

TRICYCLIC ARYL DERIVATIVES, AND COMPOSITIONS AND METHODS THEREOF

Priority Claims and Related Applications

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/393,570, filed July 29, 2022, the entire content of each of which is incorporated herein by reference for all purposes.

Technical Fields of the Invention

[0002] The invention generally relates to novel compounds and therapeutic uses thereof. More particularly, the invention provides novel tricyclic compounds that are shown to be potent and selective phosphoinositide 3-kinase α (PI3K α) inhibitors. The invention also provides pharmaceutical compositions comprising compounds of the invention and methods for treating diseases and disorders associated with or related to PI3K α activities, such as various types of cancer.

Background of the Invention

[0003] Phosphoinositide 3-kinases (PI3Ks) are a family of related intracellular signal transducer enzymes capable of phosphorylating the 3-position hydroxyl group of the inositol ring of phosphatidylinositol (PtdIns). PI3Ks have been linked to an extraordinarily diverse group of cellular functions, including cell growth, proliferation, differentiation, motility, survival and intracellular trafficking. The PI3K signaling pathway is one of the most frequently mutated in human cancer and is also a major factor in many other diseases in humans. For examples, PI3K signaling is associated with allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, diabetic complications and acute coronary syndrome.

[0004] The PI3K family is divided into three different classes: Class I, Class II, and Class III, based on their primary structure, regulation, and lipid substrate specificity. (Kalaany *et al.* 2009 *Nature* 458 (7239): 725–31; Leever *et al.* (1999) *Current Opinion in Cell Biology* 11 (2): 219–

25.) Class I PI3Ks (p110 α , p110 β , p110 δ and p110 γ) are activated by tyrosine kinases or G protein-coupled receptors to produce phosphatidylinositol-3,4,5-triphosphate (PIP 3).

Association of effectors such as PDPK1/AKT with PIP3 activates downstream signaling pathways.

[0005] The class IA PI3K p110 α (PI3K α) is mutated in many human cancers. Angiogenesis has been shown to selectively require the PI3K α isoform in the control of endothelial cell migration. Mutations in the gene encoding PI3K α (*PIK3CA*) or PI3K α up-regulation occurs in many human cancers such as ovarian cancer, cervical cancer, breast cancer, colorectal cancer, endometrial cancer, gastric carcinomas, hepatocellular carcinoma, small and non-small cell lung cancer, thyroid carcinoma, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and glioblastomas. In cancer, PI3K α mutations are often hotspot point mutations in the helical or kinase domain, such as E542K, E545K and H1047R. (Graupera *et al.* **2008** *Nature* 453: 662-6; Campbell *et al.* **2004** *Cancer Res* 64, 7678-7681; Levine *et al.* **2005** *Clin Cancer Res* 11, 2875-2878; Wang *et al.* **2005** *Hum Mutat* 25, 322; Lee *et al.* **2005** *Gynecol Oncol* 97, 26-34; Bachman, *et al.* **2004** *Cancer Biol Ther* 3, 772-775; Li *et al.* **2006** *Breast Cancer Res Treat* 96, 91-95; Saal *et al.* **2005** *Cancer Res* 65, 2554-2559; Samuels and Velculescu **2004** *Cell Cycle* 3, 1221-1224; Samuels, *et al.* **2004** *Science* 304, 554; Velho *et al.* **2005** *Eur J Cancer* 41, 1649-1654; Oda *et al.* **2005** *Cancer Res.* 65, 10669-10673; Byun *et al.* **2003** *Int J Cancer* 104, 318-327; Lee *et al.* **2005** *Oncogene* 24, 1477-1480; Tang *et al.* **2006** *Lung Cancer* 51, 181-191; Massion *et al.* **2004** *Am J Respir Crit Care Med* 170, 1088-1094; Wu *et al.* **2005** *J Clin Endocrinol Metab* 90, 4688-4693; Sujobert *et al.* **1997** *Blood* 106, 1063-1066; Hickey and Cotter **2006** *J Biol Chem* 281, 2441-2450; Hartmann *et al.* **2005** *Acta Neuropathol (Berl)* 109, 639-642.)

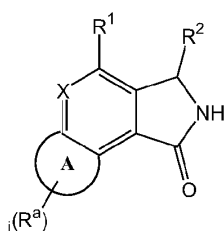
[0006] There remains an urgent and unmet need for potent and selective PI3K α inhibitors that are safe and effective in treating diseases and conditions associated with PI3K α , such as various types of cancer (*e.g.*, breast cancer, ovarian cancer, colorectal cancer, lung cancer).

Summary of the Invention

[0007] The invention provides novel tricyclic compounds and derivatives thereof as PI3K α inhibitors, which are shown herein to exhibit favorable potency and selectivity profiles over known PI3K α inhibitors. These novel compounds selectively target, bind to, inhibit and/or

modulate the activity of PI3K α . The compounds are also orally available with pharmacokinetic profiles suitable for development into an orally administered therapeutic agent for treating various diseases and disorders associated with or related to PI3K α activities, such as various types of cancer.

[0008] In one aspect, the invention generally relates to a compound having the structural formula (I):



(I)

or a pharmaceutically acceptable form or an isotope derivative thereof,

wherein

Ring A is a 4- to 7-membered monocyclic non-aromatic ring, substituted with 0-10 R^a's;

R¹ is Z^B-R^B;

R² is Z^C-R^C;

X is N, CH or CR^X;

R^X is Z^X-R^{X'};

each of Z^B, Z^C and Z^X is independently a covalent bond, O, S, NR, NRC(O), C(O)NR, C(O), C(O)O, OC(O), S(O)₂, NRS(O)₂, S(O)₂NR, or a linking group selected from C₁₋₄ saturated or unsaturated bivalent hydrocarbon radicals, wherein one or more carbons are optionally and independently substituted with a heteroatom selected from the group consisting of N, S and O;

each of R^B, R^C and R^X is independently

H, deuterium, oxo, halogen, -CN, -NO₂, -OR, -SR, -NRR', -S(O)₂R, -S(O)₂NRR', -S(O)R, -S(O)NRR', -S(O)(NR)R, -C(O)R, -C(O)OR, -C(O)NRR', -C(O)N(R)OR, -OC(O)R, -OC(O)NRR', -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NRR', -N(R)C(NR)NRR', -N(R)S(O)₂NRR', or -N(R)S(O)₂R; or

a C₁₋₆ aliphatic chain, a 5- to 10-membered monocyclic, bicyclic or bridged carbocyclyl, heterocyclic, aryl or heteroaryl ring with 0-4 ring heteroatoms independently selected from N, O and S, optionally substituted with one or more R^b, R^c or R^x, respectively;

each of R^a , R^b , R^c and R^x is independently

H, deuterium, oxo, halogen, -CN, -NO₂, -OR, -SR, -NRR', -S(O)₂R, -S(O)₂NRR', -S(O)R, -S(O)NRR', -S(O)(NR)R, -C(O)R, -C(O)OR, -C(O)NRR', -C(O)N(R)OR, -OC(O)R, -OC(O)NRR', -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NRR', -N(R)C(NR)NRR', -N(R)S(O)₂NRR' or -N(R)S(O)₂R; or

a substituted or unsubstituted group selected from C₁₋₆ alkyl or 4- to 6-membered carbocyclic ring;

each of R and R' is independently selected from H, unsubstituted or substituted C₁₋₄ alkyl, or unsubstituted or substituted 4- to 6-membered carbocyclic ring, or where R and R' are attached to the same C or N atom, together form an unsubstituted or substituted 4- to 6-membered heterocyclic ring; and

i is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

[0009] In another aspect, the invention generally relates to a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient, carrier, or diluent.

[0010] In yet another aspect, the invention generally relates to a unit dosage form comprising a pharmaceutical composition disclosed herein.

[0011] In yet another aspect, the invention generally relates to a method for inhibiting cell proliferation *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound disclosed herein.

[0012] In yet another aspect, the invention generally relates to a method for inhibiting PI3K α activity in a cell, comprising contacting the cell with a compound disclosed herein.

[0013] In yet another aspect, the invention generally relates to a method for treating a disease or disorder mediated by PI3K α , comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein.

[0014] In yet another aspect, the invention generally relates to a method for treating or reducing cancer, or a related disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein.

[0015] 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

[0016] 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.

[0017] As used herein, "at least" a specific value is understood to be that value and all values greater than that value.

[0018] The term "comprising", when used to define compositions and methods, is 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.

[0019] Unless specifically stated or obvious from context, as used herein, the term "about" is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. About can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein can be modified by the term about.

[0020] In this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference, unless the context clearly dictates otherwise.

[0021] As used herein, the terms "administration" of or "administering" a disclosed compound encompasses the delivery to a subject of a compound as described herein, or a

prodrug or other pharmaceutically acceptable form thereof, using any suitable formulation or route of administration, as discussed herein.

[0022] As used herein, the term “co-administer” refers to the presence of two pharmacological agents in a subject’s body (*e.g.*, in the blood) at the same time. The two pharmacological agents can be administered concurrently or sequentially.

[0023] The terms “disease”, “disorder” and “condition” are used interchangeably unless indicated otherwise.

[0024] As used herein, the terms “effective amount” or “therapeutically effective amount” refer to that amount of a compound or pharmaceutical composition described herein that is sufficient to effect the intended application including, but not limited to, disease treatment, as illustrated below.

[0025] In some embodiments, the amount is that is sufficient to negatively modulate or inhibit the activity of PI3K α . In some embodiments, the amount is that effective for reduction or amelioration of a symptom to stop or reversion of progression of a disease or disorder such as cancer. In some embodiments, the amount is that effective for detectable killing or inhibition of the growth or spread of cancer cells; the size or number of tumors; or other measure of the level, stage, progression or severity of the cancer.

[0026] The therapeutically effective amount can vary depending upon the intended application, or the subject and disease condition being treated, *e.g.*, the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated, the mode of administration, and the weight and age of the patient, which can readily be determined by one of ordinary skill in the art. Such amount may be administered as a single dosage or according to a regimen. The term also applies to a dose that will induce a particular response in target cells, *e.g.*, reduction of cell migration. The specific dose will vary depending on, for example, the particular compounds chosen, the species of subject and their age/existing health conditions or risk for health conditions, the dosing regimen to be followed, the severity of the disease, whether it is administered in combination with other agents, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[0027] As used herein, an “inhibitor” of “PI3K α ” refers to a compound of the invention capable of negatively modulating or inhibiting all or a portion of the activity of PI3K α .

[0028] As used herein, a “PI3K α -associated” disease or disorder refers to diseases or disorders associated with or mediated by PI3K α or having one or more PI3K α mutations. Examples of PI3K α -associated diseases or disorders include various cancer types. A PI3K α -associated disease or disorder may also refer allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, diabetic complications, or acute coronary syndrome.

[0029] As used herein, the term “contacting” refers to the bringing together of indicated moieties *in vitro* or *in vivo*. For example, “contacting” a cell with a compound disclosed herein includes the administration of the compound to a subject in need thereof, as well as, for example, introducing the compound into a sample containing a cellular or purified preparation. In some embodiments, a cell in which inhibition of PI3K α activity is desired is contacted with an effective amount of a compound disclosed herein or pharmaceutically acceptable form thereof to negatively modulate the activity of PI3K α . By negatively modulating the activity of PI3K α , the methods disclosed herein are designed to inhibit undesired cellular proliferation resulting from enhanced PI3K α activity within the cell. The cells may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to effect the desired negative modulation of PI3K α . The ability of compounds to bind PI3K α may be monitored *in vitro* using methods known in the art. The inhibitory activity of exemplary compounds in cells may be monitored, for example, by measuring the inhibition of PI3K α activity using methods known in the art.

[0030] As used herein, the terms “unsubstituted or substituted” and “optionally substituted” are used interchangeably and refer to where a given chemical moiety (*e.g.*, an alkyl group) can (but is not required to) be bonded other substituents (*e.g.*, heteroatoms). For instance, an alkyl group that is optionally substituted can be a fully saturated alkyl chain (*i.e.* a pure hydrocarbon). Alternatively, the same optionally substituted alkyl group can have substituents different from hydrogen. For instance, it can, at any point along the chain be bounded to a halogen atom, a hydroxyl group, or any other substituent described herein. Thus, the term “optionally substituted” means that a given chemical moiety has the potential to contain other functional groups, but does not necessarily have any further functional groups. Suitable substituents used in the optional substitution of the described groups include, without limitation, halogen, oxo, CN, -COOH, -CH₂CN, -O-C₁-C₆ alkyl, C₁-C₆ alkyl, -OC₁-C₆ alkenyl, -OC₁-C₆ alkynyl, -C₁-C₆ alkenyl, -C₁-C₆ alkynyl, -OH, -OP(O)(OH)₂, -OC(O)C₁-C₆ alkyl, -C(O)C₁-C₆ alkyl, -OC(O)OC₁-

C₆ alkyl, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -NHC(O)C₁-C₆ alkyl, -C(O)NHC₁-C₆ alkyl, -S(O)₂-C₁-C₆ alkyl, -S(O)NHC₁-C₆ alkyl, and S(O)N(C₁-C₆ alkyl)₂.

[0031] As used herein, a "pharmaceutically acceptable form" of a disclosed compound includes, but is not limited to, pharmaceutically acceptable salts, esters, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives of disclosed compounds. In one embodiment, a "pharmaceutically acceptable form" includes, but is not limited to, pharmaceutically acceptable salts, esters, isomers, prodrugs and isotopically labeled derivatives of disclosed compounds. In some embodiments, a "pharmaceutically acceptable form" includes, but is not limited to, pharmaceutically acceptable salts, esters, stereoisomers, prodrugs and isotopically labeled derivatives of disclosed compounds.

[0032] 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, trifluoroacetic 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.

[0033] 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.

[0034] In certain embodiments, the pharmaceutically acceptable form is a pharmaceutically acceptable ester. As used herein, the term "pharmaceutically acceptable ester" refers to esters that hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Such esters can act as a prodrug as defined herein. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfinic acids, sulfonic acids and boronic acids. Examples of esters include formates, acetates, propionates, butyrates, acrylates and ethylsuccinates. The esters can be formed with a hydroxy or carboxylic acid group of the parent compound.

[0035] 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.

[0036] 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.

[0037] 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.

[0038] 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.

[0039] As used herein, the term "subject" refers to any animal (*e.g.*, a mammal), including, but not limited to humans, non-human primates, rodents, and the like, which is to be the recipient of a particular treatment. Typically, the terms "subject" and "patient" are used interchangeably herein in reference to a human subject.

[0040] In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated with a compound disclosed herein and/or according to a herein disclosed method. In some embodiments, the subject has been identified or diagnosed as having a cancer having one or more PI3K α mutations. In some embodiments, the subject has a cancer that is positive for a PI3K α mutation. In some embodiments, the subject is suspected of having a PI3K α gene-associated cancer.

[0041] In some embodiments of any of the methods or uses described herein, an assay is used to determine whether the subject has one or more PI3K α mutations using a sample (*e.g.*, a biological sample or a biopsy sample (*e.g.*, a paraffin-embedded biopsy sample) from a subject. Various techniques may be employed, for example, next generation sequencing, immunohistochemistry, fluorescence microscopy, break apart FISH analysis, Southern blotting,

Western blotting, FACS analysis, Northern blotting, and PCR-based amplification (e.g., RT-PCR and quantitative real-time RT-PCR).

[0042] 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. Treatment is aimed to obtain beneficial or desired results including, but not limited to, therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient can still be afflicted with the underlying disorder. For prophylactic benefit, the pharmaceutical compounds and/or compositions can be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made. 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. As compared with an equivalent untreated control, such reduction or degree of prevention is at least 5%, 10%, 20%, 40%, 50%, 60%, 80%, 90%, 95%, or 100% as measured by any standard technique.

[0043] As used herein, the term “therapeutic effect” refers to a therapeutic benefit and/or a prophylactic benefit as described herein. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0044] Compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 95% (“substantially pure”), which is then used or formulated as described herein. In certain embodiments, the compounds of the present invention are more than 99% pure.

[0045] 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.

