML1 expression was induced in Tet-On HEK-GCaMP3-ML1 cells 20-24 h prior to experiments using 0.01 μg/mL doxycycline. GCaMP3-ML1 fluorescence was monitored at an excitation wavelength of 470 nm (F_{470}) using an EasyRatio Pro system (PTI). Cells were bathed in Tyrode's solution containing 145 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM Glucose, and 20 mM Hepes (pH 7.4). Lysosomal Ca^{2+} release was measured in a zero Ca^{2+} solution containing 145 mM NaCl, 5 mM KCl, 3 mM $MgCl_2$, 10 mM glucose, 1 mM EGTA, and 20 mM HEPES (pH 7.4). Ca^{2+} concentration in the nominally free Ca^{2+} solution is estimated to be 1–10 μM. With 1 mM EGTA, the free Ca^{2+} concentration is estimated to be < 10 nM based on the Maxchelator software (http://maxchelator.stanford.edu/). Experiments were carried out 0.5 to 6 hrs after plating.

[00619] The EC_{50} data for some of compounds are less than 10 uM.

TFEB nuclear translocation assay

[00620] TFEB is a transcription factor and master regulator of lysosome biogenesis and autophagy. TFEB activation is shown to induce cellular clearance in a variety of LSDs and common neurodegenerative diseases. Hence TFEB activity can be used to evaluate the cellular efficacy of TRPML agonists.

Intracellular TFEB localization is determined either by immunofluorescence in Hela cells or by fluorescent microscopy in Hela cells stably expressing TFEB-GFP. Detailed procedures are as follows.

[00621] Cells grown on cover slips were treated with TRPML1 agonist(s) or antagonist(s) for indicated time period and then fixed with 4% paraformaldehyde for 15 minutes at room temperature. For immunofluorescent detection of endogenous TFEB, cells were permeabilized with 0.3% Triton X-100, blocked with 1% bovine serum albumin (BSA) in phosphate buffered saline (PBS) and then immunostained with anti-TFEB antibody (1:200; Cell Signaling Technology) at 4°C for overnight. The stained cells were then incubated with secondary antibodies conjugated to Alexa Fluor 568 or 488 (ThermoFisher) for 1 h, then 4',6-diamidino-2-phenylindole (DAPI) for 15 min (to stain the cell nucleus) and mounted on glass slides with Fluoromount-G (Southern Biotech) for observation. Images were acquired with a Spinning-Disk Confocal microscope (Olympus) and Metamorph software (Molecular Devices).

[00622] Average ratios of nuclear versus cytosolic TFEB fluorescence intensity (>50 randomly-selected cells per experiment) were determined with ImageJ software (NIH).

[00623] Exemplary data of TFEB nuclear translocation assay are provided in **Table 2**.

[00624] Applicant's disclosure is described herein in preferred embodiments with reference to the Figures, in which like numbers represent the same or similar elements. Reference throughout this specification to "one embodiment," "an embodiment," or similar language means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, appearances of the phrases "in one embodiment," "in an embodiment," and similar language throughout this specification may, but do not necessarily, all refer to the same embodiment.

[00625] The described features, structures, or characteristics of Applicant's disclosure may be combined in any suitable manner in one or more embodiments. In the description, herein, numerous specific details are recited to provide a thorough understanding of embodiments of the invention. One skilled in the relevant art will recognize, however, that Applicant's composition and/or method may be practiced without one or more of the specific details, or with other methods, components, materials, and so forth. In other instances, well-known structures, materials, or operations are not shown or described in detail to avoid obscuring aspects of the disclosure.

[00626] Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Methods recited herein may be carried out in any order that is logically possible, in addition to a particular order disclosed.

Incorporation by Reference

[00627] References and citations to other documents, such as patents, patent applications, patent publications, journals, books, papers, web contents, have been made in this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes. Any material, or portion thereof, that is said to be incorporated by reference herein, but which conflicts with existing definitions, statements, or other disclosure material explicitly set forth herein is only incorporated to the extent that no conflict arises between that incorporated material and the present disclosure material. In the event of a conflict, the conflict is to be resolved in favor of the present disclosure as the preferred disclosure.

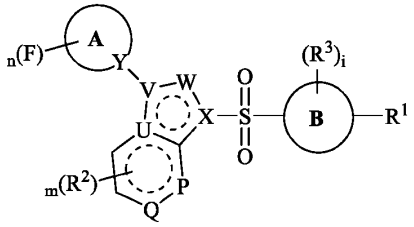
Equivalents

[00628] The representative examples are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples and the references to the scientific and patent literature included herein. The examples contain important additional information, exemplification and guidance that can be adapted to the practice of this invention in its various embodiments and equivalents thereof.