[0046] As used herein, the term an “isolated” or “substantially isolated” molecule (such as a polypeptide or polynucleotide) is one that has been manipulated to exist in a higher concentration

than in nature or has been removed from its native environment. For example, a subject antibody is isolated, purified, substantially isolated, or substantially purified when at least 10%, or 20%, or 40%, or 50%, or 70%, or 90% of non-subject-antibody materials with which it is associated in nature have been removed. For example, a polynucleotide or a polypeptide naturally present in a living animal is not "isolated," but the same polynucleotide or polypeptide separated from the coexisting materials of its natural state is "isolated." Further, recombinant DNA molecules contained in a vector are considered isolated for the purposes of the present invention. Isolated RNA molecules include in vivo or in vitro RNA replication products of DNA and RNA molecules. Isolated nucleic acid molecules further include synthetically produced molecules. Additionally, vector molecules contained in recombinant host cells are also isolated. Thus, not all "isolated" molecules need be "purified."

[0047] As used herein, the term "purified" when used in reference to a molecule, it means that the concentration of the molecule being purified has been increased relative to molecules associated with it in its natural environment, or environment in which it was produced, found or synthesized. Naturally associated molecules include proteins, nucleic acids, lipids and sugars but generally do not include water, buffers, and reagents added to maintain the integrity or facilitate the purification of the molecule being purified. According to this definition, a substance may be 5% or more, 10% or more, 20% or more, 30% or more, 40% or more, 50% or more, 60% or more, 70% or more, 80% or more, 90% or more, 95% or more, 98% or more, 99% or more, or 100% pure when considered relative to its contaminants.

[0048] 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, "C₁₋₄ alkyl" is intended to encompass, C₁, C₂, C₃, C₄, C₁₋₃, C₁₋₂, C₂₋₄, C₃₋₄ and C₂₋₃ alkyl groups.

[0049] As used herein, the term "aliphatic" or "aliphatic group" refers to a linear or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic.

[0050] As used herein, the term "alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from

one to ten carbon atoms (*e.g.*, C₁₋₁₀ alkyl). 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 C₁₋₆ alkyl group. In some embodiments, alkyl groups have 1 to 10, 1 to 8, 1 to 6, or 1 to 3 carbon atoms. Representative saturated straight chain alkyls include, but are not limited to, -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and -n-hexyl; while saturated branched alkyls include, but are not limited to, -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, and the like. The alkyl is attached to the parent molecule by a single bond. Unless stated otherwise in the specification, an alkyl group is optionally substituted by one or more of substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, -Si(R^x)₃, -OR^x, -SR^x, -OC(O)-R^x, -N(R^x)₂, -C(O)R^x, -C(O)OR^x, -OC(O)N(R^x)₂, -C(O)N(R^x)₂, -N(R^x)C(O)OR^x, -N(R^x)C(O)R^x, -N(R^x)C(O)N(R^x)₂, -N(R^x)C(NR^x)N(R^x)₂, -N(R^x)S(O)_tN(R^x)₂ (where t is 1 or 2), -P(=O)(R^x)(R^x), or -O-P(=O)(OR^x)₂ wherein each R^x is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. In a non-limiting embodiment, a substituted alkyl can be selected from fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, benzyl, and phenethyl.

[0051] Unless otherwise specifically defined, the term “aromatic” or “aryl” refers to cyclic, aromatic hydrocarbon groups that have 1 to 2 aromatic rings, including monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where containing two aromatic rings (bicyclic, etc.), the aromatic rings of the aryl group may be joined at a single point (*e.g.*, biphenyl), or fused (*e.g.*, naphthyl). The aryl group may be optionally substituted by one or more substituents,

e.g., 1 to 5 substituents, at any point of attachment. Exemplary substituents include, but are not limited to, H, halogen, -O-C₁-C₆ alkyl, C₁-C₆ alkyl, -C₁-C₆ alkenyl, -OC₁-C₆ alkynyl, -C₁-C₆ alkenyl, -C₁-C₆ alkynyl, -OH, -OP(O)(OH)₂, -OC(O)C₁-C₆ alkyl, -C(O)C₁-C₆ alkyl, -OC(O)OC₁-C₆alkyl, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(O)₂-C₁-C₆ alkyl, -S(O)NHC₁-C₆alkyl, and S(O)N(C₁-C₆ alkyl)₂. The substituents can themselves be optionally substituted. Furthermore, when containing two fused rings the aryl groups herein defined may have an unsaturated or partially saturated ring fused with a fully unsaturated ring. Exemplary ring systems of these aryl groups include indanyl, indenyl, tetrahydronaphthalenyl, and tetrahydrobenzoannulenyl.

[0052] The term “halogen” or “halo” refers to fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

[0053] As used herein, the terms “heteroaryl” or “hetero-aromatic” refer to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 p electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to three heteroatoms per ring selected from the group consisting of N, O, and S. Examples of heteroaryl groups include acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnoliny, 6,7-dihydro-5H-pyrrolo[1,2- a]imidazole, furanyl, furazanyl, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indoliny, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, methylenedioxyphenyl, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidiny, oxazolyl, oxazolidiny, pyrimidinyl, phenanthridiny, phenanthroliny, phenaziny, phenothiaziny, phenoxathiiny, phenoxaziny, phthalaziny, piperonyl, pteridiny, puriny, pyranly, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny, pyridooxazole, pyridoimidazole, pyridothiazole, pyridiny, pyridyl, pyrimidinyl, pyrroliny, 2H-pyrrolyl, pyrrolyl, quinazoliny, quinoliny, 4H-quinoliziny, quinoxaliny, quinuclidiny, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, 6H-1,2,5-thiadiaziny, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triaziny, 1,2,3- triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

“Heteroaryl” also refers to bicyclic ring systems having, in addition to carbon atoms, from one to

three heteroatoms per ring selected from the group consisting of N, O, and S in which one ring system may be saturated or partially saturated.

[0054] Heteroaryl groups may be substituted with 0, 1, 2, 3, or 4 substituents independently selected from alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonyloxy, alkylthio, alkylthioalkyl, alkynyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, formyl, haloalkoxy, haloalkyl, halogen, hydroxy, hydroxyalkyl, mercapto, nitro, -NZ₁Z₂, and (NZ₁Z₂)carbonyl. The term "NZ₁Z₂" as used herein, means two groups, Z₁ and Z₂, which are appended to the parent molecular moiety through a nitrogen atom. Z₁ and Z₂ are each independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, and formyl. Representative examples of NZ₁Z₂ include, but are not limited to, amino, methylamino, acetylamino, and acetylmethylamino.

[0055] As used herein, the term "alkoxy" refers to an -O-alkyl radical.

[0056] As used herein, the terms "cycloalkyl" and "carbocyclyl" each refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and can be saturated or partially unsaturated. Unless stated otherwise in the specification, the term is intended to include both substituted and unsubstituted cycloalkyl groups. 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. Cycloalkyl groups include groups having from 3 to 13 ring atoms (i.e., C₃₋₁₃ cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range; e.g., "3 to 13 carbon atoms" means that the cycloalkyl group can consist of 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, *etc.*, up to and including 13 carbon atoms. The term "cycloalkyl" also includes bridged and spiro-fused cyclic structures containing no heteroatoms. The term also includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of ring atoms) groups. Polycyclic aryl groups include bicycles, tricycles, tetracycles, and the like. In some embodiments, "cycloalkyl" can be a C₃₋₈ cycloalkyl radical. In some embodiments, "cycloalkyl" can be a C₃₋₅ cycloalkyl radical. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: C₃₋₆ carbocyclyl groups include, without limitation, cyclopropyl (C₃), cyclobutyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆) and the like. Examples of C₃₋₇ carbocyclyl groups include norbornyl (C₇). Examples of C₃₋₈ carbocyclyl groups include the aforementioned C₃₋₇ carbocyclyl groups as well as cycloheptyl

(C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and the like. Examples of C₃₋₁₃ carbocyclyl groups include the aforementioned C₃₋₈ carbocyclyl groups as well as octahydro-1H indenyl, decahydronaphthalenyl, spiro[4.5]decanyl and the like. Unless stated otherwise in the specification, a cycloalkyl group can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, -Si(R^a)₃, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, -N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tN(R^a)₂ (where t is 1 or 2), -P(=O)(R^a)(R^a), or -O-P(=O)(OR^a)₂ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. The terms "cycloalkenyl" and "cycloalkynyl" mirror the above description of "cycloalkyl" wherein the prefix "alk" is replaced with "alken" or "alkyn" respectively, and the parent "alkenyl" or "alkynyl" terms are as described herein. For example, a cycloalkenyl group can have 3 to 13 ring atoms, such as 5 to 8 ring atoms. In some embodiments, a cycloalkynyl group can have 5 to 13 ring atoms.

[0057] As used herein, the term "heterocycloalkyl" refers to a cycloalkyl radical, which have one or more skeletal chain atoms selected from an atom other than carbon, *e.g.*, O, N, S, P or combinations thereof. Unless stated otherwise in the specification, the term is intended to include both substituted and unsubstituted heterocycloalkyl groups. Illustrative examples of heterocycloalkyl include 2-hydroxy-aziridin-1-yl, 3-oxo-1-oxacyclobutan-2-yl, 2,2-dimethyl-tetrahydrofuran-3-yl, 3-carboxy-morpholin-4-yl, 1-cyclopropyl-4-methyl-piperazin-2-yl, 2-pyrrolinyl, 3-pyrrolinyl, dihydro-2H-pyran-2-yl, 1,2,3,4-tetrahydropyridine, 3,4-dihydro-2H-[1,4]oxazine, *etc.*

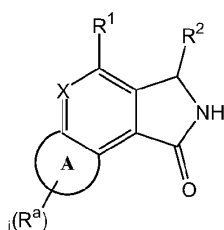
[0058] As used herein, the terms "heterocycle", "heterocyclic" or "heterocyclo" refer to fully saturated or partially unsaturated cyclic groups, for example, 3- to 8-membered monocyclic, 7- to 12-membered bicyclic, or 10- to 15-membered spirocyclic or tricyclic ring systems, which have

at least one heteroatom (selected from the group consisting of N, O, and S) 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. A heterocyclic group is optionally substituted. Examples of heterocyclic groups include, but not limited to, epoxy, azetidiny, aziridiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidiny, pyrrolidinonyl, piperidiny, piperaziny, imidazolidiny, imidazopyridiny, thiazolidiny, dithianyl, trithianyl, dioxolanyl, oxazolidiny, oxazolidinonyl, decahydroquinoliny, piperidonyl, 4-piperidinonyl, quinuclidiny, thiomorpholiny, thiomorpholiny 1,1-dioxide, morpholiny, azepanyl, oxazepanyl, azabicyclohexanyls, azabicycloheptanyl, azabicyclooctanyls, azabicyclononyls (e.g., octahydroindoliziny), azaspiroheptanyls, dihydro-1H,3H,5H-oxazolo[3,4-c]oxazolyl, tetrahydro-1'H,3'H- spiro[cyclopropane-1,2'-pyrrolizine], hexahydro-1H-pyrroliziny, hexahydro-1H-pyrrolo[2,1- c][1,4]oxaziny, octahydroindoliziny, oxaazaspiroononyls, oxaazaspirooctanyls, diazaspiroononyls, oxaazabicycloheptanyls, hexahydropyrroliziny 4(1H)-oxide, and tetrahydro- 2H-thiopyranyl 1-oxide and tetrahydro-2H-thiopyranyl 1,1-dioxide.

Detailed Description of the Invention

[0059] The invention is based in part on the discovery of novel tricyclic compounds and derivatives thereof as PI3K α inhibitors. These compounds are shown herein to selectively target, bind to, inhibit and/or modulate the activity of PI3K α . The compounds are orally available and can be used for treating various diseases and disorders associated with or related to PI3K α activities, such as various types of cancer.

[0060] In one aspect, the invention generally relates to a compound having the structural formula (I):



(I)

or a pharmaceutically acceptable form or an isotope derivative thereof,

wherein

Ring A is a 4- to 7-membered monocyclic non-aromatic ring, substituted with 0-10 R^a 's;

R^1 is Z^B-R^B ;

R^2 is Z^C-R^C ;

X is N, CH or CR^X ;

R^X is Z^X-R^X ;

each of Z^B , Z^C and Z^X is independently a covalent bond, O, S, NR, $NRC(O)$, $C(O)NR$, $C(O)$, $C(O)O$, $OC(O)$, $S(O)_2$, $NRS(O)_2$, $S(O)_2NR$, or a linking group selected from C_{1-4} saturated or unsaturated bivalent hydrocarbon radicals, wherein one or more carbons are optionally and independently substituted with a heteroatom selected from the group consisting of N, S and O;

each of R^B , R^C and R^X is independently

H, deuterium, oxo, halogen, -CN, -NO₂, -OR, -SR, -NRR', -S(O)₂R, -S(O)₂NRR', -S(O)R, -S(O)NRR', -S(O)(NR)R, -C(O)R, -C(O)OR, -C(O)NRR', -C(O)N(R)OR, -OC(O)R, -OC(O)NRR', -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NRR', -N(R)C(NR)NRR', -N(R)S(O)₂NRR', or -N(R)S(O)₂R; or

a C_{1-6} aliphatic chain, a 5- to 10-membered monocyclic, bicyclic or bridged carbocyclyl, heterocyclic, aryl or heteroaryl ring with 0-4 ring heteroatoms independently selected from N, O and S, optionally substituted with one or more R^b , R^c or R^x , respectively;

each of R^a , R^b , R^c and R^x is independently

H, deuterium, oxo, halogen, -CN, -NO₂, -OR, -SR, -NRR', -S(O)₂R, -S(O)₂NRR', -S(O)R, -S(O)NRR', -S(O)(NR)R, -C(O)R, -C(O)OR, -C(O)NRR', -C(O)N(R)OR, -OC(O)R, -OC(O)NRR', -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NRR', -N(R)C(NR)NRR', -N(R)S(O)₂NRR' or -N(R)S(O)₂R; or

a substituted or unsubstituted group selected from C₁₋₆ alkyl or 4- to 6-membered carbocyclic ring;

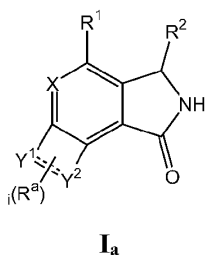
each of R and R' is independently selected from H, unsubstituted or substituted C₁₋₄ alkyl, or unsubstituted or substituted 4- to 6-membered carbocyclic ring, or where R and R' are attached to the same C or N atom, together form an unsubstituted or substituted 4- to 6-membered heterocyclic ring; and

i is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

[0061] In certain embodiments of (I), Ring A is a 4- to 7-membered carbocyclic ring with no ring heteroatoms, substituted with 0-10 R^as.

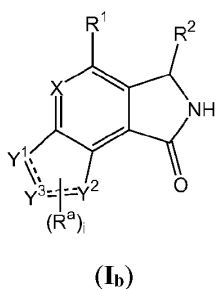
[0062] In certain embodiments of (I), Ring A is a 4- to 7-membered heterocyclic ring with 1-4 ring heteroatoms selected from N, O and S, substituted with 0-10 R^as.

[0063] In certain embodiments of (I), Ring A is a 4-membered non-aromatic ring, substituted with 0-4 R^as, having the structural formula **I_a**:



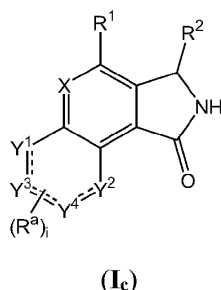
wherein each of Y¹ and Y² is independently CH, CH₂, N, NH, O or S, *provided that* at least one of Y¹ and Y² is C or CH.

[0064] In certain embodiments of (I), Ring A is a 5-membered non-aromatic ring, substituted with 0-6 R^as, having the structural formula (**I_b**):



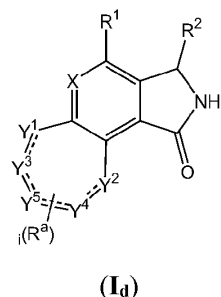
wherein each of Y¹, Y² and Y³ is independently CH, CH₂, N, NH, O, S or C(O), *provided that* at least one of Y¹, Y² and Y³ is not N or NH and at least one of Y¹, Y² and Y³ is C, CH or C(O).

[0065] In certain embodiments of (I), Ring A is a 6-membered non-aromatic ring, substituted with 0-8 R^as, having the structural formula (Ic):



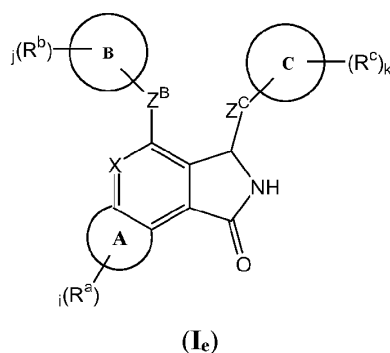
wherein each of Y¹, Y², Y³ and Y⁴ is independently CH, CH₂, N, NH, O, S, S(O)₂, or C(O), *provided that* at least two of Y¹, Y², Y³ and Y⁴ is not N or NH and at least two of Y¹, Y², Y³ and Y⁴ is C, CH or C(O).

[0066] In certain embodiments of (I), Ring A is a 7-membered non-aromatic ring, substituted with 0-8 R^as, having the structural formula (Id):



wherein each of Y¹, Y², Y³, Y⁴ and Y⁵ is independently CH, CH₂, N, NH, O, S or C(O), *provided that* at least two of Y¹, Y², Y³, Y⁴ and Y⁵ is not N or NH and at least two of Y¹, Y², Y³, Y⁴ and Y⁵ is C, CH or C(O).

[0067] In certain embodiments of (I), R^B is Ring B, a 5- to 10-membered monocyclic or bicyclic carbocyclyl, heterocyclic, aryl or heteroaryl ring with 0-4 ring heteroatoms independently selected from N, O and S, substituted with 0-6 R^bs; and R^C is Ring C, a 5- to 10-membered monocyclic or bicyclic aryl or heteroaryl ring with 0-4 ring heteroatoms independently selected from N, O and S, substituted with 0-6 R^cs, having the structural formula (Ie):

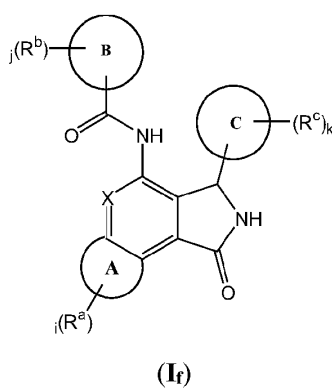


wherein

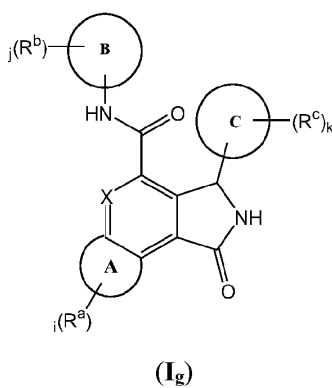
j is 0, 1, 2, 3, 4, 5 or 6; and

k is 0, 1, 2, 3, 4, 5 or 6.

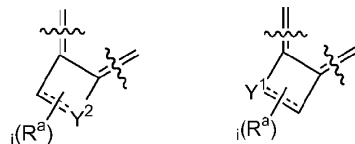
[0068] In certain embodiments of (I), Z^B is NH-C(O) and Z^C is a single bond, having the structural formula (If):



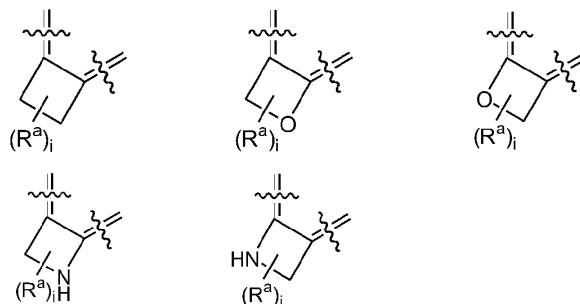
[0069] In certain embodiments of (I), Z^B is C(O)-NH and Z^C is a single bond, having the structural formula (Ig):



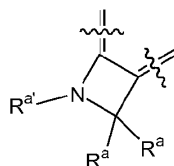
[0070] In certain embodiments of (I)-(I_g), Ring A is selected from:



[0071] In certain embodiments of (I)-(I_g), Ring A is selected from:



[0072] In certain embodiments, Ring A is:

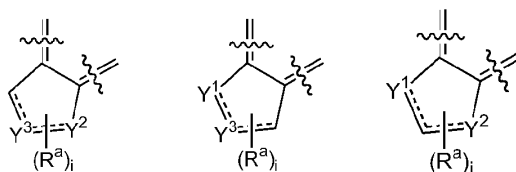


wherein R^a is CH₂CH₃, CD₂CD₃, CH₂CHF₂, CH₂CF₃ and CH₂CN.

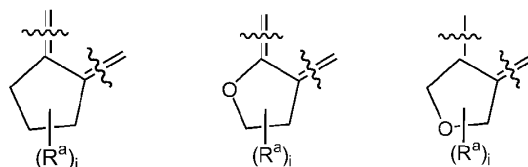
[0073] In certain embodiments, each R^a is independently H, Cl, F, CN or CH₃.

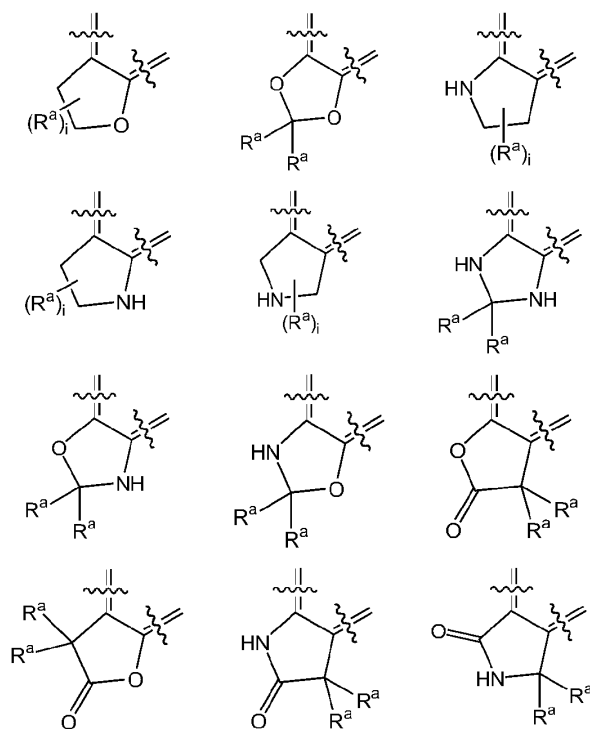
[0074] In certain embodiments, R^a is CH₂CHF₂.

[0075] In certain embodiments of (I)-(I_g), Ring A is selected from:

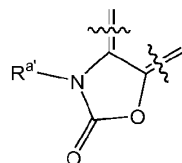


[0076] In certain embodiments of (I)-(I_g), Ring A is selected from:





[0077] In certain embodiments, Ring A is selected from:

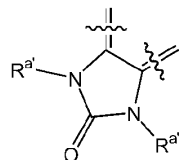


wherein

R^a is CH₂CHF₂ or CH₂CF₃; and

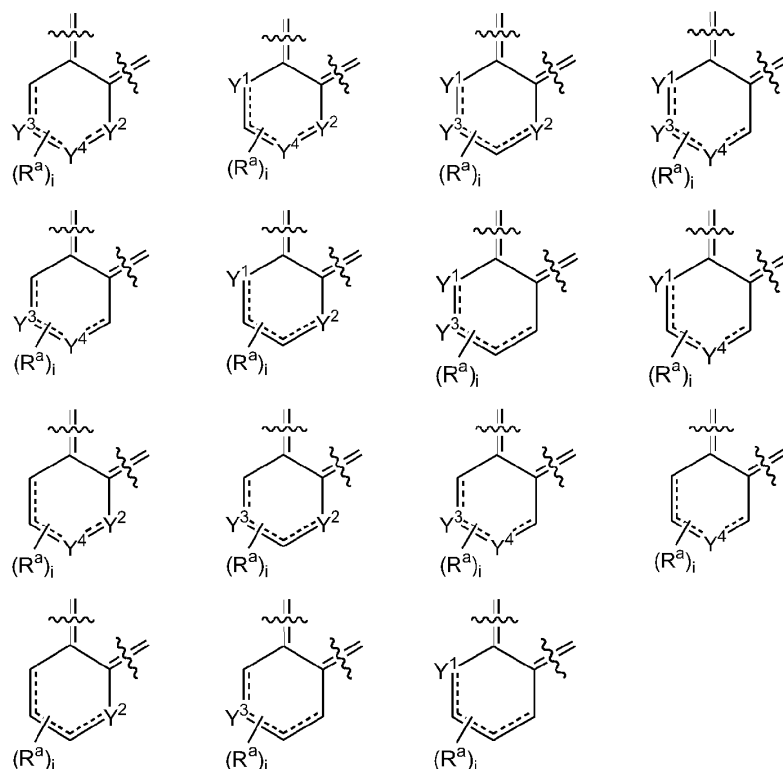
each R^a is independently H, Cl, F, CN or CH₃.

[0078] In certain embodiments, Ring A is

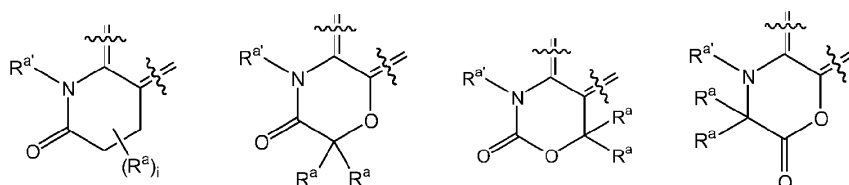


wherein one of R^a is CH₂CHF₂ or CH₂CF₃, and the other R^a is H, CH₃ or CD₃.

[0079] In certain embodiments of (I)-(I_g), Ring A is selected from:

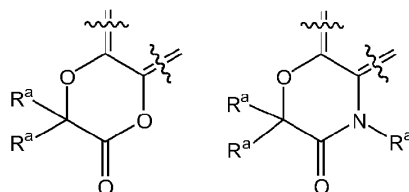


[0080] In certain embodiments, Ring A is selected from:



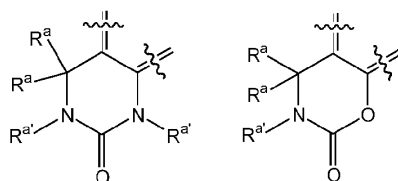
wherein R^{a'} is CH₂CHF₂ or CH₂CF₃, and R^a is H.

[0081] In certain embodiments, Ring A is selected from:



wherein one of R^a and R^{a'} is selected from H, CH₃, CD₃, CD₂CD₃, CH₂CN and CH₂CHF₂, CH₂CF₃ and CH₂CN; and the other R^a and/or R^{a'} is H.

[0082] In certain embodiments, Ring A is selected from:



wherein each R^a is H, and each $R^{a'}$ is independently selected from H, CH_3 , CD_3 , CD_2CD_3 , CH_2CN and CH_2CHF_2 , CH_2CF_3 and CH_2CN .

[0083] In certain embodiments, Ring A comprises one or more of O, NR, C(O), S(O)₂, C(O)O, C(O)NR, and NRC(O)NR, wherein each R is independently H, CH_3 , CH_2CH_3 , CD_2CD_3 , CH_2CHF_2 , CH_2CF_3 or CH_2CN .

[0084] In certain embodiments of (I)-(I_g), X is CH.

[0085] In certain embodiments of (I)-(I_g), X is CR^X .

[0086] In certain embodiments of (I)-(I_g), X is N.

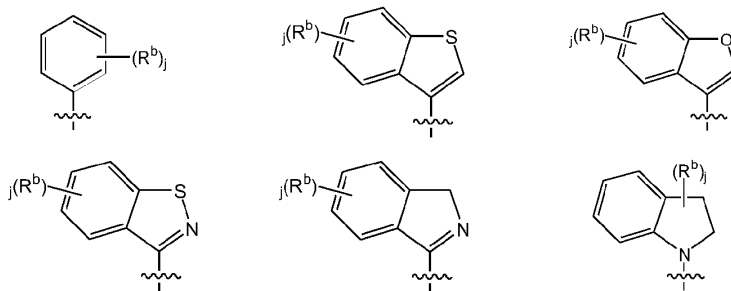
[0087] In certain embodiments of (I)-(I_g), Ring B is a substituted or unsubstituted 5- or 6-membered monocyclic carbocyclyl or heterocyclic.

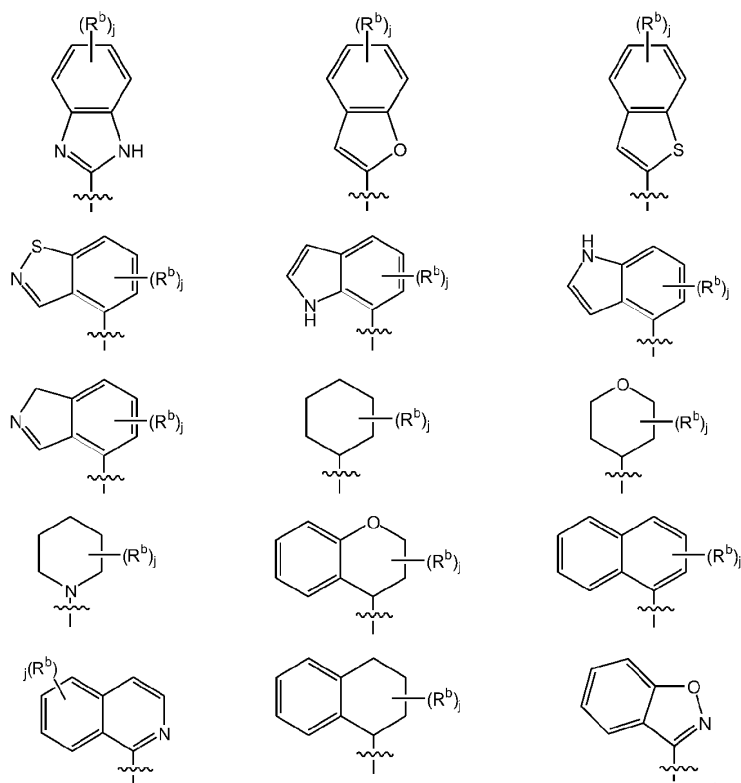
[0088] In certain embodiments of (I)-(I_g), Ring B is a substituted or unsubstituted 5- or 6-membered monocyclic aryl or heteroaryl ring.

[0089] In certain embodiments of (I)-(I_g), Ring B is a substituted or unsubstituted 8- to 10-membered bicyclic carbocyclyl or heterocyclic.

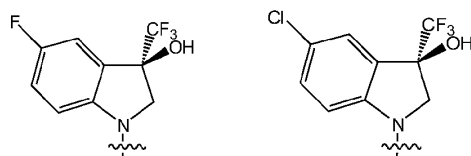
[0090] In certain embodiments of (I)-(I_g), Ring B is a substituted or unsubstituted 8- to 10-membered bicyclic aryl or heteroaryl ring.

[0091] Non-limiting examples of Ring B include:

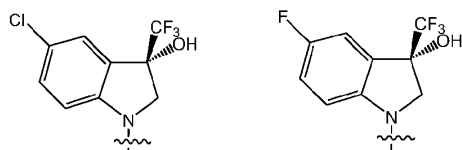




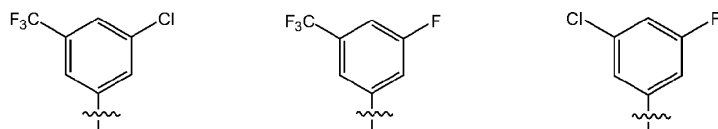
[0092] In certain embodiments of (I)-(I_e), Ring B is selected from:

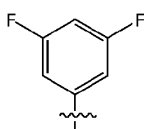
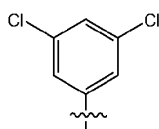


[0093] In certain embodiments of (I)-(I_e), Ring B is selected from:

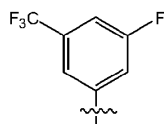


[0094] In certain embodiments of (I)-(I_e), Ring B is selected from:





[0095] In certain embodiments, Ring B is:



[0096] In certain embodiments of (I)-(Ic), Ring B is a substituted or unsubstituted phenyl, pyridyl, pyridazinyl or pyrazinyl.

[0097] In certain embodiments, Ring B is a substituted or unsubstituted phenyl.

[0098] In certain embodiments, Ring B is a substituted or unsubstituted pyridyl.

[0099] In certain embodiments, Ring B is a substituted or unsubstituted pyridazinyl.

[0100] In certain embodiments, Ring B is a substituted or unsubstituted pyrazinyl.

[0101] In certain embodiments of (I)-(Ic), Ring C is a substituted or unsubstituted phenyl, pyridyl, pyridazinyl or pyrazinyl.