What is claimed:

CLAIMS

1. A compound having the structure of formula (**I**):



(**I**)

or a pharmaceutically acceptable form or an isotope derivative thereof,

wherein

Ring A is a 4- to 9-membered carbocycle or heterocycle substituted with 1-8 F's;

Ring B is a substituted or unsubstituted phenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, or thiophene, or a substituted or unsubstituted bi- or multi-cyclic carbocyclic or heterocyclic ring system;

P is CH, N or CR^2;

Q is CH, N or CR^2;

U is C or N;

V is C or N;

W is CH, N, C(=O), C(=S) or $CR^{W1}R^{W2}$, wherein each of R^{W1} and R^{W2} is independently H or C_{1-6} alkyl;

X is C or N;

Y is C, CR^Y or N, wherein R^Y is H, F or C_{1-6} alkyl;

R^1 is selected from the group consisting of F, CHF_2, $-CF_3$, $-CH_2CF_3$, CF_2CH_3, CF_2CH_2F, CF_2CHF_2, $-CF(CH_3)_2$, $-OCF_3$ and $-OCH(CH_3)_2$;

each R^2 is independently selected from the group consisting of halogen, unsubstituted or substituted C_{1-6} alkyl and C_{1-6} alkoxy, OH, CN, NRR', N(R)C(=O)RR', C(=O)R, and C(=O)NRR';

each R^3 is independently selected from the group consisting of halogen, CN, CF_3, C_{1-5} alkyl, C_{3-7} cycloalkyl and heterocyclic;

each of R and R' is independently H, or C_{1-6} alkyl or cycloalkyl, optionally, R and R', together with the nitrogen or carbon atom to which they are attached, form a 3- to 6-membered ring, each optionally substituted with 0-3 substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, OH, OC_{1-3} alkyl, and CN;

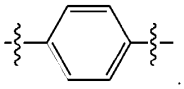
m is 0, 1, 2, 3 or 4;

n is 1, 2, 3, 4, 5, 6, 7 or 8; and

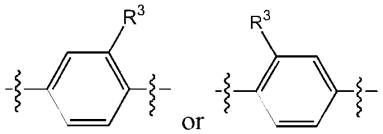
i is 0, 1 or 2.

2. The compound of claim 1, wherein Ring B is a substituted or unsubstituted phenyl.

3. The compound of claim 1, wherein *i* is 0 and Ring B is unsubstituted phenyl:



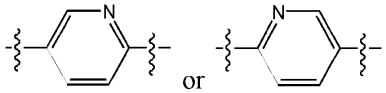
4. The compound of claim 1, wherein *i* is 0 and Ring B is a substituted phenyl:



wherein R^3 is a halogen.

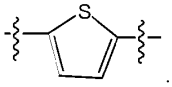
5. The compound of claim 4, wherein R^3 is F.

6. The compound of claim 1, wherein Ring B is an unsubstituted pyridinyl:



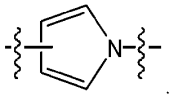
7. The compound of claim 1, wherein Ring B is a substituted or unsubstituted thiophene.

8. The compound of claim 7, wherein *i* is 0 and Ring B is unsubstituted thiophene:



9. The compound of claim 1, wherein Ring B is a substituted or unsubstituted pyrrole.

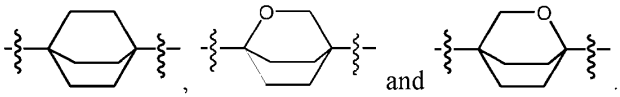
10. The compound of claim 9, wherein *i* is 0 and Ring B is unsubstituted pyrrole:



11. The compound of claim 1, wherein Ring B is bicyclo[1.1.1]pentane:



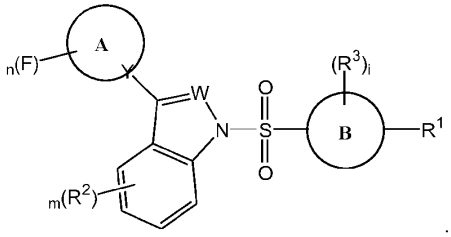
12. The compound of claim 1, wherein Ring B is selected from:



and

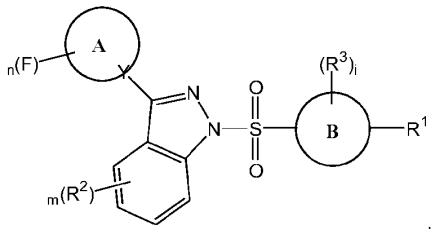
13. The compound of any one of claims 1-12, wherein X is N.