[0102] In certain embodiments, Ring C is a substituted or unsubstituted phenyl.

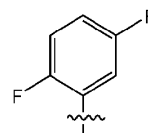
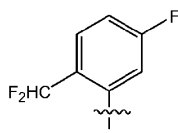
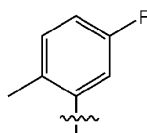
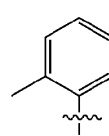
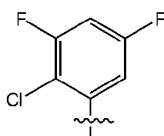
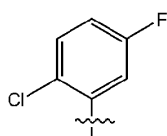
[0103] In certain embodiments, Ring C is a substituted or unsubstituted pyridyl.

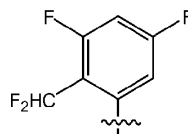
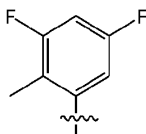
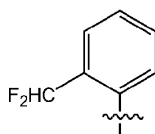
[0104] In certain embodiments, Ring C is a substituted or unsubstituted pyridazinyl.

[0105] In certain embodiments, Ring C is a substituted or unsubstituted pyrazinyl.

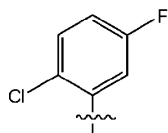
[0106] In certain embodiments of (I)-(Ic), each of Ring B and Ring C is independently a substituted or unsubstituted phenyl.

[0107] Non-limiting examples of Ring C include:

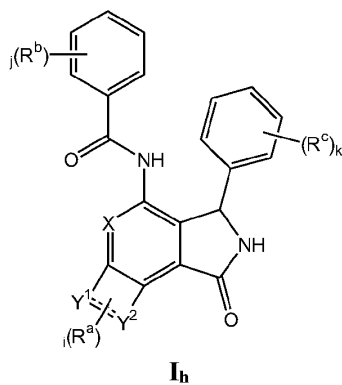




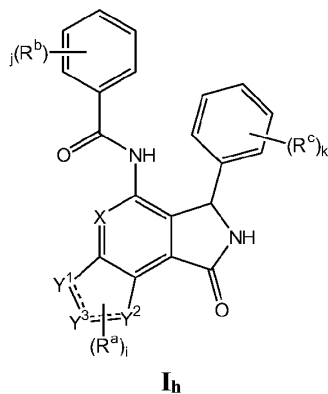
[00108] In certain embodiments, Ring C is:



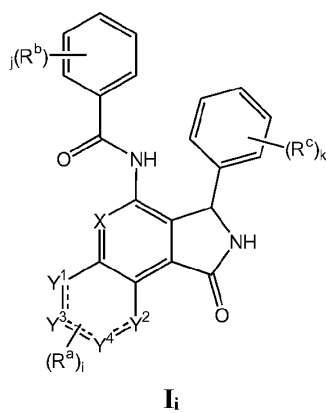
[00109] In certain embodiments of (I), the compound has the structural formula **I_h**:



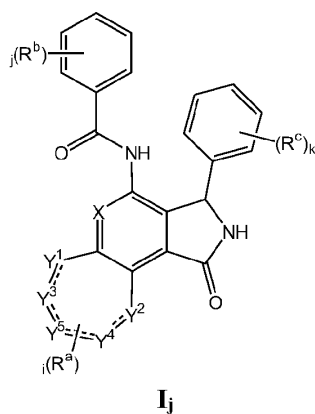
[00110] In certain embodiments of (I), the compound has the structural formula **I_h**:



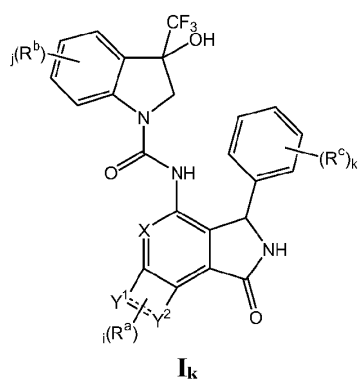
[00111] In certain embodiments of (I), the compound has the structural formula **I_i**:



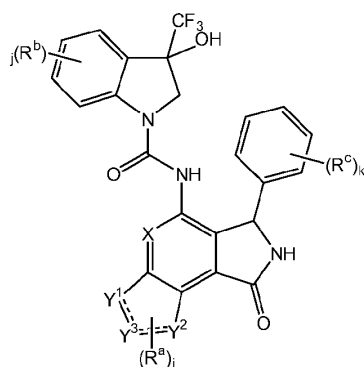
[00112] In certain embodiments of (I), the compound has the structural formula **I_j**:



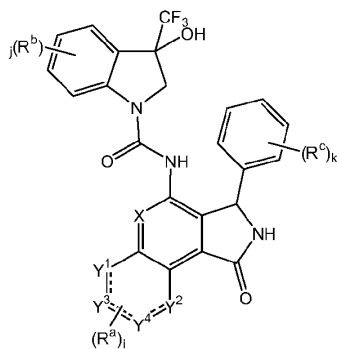
[00113] In certain embodiments of (I), the compound has the structural formula **I_k**:



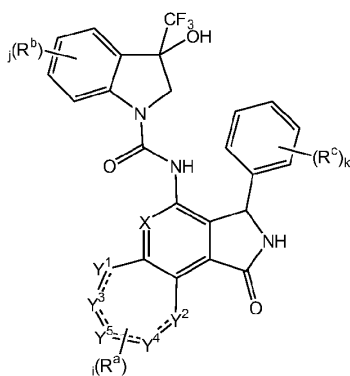
[00114] In certain embodiments of (I), the compound has the structural formula **I_l**:

**I_l**

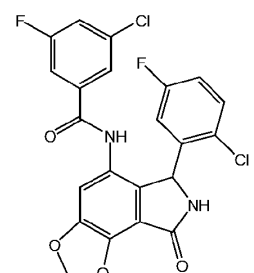
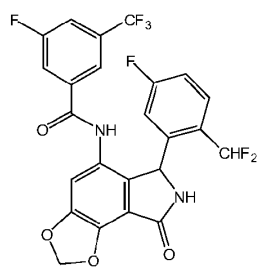
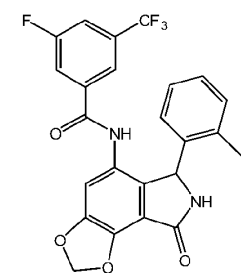
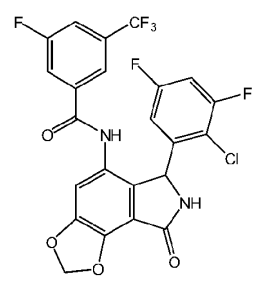
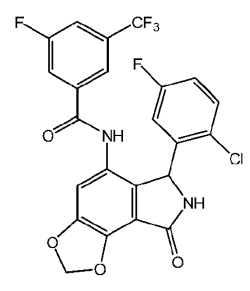
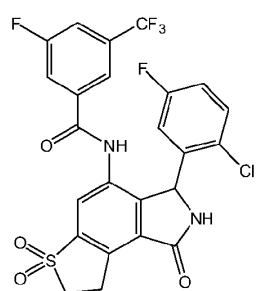
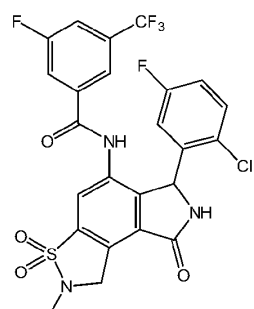
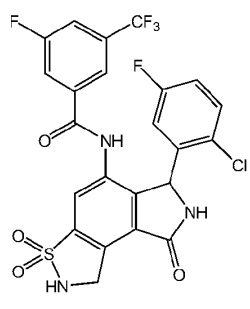
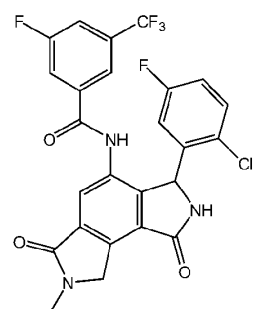
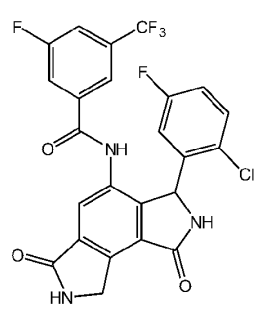
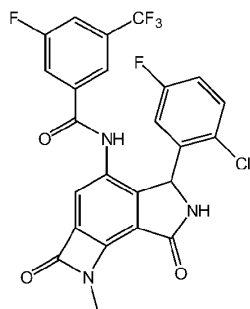
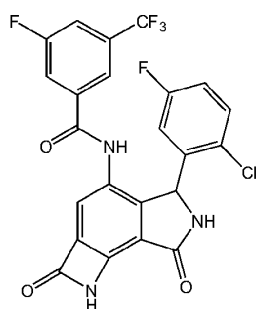
[00115] In certain embodiments of (I), the compound has the structural formula **I_m**:

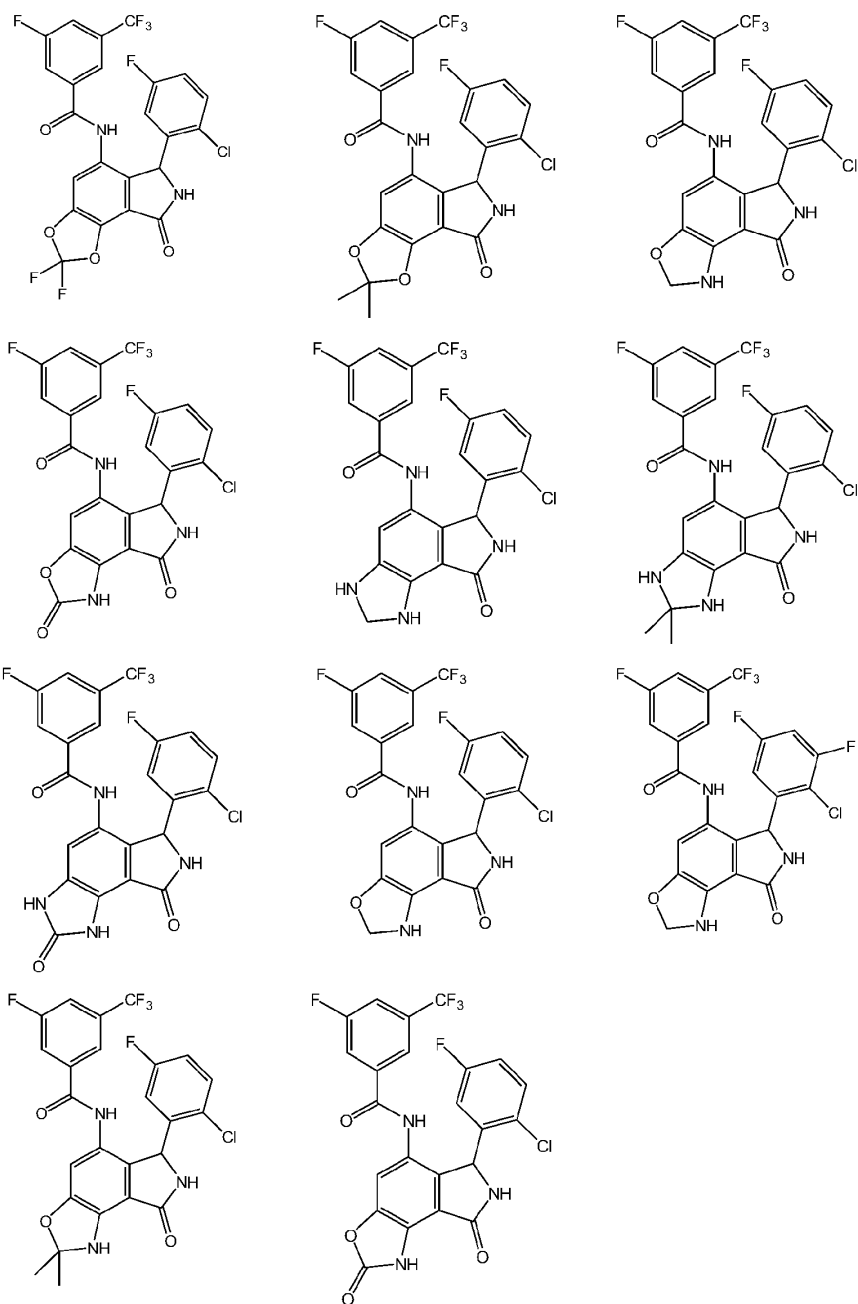
**I_m**

[00116] In certain embodiments of (I), the compound has the structural formula **I_n**:

**I_n**

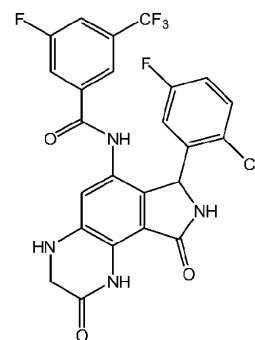
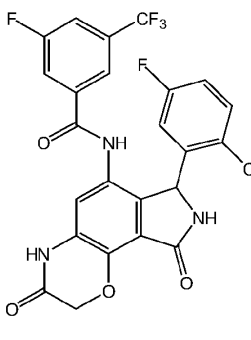
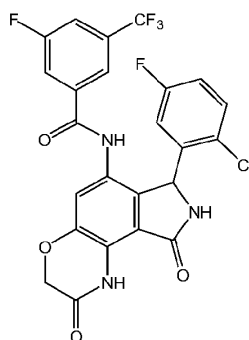
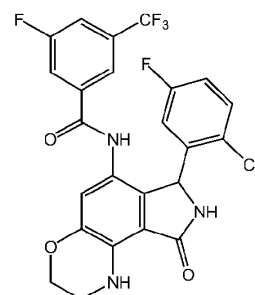
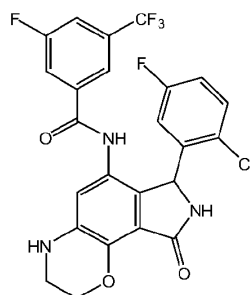
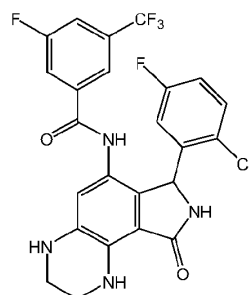
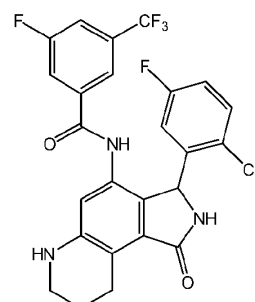
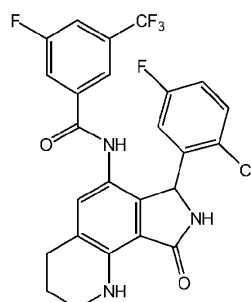
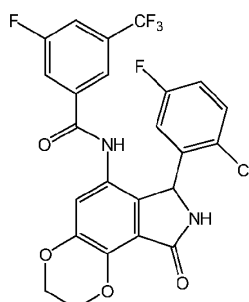
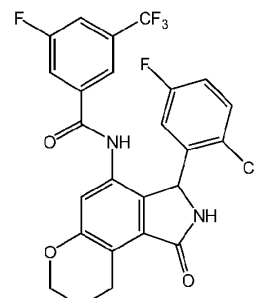
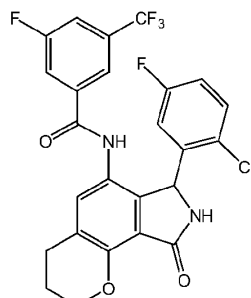
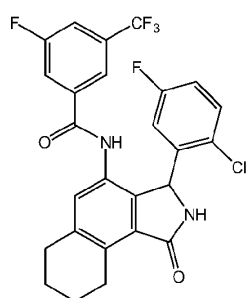
[00117] Non-limiting examples of compounds of the invention include:

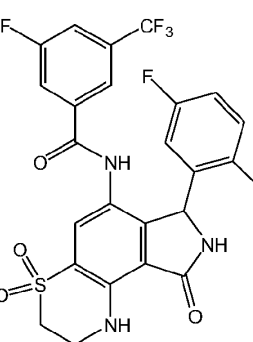
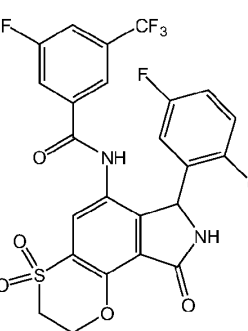
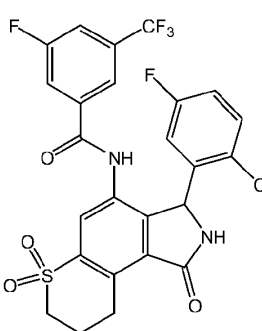
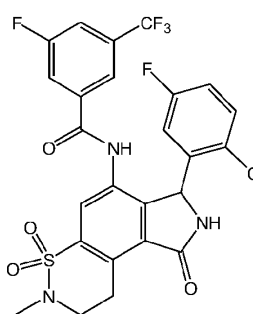
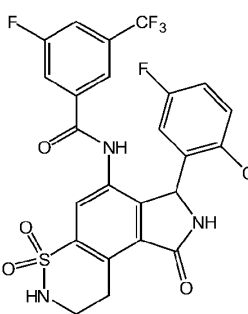
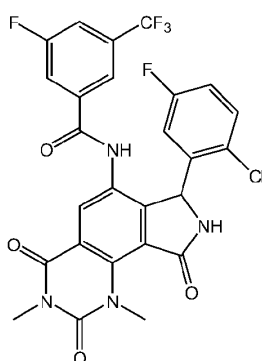
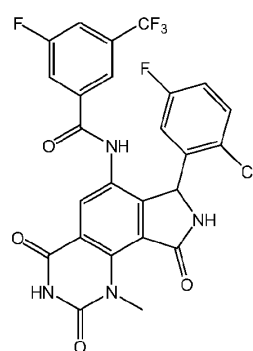
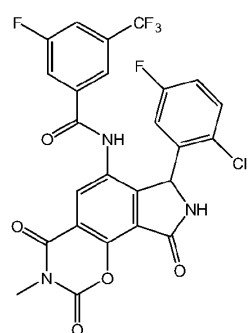
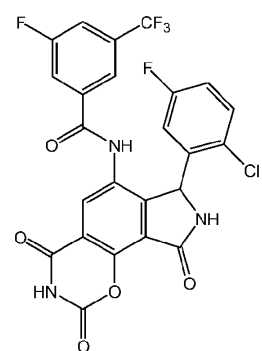
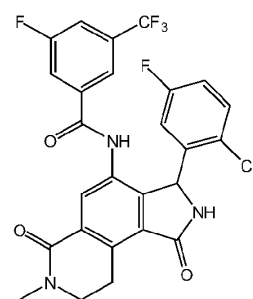
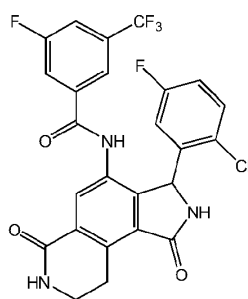
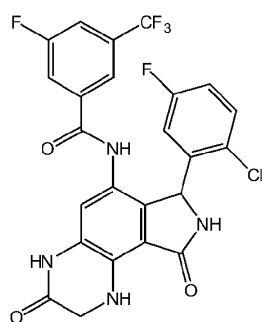


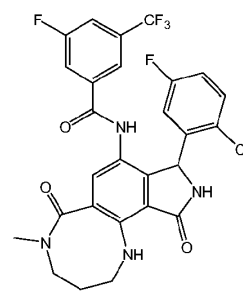
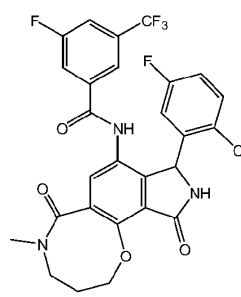
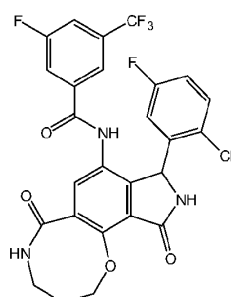
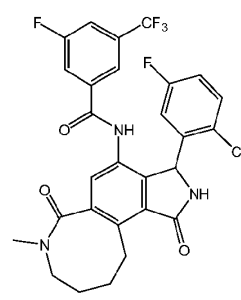
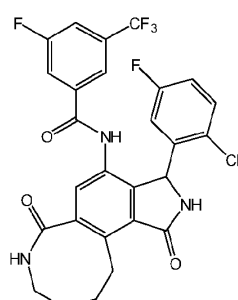
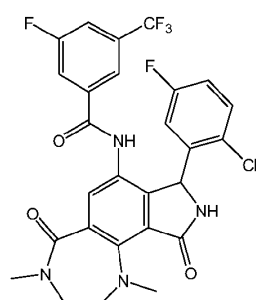
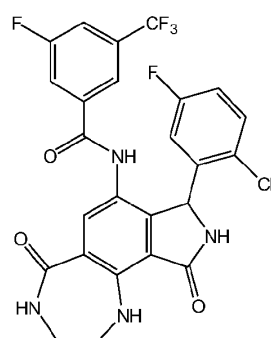
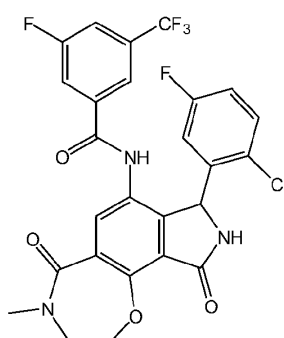
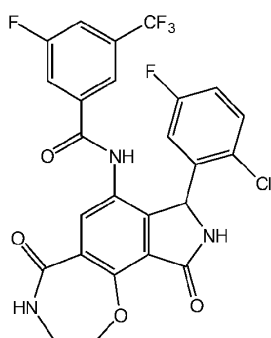
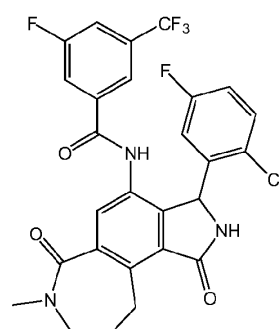
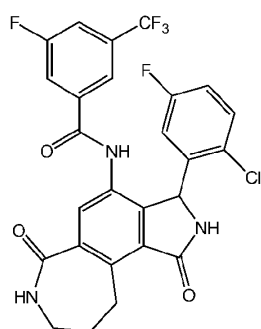
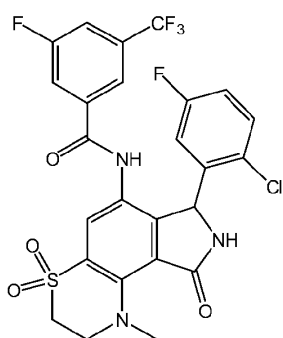


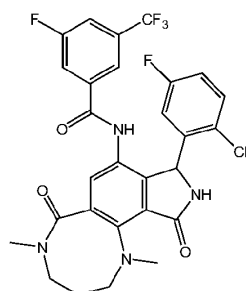
or a pharmaceutically acceptable form or an isotope derivative thereof.

[00118] Non-limiting examples of compounds of the invention include:



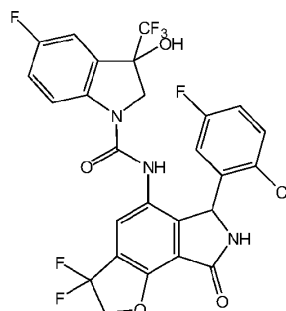
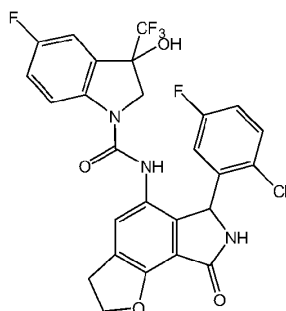
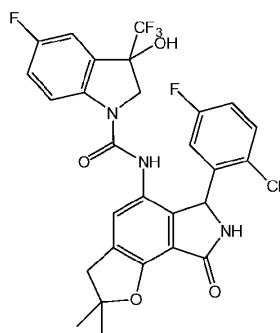
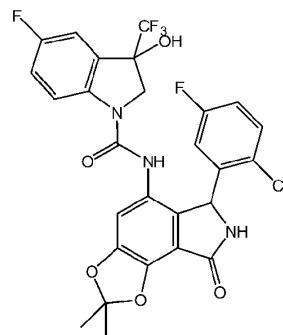
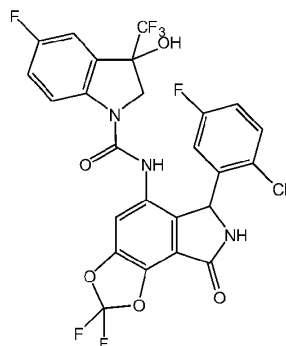
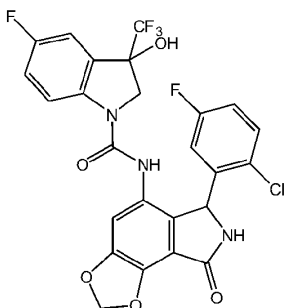
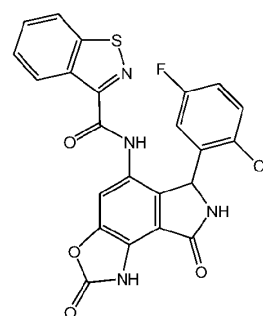
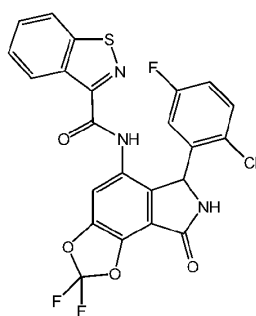
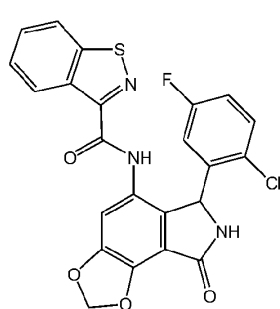


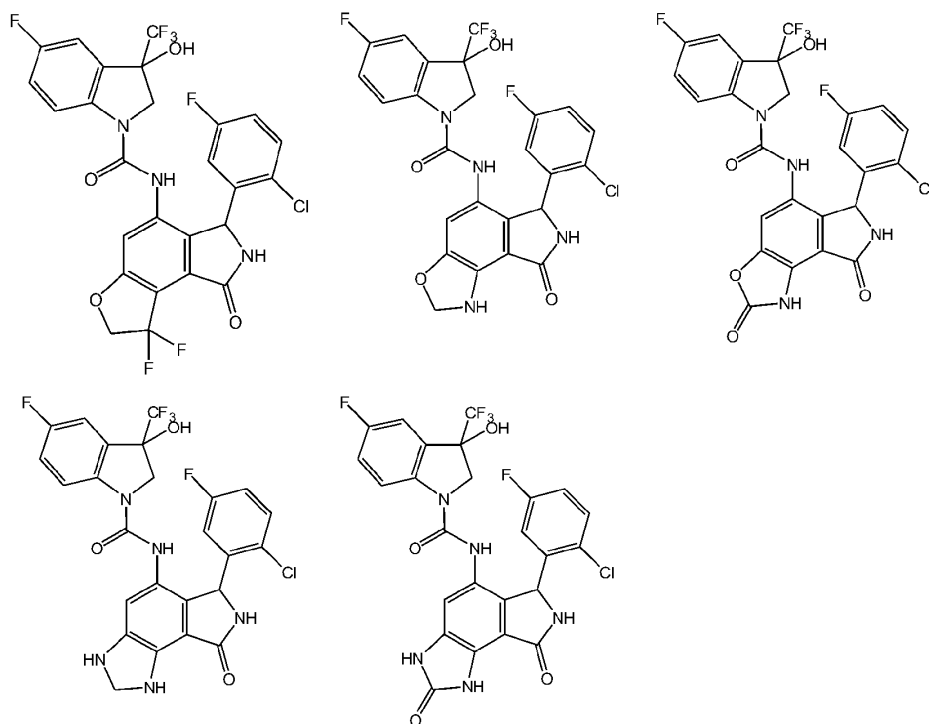




or a pharmaceutically acceptable form or an isotope derivative thereof.

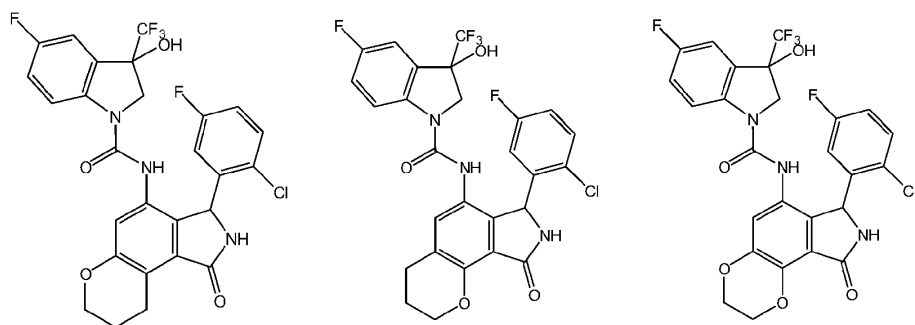
[00119] Non-limiting examples of compounds of the invention include:

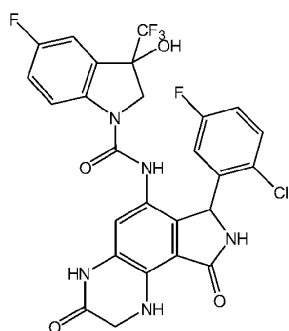
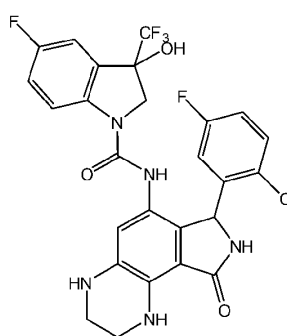
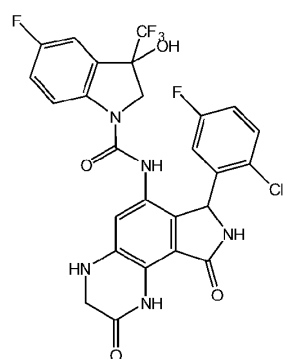
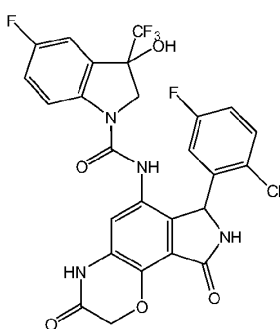
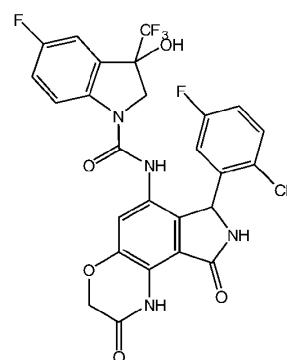
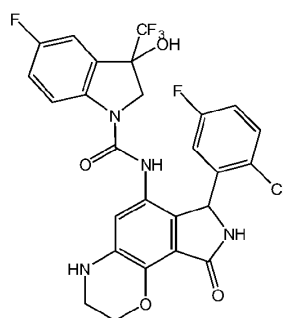
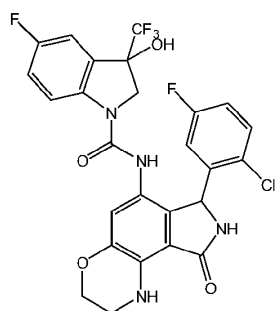




or a pharmaceutically acceptable form or an isotope derivative thereof

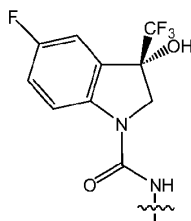
[00120] Non-limiting examples of compounds of the invention also include:



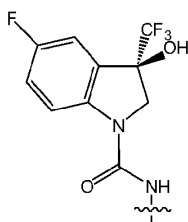


or a pharmaceutically acceptable form or an isotope derivative thereof.

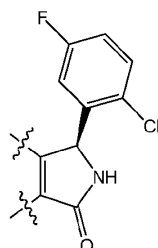
[00121] In certain embodiments, the chirality is as followings:



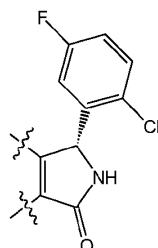
[00122] In certain embodiments, the chirality is as followings:



[00123] In certain embodiments, a compound of the invention exhibits the following chirality at the carbon to which R^2 is bond:



[00124] In certain embodiments, a compound of the invention exhibits the following chirality at the carbon to which R^2 is bond:



[00125] Non-limiting exemplary compounds of the invention can also be found in **Table 1** in the Examples section.

[00126] In certain embodiments, a compound of invention has one or more deuterium atoms in place of hydrogen. In certain embodiments, a compound of invention has one deuterium atom in place of a hydrogen atom.