14. The compound of claim 13, wherein P is CH, Q is CH, U is C and V is C:



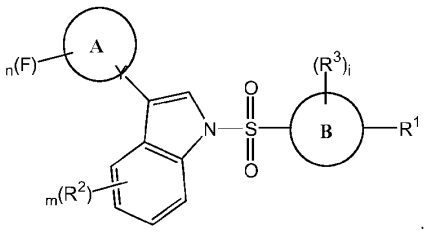
(I_a)

15. The compound of claim 14, wherein W is N:



(I_b)

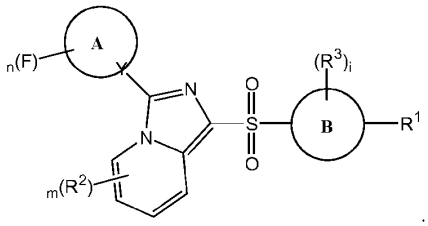
16. The compound of claim 14, wherein W is CH:



(I_c)

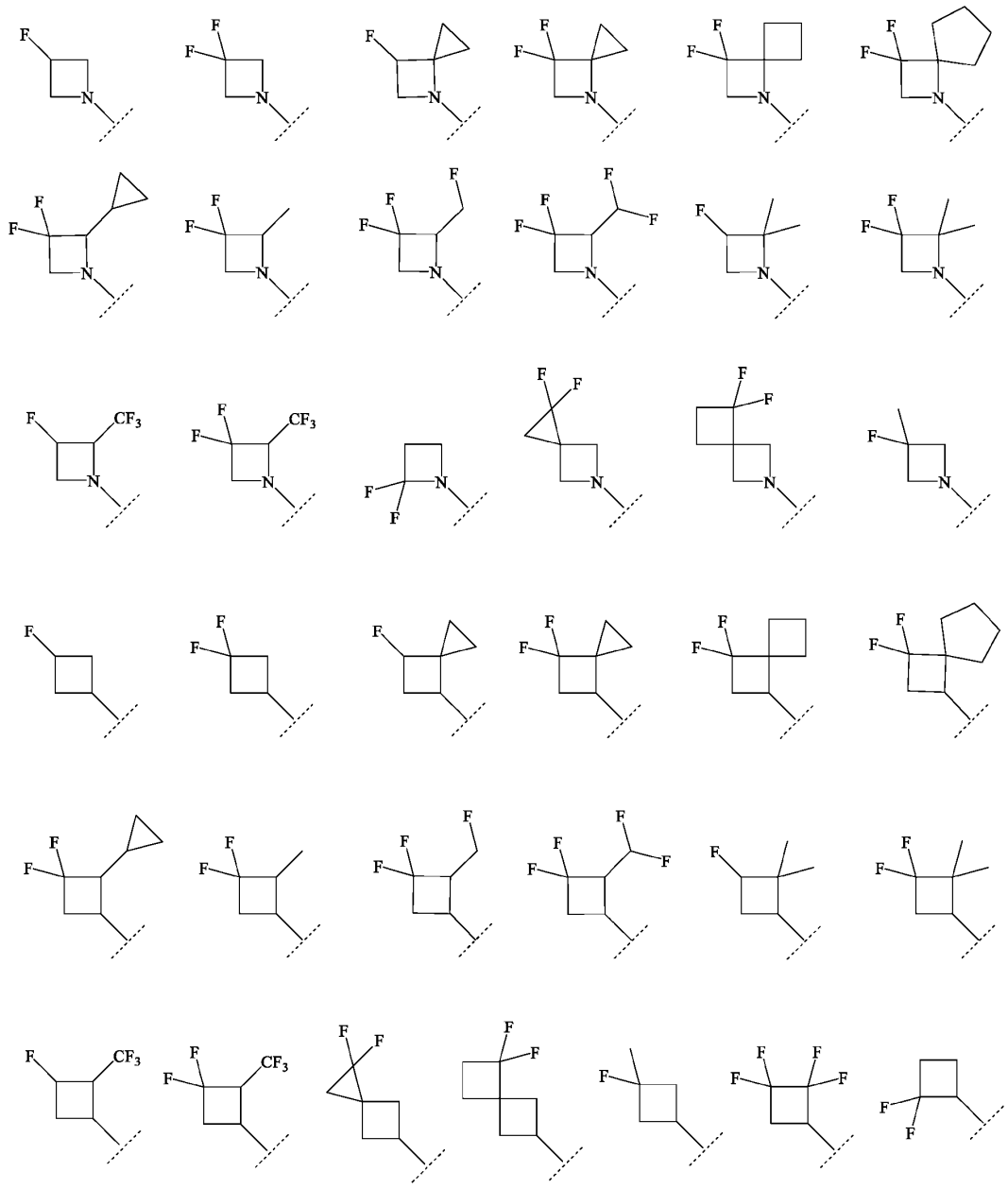
17. The compound of any one of claims 1-12, wherein X is C.