[00127] In another aspect, the invention generally relates to a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient, carrier, or diluent.

[00128] In certain embodiments, the pharmaceutical composition is suitable for oral administration.

[00129] In yet another aspect, the invention generally relates to a unit dosage form comprising a pharmaceutical composition disclosed herein.

[00130] In certain embodiments, the unit dosage form is in the form of a tablet or capsule.

[00131] 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.

[00132] 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 (17th ed. 1985).

[00133] 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.

[00134] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds described herein or derivatives thereof are admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (i) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (ii) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (iii) humectants, as for example, glycerol, (iv)

disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (v) solution retarders, as for example, paraffin, (vi) absorption accelerators, as for example, quaternary ammonium compounds, (vii) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (viii) adsorbents, as for example, kaolin and bentonite, and (ix) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like. Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others known in the art.

[00135] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers, such as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan, or mixtures of these substances, and the like. Besides such inert diluents, the composition can also include additional agents, such as wetting, emulsifying, suspending, sweetening, flavoring, or perfuming agents.

[00136] In yet another aspect, the invention generally relates to a method for inhibiting cell proliferation *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound disclosed herein.

[00137] In yet another aspect, the invention generally relates to a method for inhibiting PI3K α activity in a cell, comprising contacting the cell with a compound disclosed herein.

[00138] In yet another aspect, the invention generally relates to a method for treating a disease or disorder mediated by PI3K α , comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein.

[00139] In certain embodiments, the disease or disorder is a cellular proliferative disease.

[00140] In yet another aspect, the invention generally relates to a method for treating or reducing cancer, or a related disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein.

[00141] In certain embodiments, the cancer is selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcoma, leukemia, neuroma, melanoma, and lymphoma.

[00142] Examples of cancers targeted in the present invention include, but are not particularly limited to, head and neck cancer, digestive organ cancer (esophageal cancer, stomach cancer, duodenal cancer, liver cancer, biliary cancer (e.g., gallbladder and bile duct cancer), pancreatic cancer, colorectal cancer (e.g., colon cancer, and rectal cancer), etc.), lung cancer (e.g., non-small-cell lung cancer, small-cell lung cancer, and mesothelioma), breast cancer, genital cancer (ovarian cancer, uterine cancer (e.g., cervical cancer and endometrial cancer), etc.), urological cancer (e.g., kidney cancer, bladder cancer, prostate cancer, and testicular tumor), hematopoietic tumor (e.g., leukemia, lymphoma, malignant lymphoma, and multiple myeloma), sarcoma (e.g., osteosarcoma, and soft-tissue sarcoma), skin cancer, brain tumor, a carcinoma, squamous carcinoma, adenocarcinoma, neuroma, melanoma and the like. Examples include lung cancer, pancreatic cancer, rectal cancer, colon cancer colorectal cancer and uterine cancer. In certain embodiments, squamous carcinoma is a cancer of uterine cervix, tarsus, conjunctiva, vagina, lung, oral cavity, skin, bladder, tongue, larynx or esophagus. In one embodiment, adenocarcinoma is a cancer of prostate, small intestine, endometrium, uterine cervix, large intestine, lung, pancreas, esophagus, rectum, uterus, stomach, breast or ovary. In certain embodiments, tumor is rectal cancer, colon cancer, colorectal cancer, pancreatic cancer, lung cancer, breast cancer leukemia or uterine cancer.

[00143] In certain embodiments, the cancer is selected from the group consisting of ovarian cancer, cervical cancer, breast cancer, pancreatic cancer, colorectal cancer, small and non-small cell lung cancer, endometrial cancer, appendix cancer, cholangiocarcinoma, bladder urothelial cancer, gastric carcinomas, bile duct cancer, hepatocellular carcinoma, thyroid carcinoma, and a hematologic malignancy.

[00144] In certain embodiments, the cancer is selected from the group consisting of acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and glioblastomas.

[00145] In certain embodiments, the subject has a mutated class IA PI3K p110 α .

[00146] In certain embodiments, the subject has at least one of the following PI3K α mutations: H1047R, E542K, and E545K.

[00147] In certain embodiments, the subject does not have a PI3K α mutant protein.

[00148] In certain embodiments, the subject being treated is further administered one or more of chemotherapy, radiotherapy, targeted therapy, immunotherapy, and hormonal therapy.

[00149] 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.

[00150] In yet another aspect, the invention generally relates to use of a compound disclosed herein for treating a disease or disorder.

[00151] The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the route of administration, the disposition of the compound and the discretion of the prescribing physician. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be used without causing any harmful side effect, with such larger doses typically divided into several smaller doses for administration throughout the day.

[00152] Any appropriate route of administration can be employed, for example, oral, intramuscular, intravenous, transdermal, subcutaneous, sublingual, parenteral, nasal, pulmonary, inhalational, buccal, intraperitoneal, rectal, intrapleural, and intrathecal administration. Most suitable means of administration for a particular patient will depend on the nature and severity of the disease or condition being treated or the nature of the therapy being used and on the nature of the active compound.

[00153] In certain preferred embodiments, the compound is administered orally.

Pharmaceutical 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.

[00154] 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 hydroxypropylmethylcellulose acetate succinate.

[00155] 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.

[00156] 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.

[00157] 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.

[00158] 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.

[00159] Compounds of the present invention may also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

[00160] 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.

[00161] 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.

[00162] 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.

[00163] Methods of treatment disclosed herein may be employed in combination with or in addition to other therapies. In certain embodiments, the subject being treated is further administered one or more of chemotherapy, radiotherapy, targeted therapy, immunotherapy, and hormonal therapy.

[00164] Exemplary additional therapeutically active agents include, but are not limited to, small organic molecules such as drug compounds, *e.g.*, compounds approved by the U.S. Food and Drug Administration (FDA) as provided in the Code of Federal Regulations (CFR), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins and cells.

[00165] In certain embodiments, a compound of the invention may be administered in combination with endocrine therapy, *e.g.*, agents such as letrozole, fulvestrant, tamoxifen, exemestane, or anastrozole.

[00166] In some embodiments, a compound of the invention may be administered in combination with a chemotherapeutic agent, *e.g.*, docetaxel, paclitaxel, cisplatin, carboplatin, capecitabine, gemcitabine or vinorelbine. In other embodiments, a compound of the invention may be administered in combination with an anti-HER2 agent, *e.g.*, trastuzumab or pertuzumab.

[00167] In certain embodiments, the method disclosed herein is in combination with one or more of immune check point blockade, co-signaling of T cells, and tumor targeting antibody therapies.

[00168] In certain embodiments, the method further comprises administering a chemotherapeutic agent to the subject.

[00169] In certain embodiments, the method further comprises administering a radiotherapy to the subject. In certain embodiments, the method further comprises administering a targeted therapy to the subject. In certain embodiments, the method further comprises administering an immunotherapy to the subject. In certain embodiments, the method further comprises administering hormonal therapy to the subject.

[00170] As used herein, the term "chemotherapeutic agent" refers to a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include Erlotinib (TARCEVA®, Genentech/OSI Pharm.), Bortezomib (VELCADE®, Millennium Pharm.), Fulvestrant (FASLODEX®, AstraZeneca), Sutent (SU11248, Pfizer), Letrozole (FEMARA®, Novartis), Imatinib mesylate (GLEEVEC®, Novartis), PTK787/ZK 222584 (Novartis), Oxaliplatin (Eloxatin®, Sanofi), 5-FU (5-fluorouracil), Leucovorin, Rapamycin (Sirolimus, RAPAMUNE®, Wyeth), Lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), Lonafermin (SCH 66336), Sorafenib (BAY43-9006, Bayer Labs), and Gefitinib (IRESSA®, AstraZeneca), AG1478, AG1571 (SU 5271; Sugen), alkylating agents such as thiotepa and CYTOXAN® cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylmelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analog topotecan); bryostatin; callystatin;

CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (*e.g.*, calicheamicin, especially calicheamicin gammall and calicheamicin omegall (Angew Chem. Intl. Ed. Engl. (1994) 33: 183-186); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabycin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6- diazo-5-oxo-L-norleucine, ADRIAMYCIN[®] (doxorubicin), morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esonibicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6- mercaptopurine, thiamnirprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiothane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK[®] polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes

(especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, *e.g.*, TAXOL[®] (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE[®] (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumburg, Ill.), and TAXOTERE[®] (doxorubicin; Rhone-Poulenc Rorer, Antony, France); chlorambucil; GEMZAR[®] (gemcitabine); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP- 16); ifosfamide; mitoxantrone; vincristine; NAVELBINE[®] (vinorelbine); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA[®]); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

[00171] Examples of the second (or further) agent or therapy may include, but are not limited to, immunotherapies (*e.g.* PD-1 inhibitors (pembrolizumab, nivolumab, cemiplimab), PD-L1 inhibitors (atezolizumab, avelumab, durvalumab), CTLA4 antagonist, cell signal transduction inhibitors (*e.g.*, imatinib, gefitinib, bortezomib, erlotinib, sorafenib, sunitinib, dasatinib, vorinostat, lapatinib, temsirolimus, nilotinib, everolimus, pazopanib, trastuzumab, bevacizumab, cetuximab, ranibizumab, pegaptanib, panitumumab and the like), mitosis inhibitors (*e.g.*, paclitaxel, vincristine, vinblastine and the like), alkylating agents (*e.g.*, cisplatin, cyclophosphamide, carboplatin, ifosfamide and the like), anti-metabolites (*e.g.*, methotrexate, 5-FU and the like), intercalating anticancer agents, (*e.g.*, actinomycin, anthracycline, bleomycin, mitomycin-C and the like), topoisomerase inhibitors (*e.g.*, irinotecan, topotecan, teniposide and the like), immunotherapeutic agents (*e.g.*, interleukin, interferon and the like) and antihormonal agents (*e.g.*, tamoxifen, raloxifene and the like).

[00172] 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, *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.

[00173] 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.

[00174] 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.

[00175] Isotopically-labeled compounds are also within the scope of the present disclosure. As used herein, an "isotopically-labeled compound" refers to a presently disclosed compound including pharmaceutical salts and prodrugs thereof, each as described herein, in which one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds presently disclosed include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively.

[00176] By isotopically-labeling the presently disclosed compounds, the compounds may be useful in drug and/or substrate tissue distribution assays. Tritiated (^3H) and carbon-14 (^{14}C) labeled compounds are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (^2H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds presently disclosed, including pharmaceutical salts, esters, and prodrugs thereof, can be prepared by any means known in the art.

[00177] Further, substitution of normally abundant hydrogen (^1H) with heavier isotopes such as deuterium can afford certain therapeutic advantages, *e.g.*, resulting from improved absorption,

distribution, metabolism and/or excretion (ADME) properties, creating drugs with improved efficacy, safety, and/or tolerability. Benefits may also be obtained from replacement of normally abundant ^{12}C with ^{13}C . (See, WO 2007/005643, WO 2007/005644, WO 2007/016361, and WO 2007/016431.)

[00178] Stereoisomers (*e.g.*, cis and trans isomers) and all optical isomers of a presently disclosed compound (*e.g.*, R and S enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers are within the scope of the present disclosure.

[00179] Compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 95% (“substantially pure”), which is then used or formulated as described herein. In certain embodiments, the compounds of the present invention are more than 99% pure.

[00180] 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.

[00181] Any appropriate route of administration can be employed, for example, parenteral, intravenous, subcutaneous, intramuscular, intraventricular, intracorporeal, intraperitoneal, rectal, or oral administration. Most suitable means of administration for a particular patient will depend on the nature and severity of the disease or condition being treated or the nature of the therapy being used and on the nature of the active compound.

[00182] Compositions for parenteral injection comprise pharmaceutically-acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00183] These compositions can also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paragen, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents

such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption, such as aluminum monostearate and gelatin.

[00184] Compounds of the present invention may also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically-acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

[00185] Total daily dose of the compositions of the invention to be administered to a human or other mammal host in single or divided doses may be in amounts, for example, from 0.0001 to 300 mg/kg body weight daily and more usually 1 to 300 mg/kg body weight. The dose, from 0.0001 to 300 mg/kg body, may be given twice a day.

[00186] Materials, compositions, and components disclosed herein can be used for, can be used in conjunction with, can be used in preparation for, or are products of the disclosed methods and compositions. It is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutations of these compounds may not be explicitly disclosed, each is specifically contemplated and described herein. For example, if a method is disclosed and discussed and a number of modifications that can be made to a number of molecules including in the method are discussed, each and every combination and permutation of the method, and the modifications that are possible are specifically contemplated unless specifically indicated to the contrary. Likewise, any subset or combination of these is also specifically contemplated and disclosed. This concept applies to all aspects of this disclosure including, but not limited to, steps in methods using the disclosed compositions. Thus, if there are a variety of additional steps that can be performed, it is understood that each of these additional steps can be performed with any specific method steps or combination of method steps of the disclosed methods, and that each

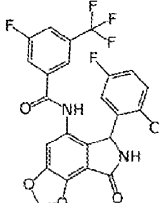
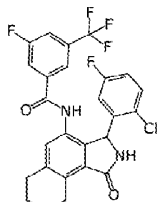
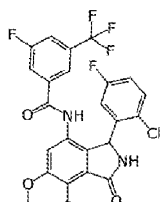
such combination or subset of combinations is specifically contemplated and should be considered disclosed.

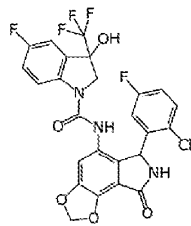
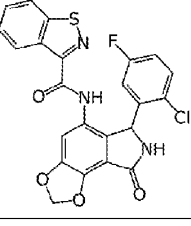
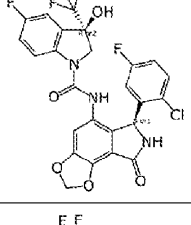
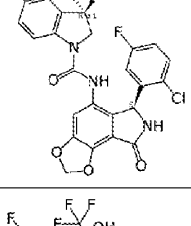
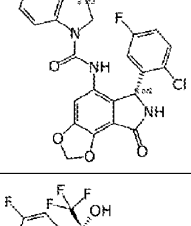
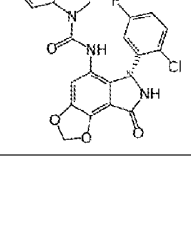
Examples

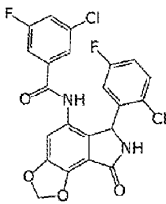
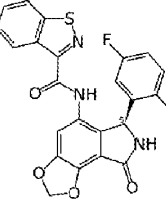
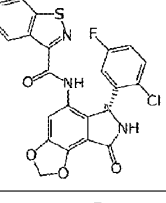
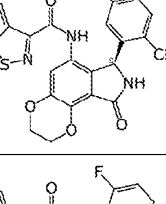
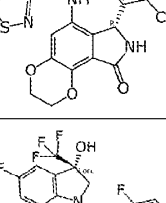
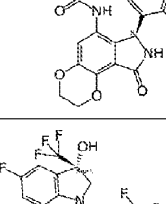
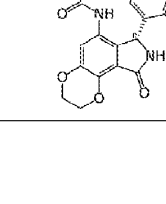
[00187] The following examples are given for the purpose of illustrating the invention, but not for limiting the scope or spirit of the invention.

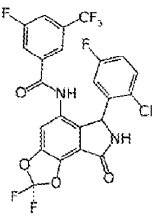
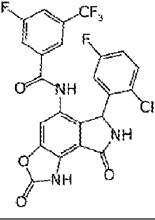
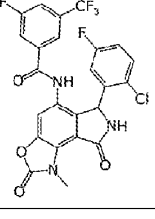
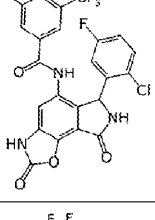
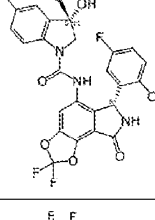
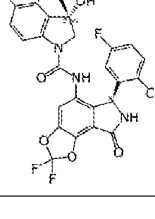
[00188] Compounds of the invention, including those specifically disclosed herein above and herein below, may be prepared as described in the following schemes. Although the present invention has been described in detail with preferred embodiments, those of ordinary skill in the art should understand that modifications, variations, and equivalent replacements made to the present invention within the scope of the present invention belong to the protection of the present invention.