18. The compound of claim 17, wherein P is CH, Q is CH, U is N, V is C and W is N:

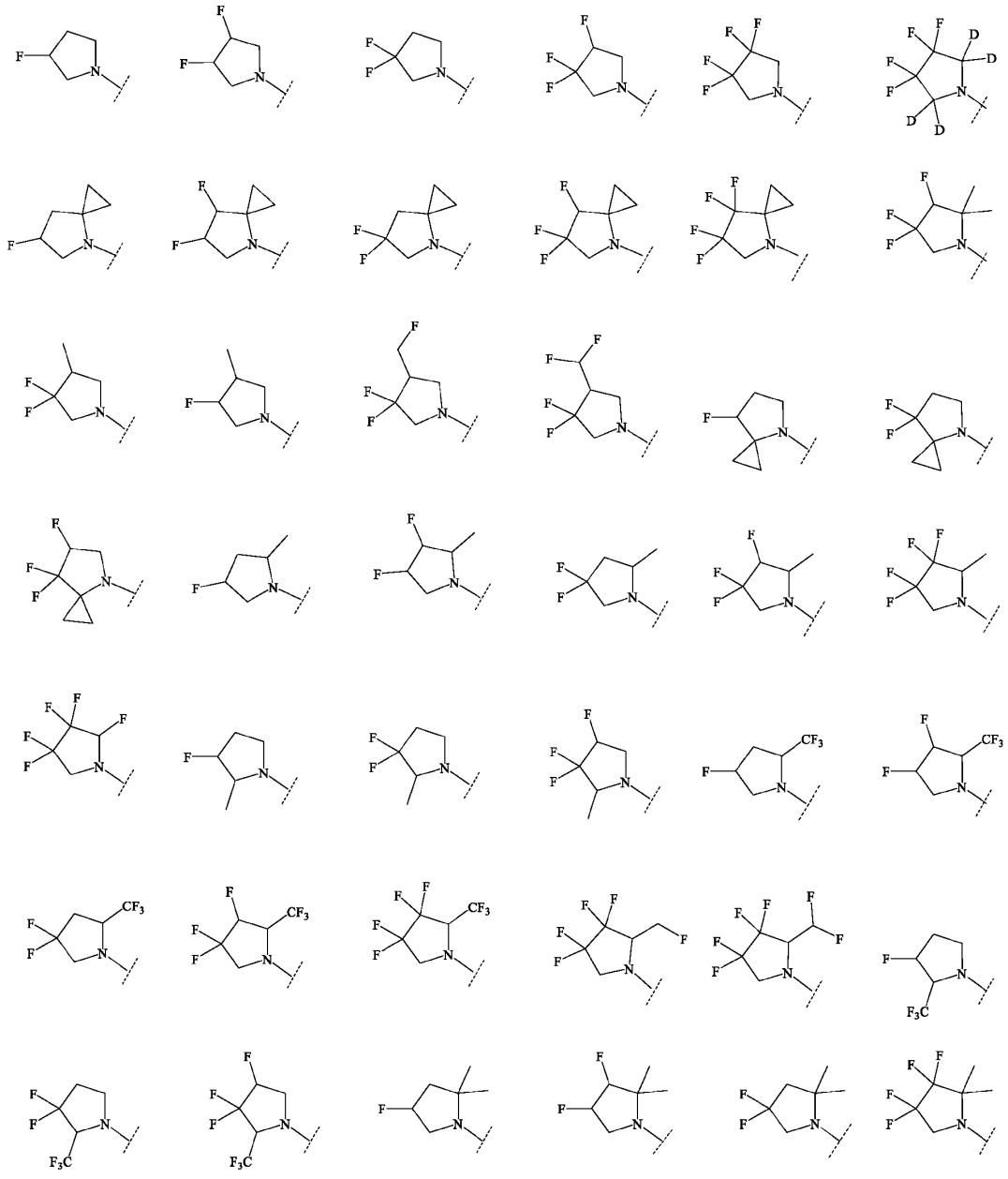


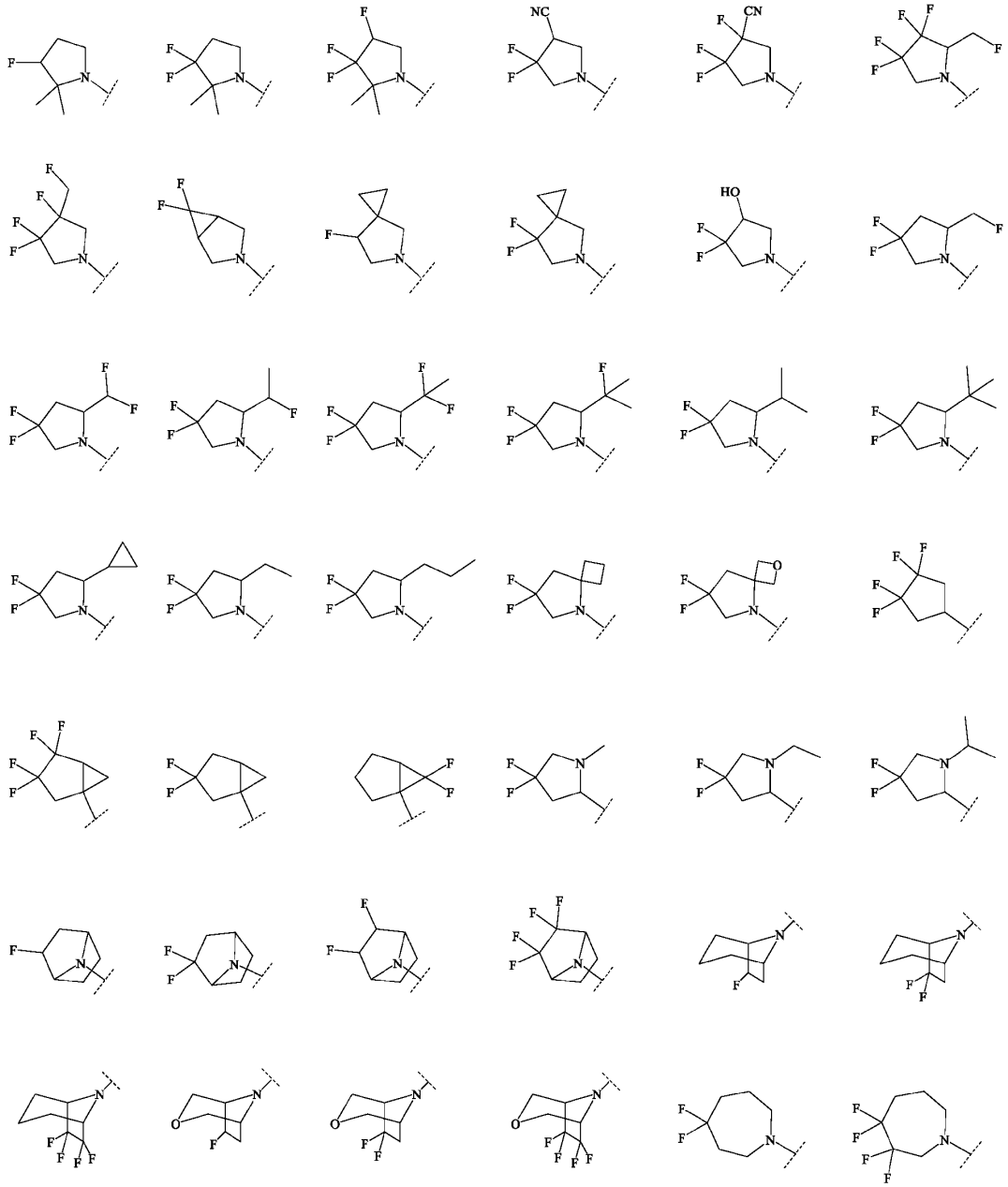
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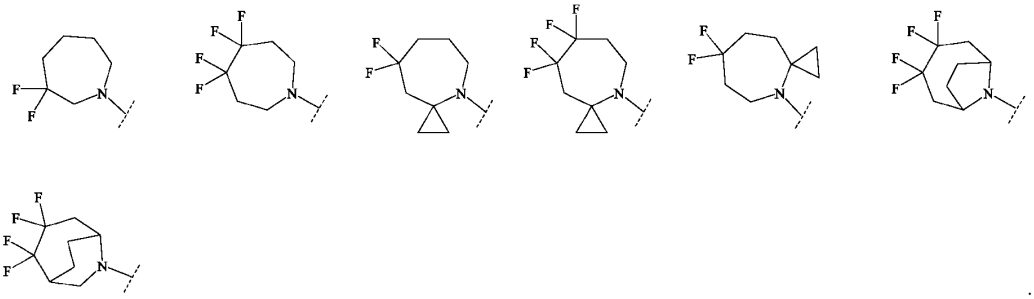
19. The compound of any one of claims 1-18, wherein Y is N.
20. The compound of any one of claims 1-18, wherein Y is C.
21. The compound of any one of claims 1-18, wherein Y is CH.
22. The compound of any one of claims 1-21, wherein Ring A is a 4-membered carbocyclic or heterocycle substituted with one or more F's.
23. The compound of any one of claims 1-21, wherein Ring A is a 5-membered carbocyclic or heterocycle substituted with one or more F's.
24. The compound of any one of claims 1-21, wherein Ring A is a 6-membered carbocyclic or heterocycle substituted with one or more F's.
25. The compound of any one of claims 1-21, wherein Ring A is a heterobicycle substituted with one or more F's.
26. The compound of any one of claims 22-25, wherein Ring A is substituted with two or more F's.
27. The compound of any one of claims 1-21, wherein Ring A has a structural formula selected from:



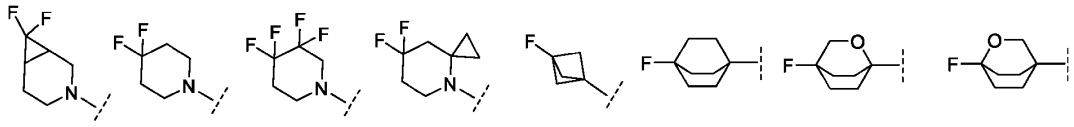
28. The compound of any one of claims 1-21, wherein Ring A has a structural formula selected from:



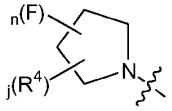




29. The compound of any one of claims 1-21, wherein Ring A has a structural formula selected from:



30. The compound of any one of claims 1-21, wherein Ring A is:



wherein

each R^4 is independently D, OH, CN, or C_{1-2} alkyl optionally substituted with 0-3 F's, or two R^4's along with the carbon atom they are bound to form a 3- or 4-membered carbocyclic or heterocyclic ring, or two R^4's along with the carbon atoms they are bound to atom for a 3- to 7-membered carbocyclic or heterocyclic ring

n is 1, 2, 3, 4, 5 or 6; and

j is 0, 1, 2, 3 or 4.

31. The compound of claim 30, wherein *j* is 0.

32. The compound of claim 30, wherein *j* is 1 or 2.

33. The compound of any one of claims 1-32, wherein R^1 is CHF_2.

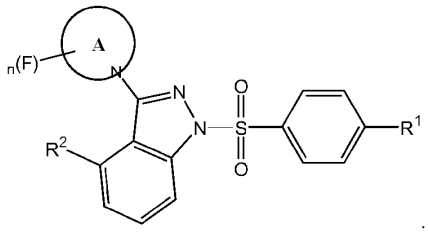
34. The compound of any one of claims 1-32, wherein R^1 is CF_2CH_3.

35. The compound of any one of claims 1-32, wherein R^1 is CF_2CH_2F.

36. The compound of any one of claims 1-32, wherein R^1 is CF_2CHF_2.

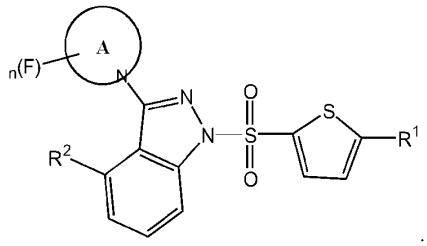
37. The compound of any one of claims 1-32, wherein R^1 is F.

38. The compound of claim 1, having the structural formula:



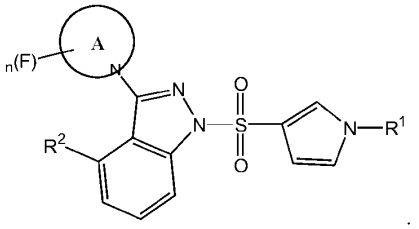
(I_e)

39. The compound of claim 1, having the structural formula:



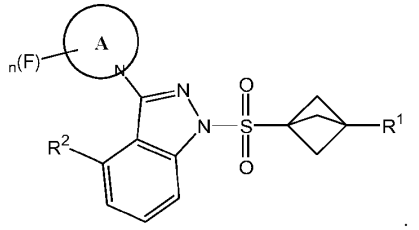
(I_f)

40. The compound of claim 1, having the structural formula:



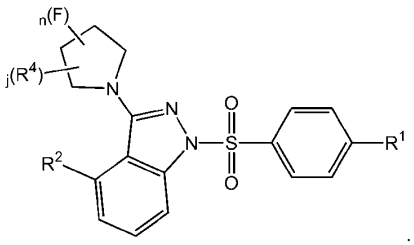
(I_g)

41. The compound of claim 1, having the structural formula:



(I_h)

42. The compound of claim 1 or 30, having the structural formula:



(I_m)