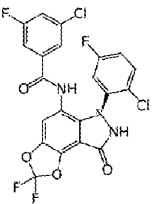
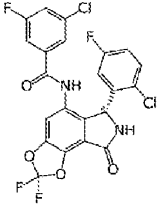
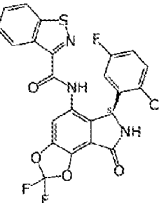
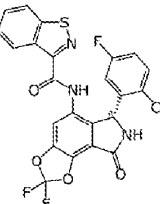
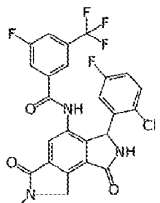
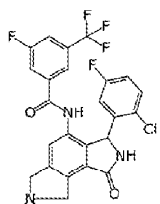
Table 1. Exemplary Compounds

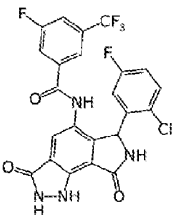
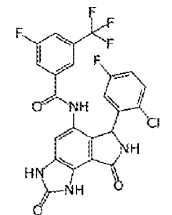
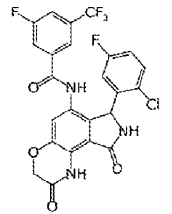
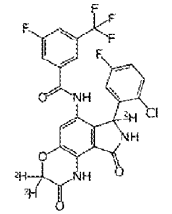
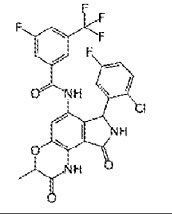
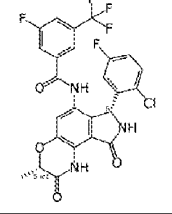
Example #	Structure	SMILES
Example 1		<chem>FC(F)(F)C1=CC(F)=CC(C(=O)NC2=C3C(C4=CC(F)=CC=C4C1)NC(=O)C3=C3C(=C2)OCO3)=C1</chem>
Example 2		<chem>FC(F)(F)C1=CC(F)=CC(C(=O)NC2=C3C(C4=CC(F)=CC=C4C1)NC(=O)C3=C3C(=C2)CCCC3)=C1</chem>
Example 3		<chem>FC(F)(F)C1=CC(F)=CC(C(=O)NC2=C3C(C4=CC(F)=CC=C4C1)NC(=O)C3=C3C(=C2)OCCO3)=C1</chem>

Example 4		<chem>FC1=CC=C(Cl)C(C2NC(=O)C3=C4C(=CC(NC(=O)N5CC(O)(C(F)(F)F)C6=C5C=CC(F)=C6)=C23)OCO4)=C1</chem>
Example 5		<chem>FC1=CC=C(Cl)C(C2NC(=O)C3=C4C(=CC(NC(=O)N5C=C6=C5C=CC=C6)=C23)OCO4)=C1</chem>
Example 6		<chem>FC1=CC=C(Cl)C([C@H]2NC(=O)C3=C4C(=CC(NC(=O)N5C[C@@](O)(C(F)(F)F)C6=C5C=CC(F)=C6)=C23)OCO4)=C1</chem>
Example 7		<chem>FC1=CC=C(Cl)C([C@H]2NC(=O)C3=C4C(=CC(NC(=O)N5C[C@@](O)(C(F)(F)F)C6=C5C=CC(F)=C6)=C23)OCO4)=C1</chem>
Example 8		<chem>FC1=CC=C(Cl)C([C@@H]2NC(=O)C3=C4C(=CC(NC(=O)N5C[C@](O)(C(F)(F)F)C6=C5C=CC(F)=C6)=C23)OCO4)=C1</chem>
Example 9		<chem>FC1=CC=C(Cl)C([C@@H]2NC(=O)C3=C4C(=CC(NC(=O)N5C[C@](O)(C(F)(F)F)C6=C5C=CC(F)=C6)=C23)OCO4)=C1</chem>

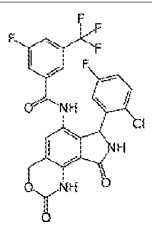
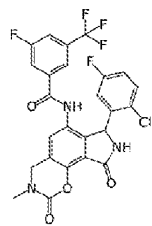
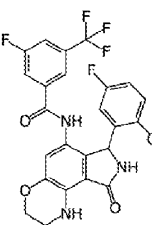
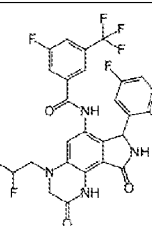
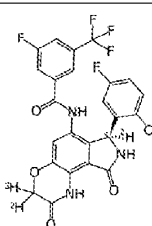
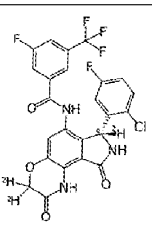
Example 10		<chem>FC1=CC(C(=O)NC2=C3C(C4=CC(F)=CC=C4Cl)NC(=O)C3=C3C(=C2)OCO3)=CC(Cl)=C1</chem>
Example 11		<chem>FC1=CC=C(Cl)C([C@H]2NC(=O)C3=C4C(=CC(NC(=O)C5=NSC6=C5C=CC=C6)=C23)OCO4)=C1</chem>
Example 12		<chem>FC1=CC=C(Cl)C([C@@H]2NC(=O)C3=C4C(=CC(NC(=O)C5=NSC6=C5C=CC=C6)=C23)OCO4)=C1</chem>
Example 13		<chem>FC1=CC=C(Cl)C([C@H]2NC(=O)C3=C4C(=CC(NC(C5=NSC6=CC=CC=C65)=O)=C23)OCCO4)=C1</chem>
Example 14		<chem>FC1=CC=C(Cl)C([C@@H]2NC(=O)C3=C4C(=CC(NC(C5=NSC6=CC=CC=C65)=O)=C23)OCCO4)=C1</chem>
Example 15		<chem>FC1=CC=C(Cl)C([C@H]2NC(=O)C3=C4C(=CC(NC(N5C([C@](O)(C(F)(F)F)C6=C5C=CC(F)=C6)=O)=C23)OCCO4)=C1</chem>
Example 16		<chem>FC1=CC=C(Cl)C([C@@H]2NC(=O)C3=C4C(=CC(NC(N5C([C@](O)(C(F)(F)F)C6=C5C=CC(F)=C6)=O)=C23)OCCO4)=C1</chem>

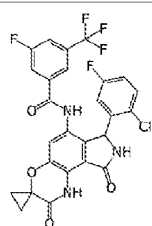
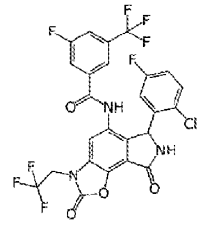
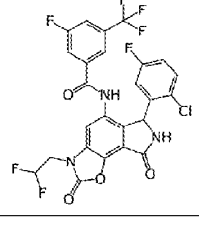
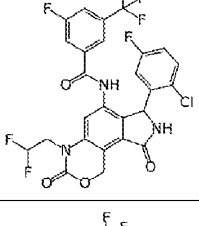
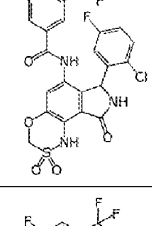
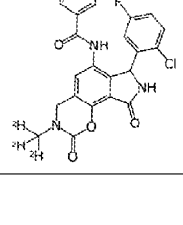
Example 17		<chem>FC1=CC(C(=O)NC2=C3C(C4=CC(F)=CC=C4Cl)NC(=O)C3=C3C(=C2)OC(F)(F)O3)=CC(C(F)(F)F)=C1</chem>
Example 18		<chem>FC1=CC(C(=O)NC2=C3C(C4=CC(F)=CC=C4Cl)NC(=O)C3=C3C(=C2)OC(=O)N3)=CC(C(F)(F)F)=C1</chem>
Example 19		<chem>FC1=CC(C(=O)NC2=C3C(C4=CC(F)=CC=C4Cl)NC(=O)C3=C3C(=C2)OC(=O)N3C)=CC(C(F)(F)F)=C1</chem>
Example 20		<chem>FC1=CC(C(=O)NC2=C3C(C4=CC(F)=CC=C4Cl)NC(=O)C3=C3C(=C2)NC(=O)O3)=CC(C(F)(F)F)=C1</chem>
Example 21		<chem>FC1=CC=C(Cl)C([C@H]2NC(=O)C3=C4C(=CC(NC(N5C[C@](O)(C(F)(F)F)C6=C5C=CC(F)=C6)=O)=C23)OC(F)(F)O4)=C1</chem>
Example 22		<chem>FC1=CC=C(Cl)C([C@H]2NC(=O)C3=C4C(=CC(NC(N5C[C@](O)(C(F)(F)F)C6=C5C=CC(F)=C6)=O)=C23)OC(F)(F)O4)=C1</chem>

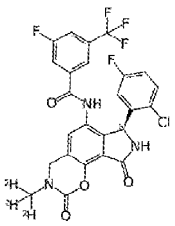
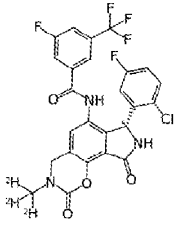
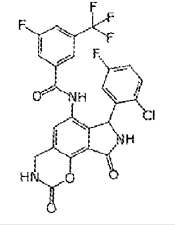
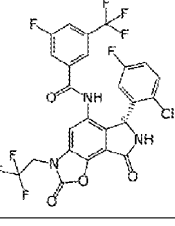
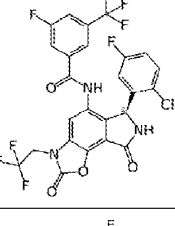
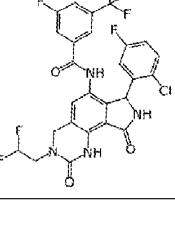
Example 23		<chem>FC1=CC(C(=O)NC2=C3[C@H](C4=CC(F)=CC=C4Cl)NC(=O)C3=C3C(=C2)OC(F)(F)O3)=CC(Cl)=C1</chem>
Example 24		<chem>FC1=CC(C(=O)NC2=C3[C@H](C4=CC(F)=CC=C4Cl)NC(=O)C3=C3C(=C2)OC(F)(F)O3)=CC(Cl)=C1</chem>
Example 25		<chem>FC1=CC=C(Cl)C([C@H]2NC(=O)C3=C4C(=CC(NC(C5=NSC6=C5C=CC(=O)=C23)OC(F)(F)O4)=C1</chem>
Example 26		<chem>FC1=CC=C(Cl)C([C@@H]2NC(=O)C3=C4C(=CC(NC(C5=NSC6=C5C=CC(=O)=C23)OC(F)(F)O4)=C1</chem>
Example 27		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=O)N(CC3=C1C(=O)NC2C1=CC(F)=CC=C1Cl</chem>
Example 28		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3CN(C)CC3=C1C(=O)NC2C1=CC(F)=CC=C1Cl</chem>

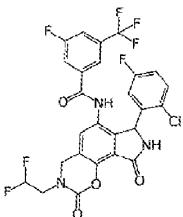
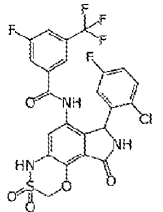
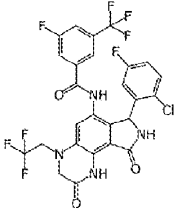
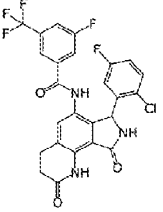
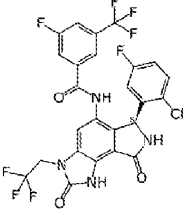
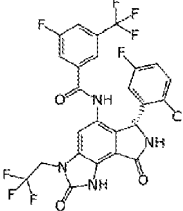
Example 29		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)NC2C1=CC(F)=CC=C1Cl)N)NC3=O</chem>
Example 30		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)NC(=O)N3)C(=O)NC2C1=CC(F)=CC=C1Cl</chem>
Example 32		<chem>FC1=CC(C(=O)NC2=C3C(C4=CC(F)=CC=C4Cl)NC(=O)C3=C3C(=C2)OCC(=O)N3)=CC(C(F)(F)F)=C1</chem>
Example 35		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)OC([2H])([2H])C(=O)N3)C(=O)NC2(C1=CC(F)=CC=C1Cl)[2H]</chem>
Example 36		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)OC(C)C(=O)N3)C(=O)NC2C1=CC(F)=CC=C1Cl</chem>
Example 37		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)O[C@@H](C)C(=O)N3)C(=O)N[C@@H]2C1=CC(F)=CC=C1Cl</chem>

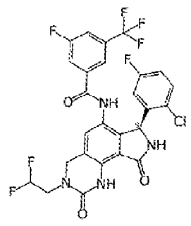
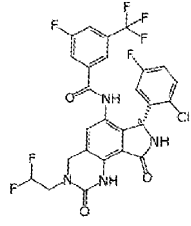
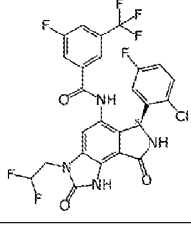
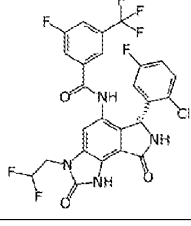
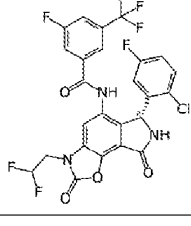
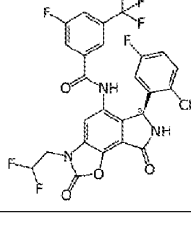
Example 38		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)O[C@H](C)C(=O)N3)C(=O)N[C@H]2C1=CC(F)=CC=C1Cl</chem>
Example 39		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)O[C@H](C)C(=O)N3)C(=O)N[C@@H]2C1=CC(F)=CC=C1Cl</chem>
Example 40		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)O[C@@H](C)C(=O)N3)C(=O)N[C@@H]2C1=CC(F)=CC=C1Cl</chem>
Example 41		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)OC(F)(F)C(=O)N3)C(=O)NC2C1=CC(F)=CC=C1Cl</chem>
Example 42		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)OC(F)(F)C(=O)N3)C(=O)N[C@@H]2C1=CC(F)=CC=C1Cl</chem>
Example 43		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)OC(F)(F)C(=O)N3)C(=O)N[C@H]2C1=CC(F)=CC=C1Cl</chem>

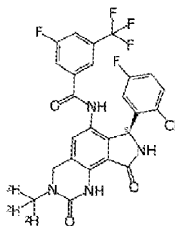
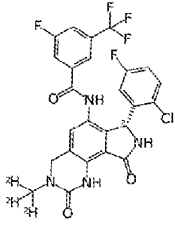
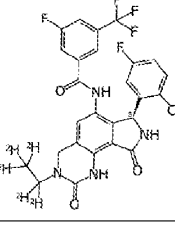
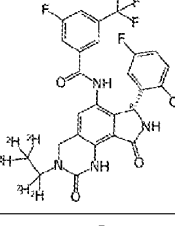
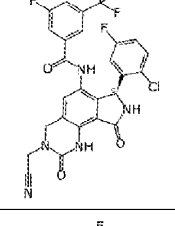
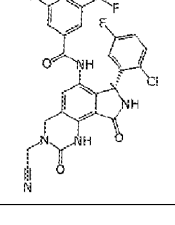
Example 44		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)NC2C1=CC(F)=CC=C1Cl)N C(=O)OC3</chem>
Example 45		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)NC2C1=CC(F)=CC=C1Cl)O C(=O)N(C)C3</chem>
Example 46		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)OCC N3)C(=O)NC2C1=CC(F)=CC=C1Cl</chem>
Example 47		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)NC2C1=CC(F)=CC=C1Cl)N C(=O)CN3CC(F)F</chem>
Example 48		<chem>O1C([2H])([2H])C(=O)NC2=C3C(=O)N[C@@](C4=CC(F)=CC=C4Cl)([2H])C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>
Example 49		<chem>O1C([2H])([2H])C(=O)NC2=C3C(=O)N[C@@](C4=CC(F)=CC=C4Cl)([2H])C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>

Example 50		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)OC1(C(=O)N3)CC1)C(=O)NC2C1=CC(F)=CC=C1Cl</chem>
Example 51		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)NC2C1=CC(F)=CC=C1Cl)OC(=O)N3CC(F)(F)F</chem>
Example 52		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)NC2C1=CC(F)=CC=C1Cl)OC(=O)N3CC(F)F</chem>
Example 53		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)NC2C1=CC(F)=CC=C1Cl)COC(=O)N3CC(F)F</chem>
Example 54		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)OCS(=O)(=O)N3)C(=O)NC2C1=CC(F)=CC=C1Cl</chem>
Example 55		<chem>C1N(C([2H])([2H])([2H])C(=O)OC2=C3C(=O)NC(C4=CC(F)=CC=C4Cl)C3=C(NC(=O)C3=C(C(F)(F)F)=CC(F)=C3)C=C12</chem>