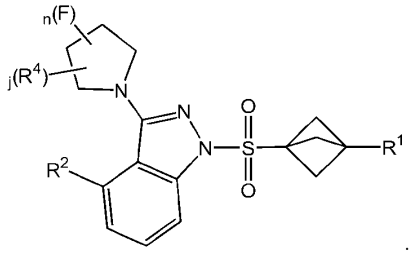
wherein

each R^4 is independently C_{1-2} alkyl optionally substituted with 0-3 F's, or two R^4's along with the carbon atom they are bound to form a 3- or 4-membered carbocyclic or heterocyclic, or two R^4's along with the carbon atoms they are bound to atom for a 3- to 6-membered carbocyclic or heterocyclic ring;

n is 1, 2, 3, 4, 5 or 6; and

j is 0, 1, 2, 3 or 4.

43. The compound of claim 1 or 30, having the structural formula:



(I_n)

wherein

each R^4 is independently C_{1-2} alkyl optionally substituted with 0-3 F's, or two R^4's along with the carbon atom they are bound to form a 3- or 4-membered carbocyclic or heterocyclic, or two R^4's along with the carbon atoms they are bound to atom for a 3- to 6-membered carbocyclic or heterocyclic ring;

n is 1, 2, 3, 4, 5 or 6; and

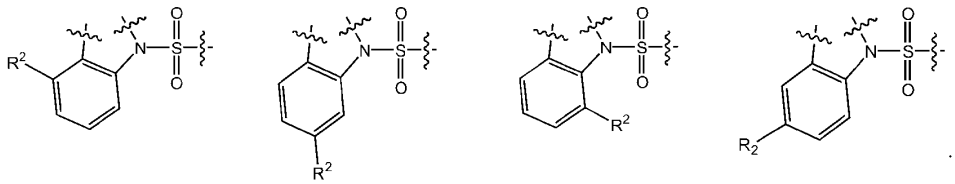
j is 0, 1, 2, 3 or 4.

44. The compound of claim 42 or 43, wherein each R^4 is independently D, OH, CN, or C_{1-2} alkyl optionally substituted with 0-3 F's.

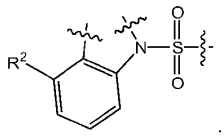
45. The compound of claim 42 or 43, wherein two R^4's along with the carbon atom they are

bound to form a 3- or 4-membered carbocyclic or heterocyclic ring.

46. The compound of claim 42 or 43, wherein two R^{4}'s along with the carbon atoms they are bound to atom for a 3- to 7-membered carbocyclic or heterocyclic ring.
47. The compound of 46, wherein *j* is 0.
48. The compound of 46, wherein *j* is 1 or 2.
49. The compound of claim 44, wherein *j* is 1 and R^4 is bound to a carbon atom adjacent to the N atom.
50. The compound of claim 49, wherein R^4 is CF_3.
51. The compound of claim 44, wherein *j* is 2 and both R^{4}'s are bound to a carbon atom adjacent to the N atom of Ring A.
52. The compound of claim 51, wherein one or both of the two R^{4}'s is a C_{1-3} alkyl, optionally substituted with 1-5 F's.
53. The compound of claim 45, wherein *j* is 2 and the two R^{4}'s, along with the carbon atom they are bound to, form a cyclopropyl group.
54. The compound of claim 46, wherein *j* is 2 and the two R^{4}'s along with the carbon atoms they are bound to atom for a 5- to 7-membered carbocyclic or heterocyclic ring.
55. The compound of any one of claims 38-54, wherein *n* is an integer selected from 1-4.
56. The compound of claim 55, wherein *n* is 1.
57. The compound of claim 55, wherein *n* is 2.
58. The compound of claim 55, wherein *n* is 3 or 4.
59. The compound of any one of claims 38-58, wherein R^1 is CF_2CH_3.
60. The compound of any one of claims 38-58, wherein R^1 is CF_2CH_2F.
61. The compound of any one of claims 38-58, wherein R^1 is CF_2CHF_2.
62. The compound of any one of claims 38-58, wherein R^1 is CHF_2.
63. The compound of any one of claims 38-58, wherein R^1 is F.
64. The compound of any one of claims 1-63, wherein *m* is 1.
65. The compound of claim 64, wherein R^2 has a positioning selected from:



66. The compound of claim 64, wherein R^2 has a positioning of:



67. The compound of any of claims 64-66, wherein R^2 is a halogen.

68. The compound of claim 67, wherein R^2 is Cl.

69. The compound of any of claims 64-66, wherein R^2 is amino, OH, C_1 alkyl or alkoxy, optionally substituted with 0-3 F's.

70. A compound selected from **Table 1**.

71. The compound of any of claims 1-70, having one or more deuterium atoms in place of one or more hydrogen atoms.

72. The compound of claim 71, having one deuterium atom in place of one hydrogen atom.

73. A pharmaceutical composition comprising a compound of any of claims 1-72.

74. A unit dosage form comprising a pharmaceutical composition of claim 73.

75. The unit dosage form of claim 74, being a tablet.

76. The unit dosage form of claim 74, being a capsule.

77. A method for treating or reducing a disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-72.

78. The method of claim 77, wherein the disease or disorder is mediated by loss-of-function in TRPML1.

79. The method of claim 78, wherein the disease or disorder is mucolipidosis type IV (ML4).

80. The method of claim 77, wherein the disease or disorder is a lysosome storage disease, or a related disease or disorder.

81. The method of claim 77, wherein the disease or disorder is a neurodegenerative disease, or a related disease or disorder.

82. The method of claim 81, wherein the disease or disorder is Alzheimer's disease, Parkinson's disease, and Huntington's disease, amyotrophic lateral sclerosis (ALS) or frontotemporal dementia, or a related disease or disorder.

83. The method of claim 77, wherein the disease or disorder is a neuronal ceroid lipofuscinoses (NCLs) or Batten disease, or a related disease or disorder.

84. The method of claim 77, wherein the disease or disorder is Niemann–Pick type C (NPC), or a related disease or disorder.
85. The method of claim 77, wherein the disease or disorder is Charcot-Marie-Tooth disease (CMT), or a related disease or disorder.
86. The method of claim 77, wherein the disease or disorder is age-related macular degeneration (AMD), or a related disease or disorder.
87. The method of claim 77, wherein the disease or disorder is cystic fibrosis (CF), or a related disease or disorder.
88. The method of claim 77, wherein the disease or disorder is autosomal dominant polycystic kidney disease (ADPKD), or a related disease or disorder.
89. The method of claim 77, wherein the disease or disorder is selected from cancers in which TRPML1 is overexpressed in cancer cells.
90. The method of claim 77, wherein the disease or disorder is muscular dystrophy, or a related disease or disorder.
91. The method of claim 77, wherein the disease or disorder is oxidative stress or reactive oxygen species (ROS), or a related disease or disorder.
92. A method for treating or reducing the effect of aging comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-72.
93. The method of claim 77, wherein the effect of aging comprises skin aging.
94. The method of claim 77, wherein the effect of aging comprises photoaging.
95. A method for treating or reducing oxidative stress or reactive oxygen species (ROS) related diseases or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-72.
96. A method for treating or reducing oxidative stress or reactive oxygen species (ROS) related diseases or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-72.
97. The method of any one of claims 77-96, wherein administration is via oral administration.
98. The method of any one of claims 77-96, wherein administration is via topical administration.

99. Use of a compound of any of claims 1-72, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a disease or disorder.
100. The use of claim 99, wherein the disease or disorder is mediated by loss-of-function in TRPML1.
101. The use of claim 99, wherein the disease or disorder is mucolipidosis type IV (ML4).
102. The use of claim 99, wherein the disease or disorder is a lysosome storage disease, or a related disease or disorder.
103. The use of claim 99, wherein the disease or disorder is selected from the group consisting of age-related neurodegenerative disease, or a related disease or disorder.
104. The use of claim 103, wherein the disease or disorder is Alzheimer's disease, Parkinson's disease, and Huntington's disease, amyotrophic lateral sclerosis (ALS) or frontotemporal dementia, or a related disease or disorder.
105. The use of claim 99, wherein the disease or disorder is a neuronal ceroid lipofuscinoses (NCLs) or Batten diseases, or a related disease or disorder.
106. The use of claim 99, wherein the disease or disorder is a Niemann–Pick type C (NPC), or a related disease or disorder.
107. The use of claim 99, wherein the disease or disorder is a Charcot-Marie-Tooth disease (CMT), or a related disease or disorder.
108. The use of claim 99, wherein the disease or disorder is age-related macular degeneration (AMD), or a related disease or disorder.
109. The use of claim 99, wherein the disease or disorder is cystic fibrosis (CF), or a related disease or disorder.
110. The use of claim 99, wherein the disease or disorder is autosomal dominant polycystic kidney disease (ADPKD), or a related disease or disorder.
111. The use of claim 99, wherein the disease or disorder is selected from cancers in which TRPML1 is overexpressed in cancer cells.
112. The use of claim 99, wherein the disease or disorder is muscular dystrophy, or a related disease or disorder.
113. The use of claim 99, wherein the disease or disorder is oxidative stress or reactive oxygen species (ROS), or a related disease or disorder.
114. The use of claim 99, wherein the disease or disorder is skin aging.

115. The use of claim 99, wherein the disease or disorder is photoaging.