Example 56		<chem>C1N(C([2H]))([2H])[2H])C(=O)OC2=C3C(=O)N[C@H](C4=CC(F)=CC=C4Cl)C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>
Example 57		<chem>C1N(C([2H]))([2H])[2H])C(=O)OC2=C3C(=O)N[C@@H](C4=CC(F)=CC=C4Cl)C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>
Example 58		<chem>C1NC(=O)OC2=C3C(=O)NC(C4=CC(F)=CC=C4Cl)C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>
Example 59		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)N[C@H]2C1=CC(F)=CC=C1Cl)OC(=O)N3CC(F)(F)F</chem>
Example 60		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)N[C@@H]2C1=CC(F)=CC=C1Cl)OC(=O)N3CC(F)(F)F</chem>
Example 61		<chem>C1N(CC(F)F)C(=O)NC2=C3C(=O)NC(C4=CC(F)=CC=C4Cl)C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>

Example 62		<chem>C1N(CC(F)F)C(=O)OC2=C3C(=O)NC(C4=CC(F)=CC=C4Cl)C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>
Example 63		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)NC2C1=CC(F)=CC=C1Cl)OCS(=O)(=O)N3</chem>
Example 64		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)NC2C1=CC(F)=CC=C1Cl)NC(=O)CN3CC(F)(F)F</chem>
Example 65		<chem>C1=C2C(=C3C(=C1NC(=O)C1=CC(F)=CC(C(F)(F)F)=C1)C(C1=C(Cl)C=CC(F)=C1)NC3=O)NC(=O)CC2</chem>
Example 66		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)N[C@@H]2C1=CC(F)=CC=C1Cl)NC(=O)N3CC(F)(F)F</chem>
Example 67		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)N[C@H]2C1=CC(F)=CC=C1Cl)NC(=O)N3CC(F)(F)F</chem>

Example 68		<chem>C1N(CC(F)F)C(=O)NC2=C3C(=O)N[C@H](C4=CC(F)=CC=C4Cl)C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>
Example 69		<chem>C1N(CC(F)F)C(=O)NC2=C3C(=O)N[C@@H](C4=CC(F)=CC=C4Cl)C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>
Example 70		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)N[C@@H]2C1=CC(F)=CC=C1Cl)NC(=O)N3CC(F)F</chem>
Example 71		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)N[C@H]2C1=CC(F)=CC=C1Cl)NC(=O)N3CC(F)F</chem>
Example 72		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)N[C@H]2C1=CC(F)=CC=C1Cl)OC(=O)N3CC(F)F</chem>
Example 73		<chem>C12=C(NC(C3=CC(C(F)(F)F)=CC(F)=C3)=O)C=C3C(=C1C(=O)N[C@@H]2C1=CC(F)=CC=C1Cl)OC(=O)N3CC(F)F</chem>

Example 74		<chem>C1N(C([2H])([2H])[2H])C(=O)NC2=C3C(=O)N[C@H](C4=CC(F)=CC=C4Cl)C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>
Example 75		<chem>C1N(C([2H])([2H])[2H])C(=O)NC2=C3C(=O)N[C@@H](C4=CC(F)=CC=C4Cl)C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>
Example 76		<chem>C1N(C([2H])([2H])C([2H])([2H])[2H])C(=O)NC2=C3C(=O)N[C@H](C4=CC(F)=CC=C4Cl)C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>
Example 77		<chem>C1N(C([2H])([2H])C([2H])([2H])[2H])C(=O)NC2=C3C(=O)N[C@@H](C4=CC(F)=CC=C4Cl)C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>
Example 78		<chem>C1N(CC#N)C(=O)NC2=C3C(=O)N[C@H](C4=CC(F)=CC=C4Cl)C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>
Example 79		<chem>C1N(CC#N)C(=O)NC2=C3C(=O)N[C@@H](C4=CC(F)=CC=C4Cl)C3=C(NC(=O)C3=CC(C(F)(F)F)=CC(F)=C3)C=C12</chem>

Example 80		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)N(C(C(F)(F)F)C(=O)N3C)C(=O)NC2C1=CC(F)=CC=C1Cl</chem>
Example 81		<chem>C12=C(C3=C(C=C1NC(C1=CC(C(F)(F)F)=CC(F)=C1)=O)N(C(C(F)(F)F)C(=O)N3C([2H])([2H])([2H])C(=O)NC2C1=CC(F)=CC=C1Cl</chem>
Example 82		<chem>FC(F)(F)C1=CC(F)=CC(C(NC2=C(C(N(C(N3C)=O)CC(F)F)=C3C4=C2C(C5=C(Cl)C=CC(F)=C5)NC4=O)=O)=C1</chem>
Example 83		<chem>FC(F)(F)C1=CC(F)=CC(C(NC2=C(C(N(C(N3C([2H])([2H])([2H])=O)CC(F)F)=C3C4=C2C(C5=C(Cl)C=CC(F)=C5)NC4=O)=O)=C1</chem>

Exemplary Synthetic Procedures

List of Abbreviations

aq: aqueous

Ac = Acetyl

AcO = Acetate

Ac₂O = Acetic anhydride

AIBN = a,a'-Azobisisobutyronitrile

All = Allyl

Alloc = Allyloxycarbonyl

Am	= Amyl (Pentyl)
Ar	= Aryl
B2Pin2	= bis(pinacolato)diboron
9-BBN	= 9-Borabicyclononane
BHT	= tert-Butylhydroxytoluene
BINAP	= 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BMS	= Borane-methylsulphide complex
Bn	= Benzyl
Boc	= tert-Butoxycarbonyl
BOP	= Bis(2-oxo-3-oxazolidinyl)phosphine
Bu or n-Bu	= n-Butyl
s-Bu or sBu	= sec-Butyl
t-Bu or tBu	= tert-Butyl
BuOH	= Butanol
Bz	= Benzoyl
Bzl	= Benzyl
CAN	= Ceric ammonium nitrate
cataCXium A Pd G3	= mesylate [(di(1-adamantyl)-n-butylphosphine)-2-(2'-amino-1,1'-biphenyl)]palladium(II)
CBS	= Corey-Bashki-Shibat
Cbz	= Benzyloxycarbonyl
CbzCl	= Benzyl chloroformate ox
Cod	= Cyclooctadiene
Cp	= Cyclopentadienyl
CSA	= Camphorsulphonic acid
DABCO	= 1,4-Diazabicyclo[2.2.2]octane, Triethylendiamine
DAST	= Diethylaminosulphur trifluoride
dba	= Dibenzylideneacetone
DBU	= 1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	= 1,3-Dicyclohexylcarbodiimide
DCM	= Dichloromethane

DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD = Diethyl azodicarboxylate
DHP = Dihydropyran
DHQD = Dihydroquinidine
DIBAL = Diisobutylaluminium hydride
DIBAL-H = Diisobutylaluminium hydride
DIC = Diisopropylcarbodiimide
DIPEA = Diisopropylethylamine
DMA = N,N-Dimethylacetamide
DMAC = N,N-Dimethylacetamide
DMAP = 4-Dimethylaminopyridine
DME = 1,2-Dimethoxyethane
DMF = N,N-Dimethylformamide
DMP = Dess-Martin periodinane
DMPU = 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS = Dimethylsulphide
DMSO = Dimethylsulphoxide
DPA = Diisopropylamine
DPPA = Diphenylphosphoryl azide
Ddpb = 1,4-bis(diphenylphosphino)butane
Dppe = 1,2-bis(diphenylphosphino)ethane
Dppf = 1,2-bis(diphenylphosphino)ferrocene
dppp = 1,3-bis(diphenylphosphino)propane
Dtbbpy = 4, 4'-di-tert-butyl-2,2'-dipyridyl
EA = Ethyl acetate
EDC = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDCI = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
Eq = equivalent
ESI or ES = Electrospray ionization
Et = ethyl
Et2O = Diethyl ether

EtOAc	=	Ethyl acetate
Fmoc	=	9-Fluorenylmethoxycarbonyl
HATU	=	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HMDS	=	Hexamethyldisilazane
HMPA	=	Hexamethylphosphoramide
HOAt	=	7-Aza-1-hydroxybenzotriazole
HOBt	=	1-Hydroxybenzotriazole
HPLC	=	high pressure liquid chromatography
IPA	=	Isopropyl alcohol
Im	=	Imidazole
KHMDS	=	Potassium bis(trimethylsilyl)amide
KOAc	=	Potassium acetate
LAH	=	Lithium aluminium hydride
LDA	=	Lithium diisopropylamide
LHMDS	=	Lithium bis(trimethylsilyl)amide
MCPBA	=	meta-chloroperoxybenzoic acid
Me	=	Methyl
MeCN	=	Acetonitrile
MeOH	=	Methanol
MOM	=	Methoxymethyl
Mg	=	magnesium
MS	=	Molecular sieves
Ms	=	Methanesulphonyl
MTBE	=	Methyl tert-butyl ether
m/z	=	mass divided by charge
Na ₂ SO ₄	=	Sodium Sulphate
NaHMDS	=	Sodium bis(trimethylsilyl)amide
NaCNBH ₃	=	Sodium cyanoborohydride
NBS	=	N-Bromosuccinimide
NCS	=	N-Chlorosuccinimide

NIS = N-Iodosuccinimide
NMM = N-Methylmorpholine
NMO = N-Methylmorpholine-N-oxide
NMP = N-Methylpyrrolidone
NMR = Nuclear magnetic resonance
Ns = p-Nitrophenylsulphonyl
Pd(dppf)Cl₂ = [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium
Pd(PPh₃)₄ = tetrakis(triphenylphosphine)palladium
PDC = Pyridinium dichlorochromate
PCC = Pyridinium chlorochromate
PE = Petroleum ether
Ph = Phenyl
Piv = Pivaloyl, 2,2-dimethylacetyl
PMB = p-Methoxybenzyl
PPA = Polyphosphoric acid
PPTS = Pyridinium p-toluensulphonate
n-Pr = n-Propyl
Pr = Propyl
i-Pr or iPr = iso-propyl
PTC = Phase transfer catalyst
PTSA = p-Toluenesulphonic acid
Pv = Pivaloyl, 2,2-dimethylacetyl
Py = Pyridine
Red-Al® = Sodium bis(2-methoxyethoxy)aluminium hydride
RT = room temperature
SFC = supercritical fluid chromatography
Prep-SFC = Preparative SFC
SEM = 2-(Trimethylsilyl)ethoxymethyl
TBAF = Tetrabutylammonium fluoride
TBDMS = tert-Butyldimethylsilyl
TBDPS = tert-Butyldiphenylsilyl

TBHP = tert-Butylhydroperoxyde
TBS = tert-Butyldimethylsilyl
TEA = Triethylamine
TES = Triethylsilyl
Tf = Trifluoromethanesulfonyl
TfO = Trifluoromethanesulfonate
Tf2O = Trifluoromethanesulfonyl anhydride
TfOH = Trifluoromethanesulfonic acid
TFA = Trifluoroacetic acid
TFAA = Trifluoroacetic anhydride
Thexyl = 2,3-dimethyl-2-butyl
THF = Tetrahydrofurane
THP = Tetrahydropyranyl
TIPS = Triisopropylsilyl
TMEDA = N,N,N',N'-Tetramethylethylenediamine
TMG = Tetramethylguanidine
TMS = Trimethylsilyl
Tol = p-Toluyll
TPAP = Tetra-n-propylammonium perruthenate
TPS = Tripropylsilyl
Tr = Trityl, triphenylmethyl
Troc = 2,2,2-Trichloroethoxycarbonyl
Trt = Trityl, triphenylmethyl
Ts = p-Toluenesulphonyl
p-TsOH = p-Toluenesulphonic acid
UV = ultraviolet
Z = Benzyloxycarbonyl
UV: ultraviolet

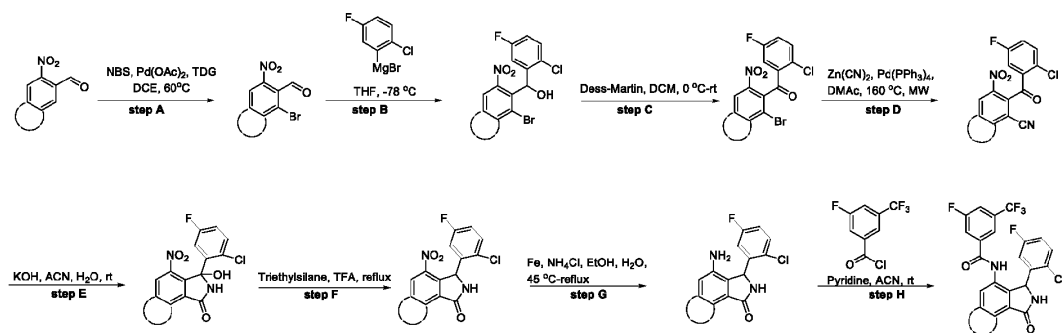
General LC-MS Method:

[00189] Shimadzu LCMS2020, Reverse-phase column (Shim-Pack Scepter C18, 33 x 3.0 mm, 3um), elution with A: H₂O/MeCN/FA = 90/10/0.05; B: MeCN; Detection: MS, ELS, UV (100 μL split to MS with in-line UV detector); MS ionization method: Electrospray (positive and negative ion). ES-API = electrospray-atmospheric pressure ionization.

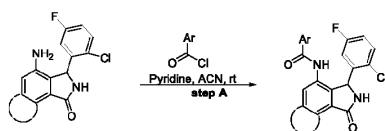
General HPLC Purification Method:

[00190] Instrument = Shimadzu FRC-40; Shimadzu LH-40; Shimadzu LC-8A; GX-281.
Column = YMC-Triart C18, 250*20 mm, 5um; Welch Ultimate XB-C18, 250*21.2 mm, 5um.
Detection wavelength = 220, 254 nM. Flow rate = 15ml/min-20ml/min; Run time = 8 min;
Column temperature = 25 °C.

General Synthetic Route I

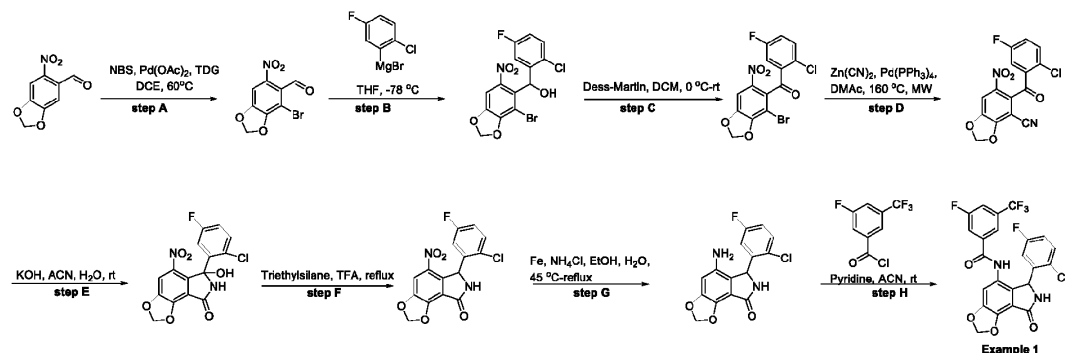


General Synthesis Route II



Example 1 N-(6-(2-chloro-5-fluorophenyl)-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide was synthesized via **General**

Synthesis Route I



[00191] **Step A:** To a solution of 6-nitrobenzo[d][1,3]dioxole-5-carbaldehyde (4.3 g, 22.0 mmol, 1.0 eq) in DCE (137 mL) and TFA (27 mL) was added NBS (4.7 g, 26.4 mmol, 1.2 eq), Palladium (II) Acetate (0.495 g, 2.2 mmol, 0.1 eq) and 4-chloro-2-(trifluoromethyl)aniline (TDG) (0.862 g, 4.4 mmol, 0.2 eq). Then the reaction mixture was stirred at 60 °C for 12 h. The mixture was added water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic phases were washed with brine (20 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was triturated with petroleum ether / EtOAc = 3 / 1 and filtered to afford 4-bromo-6-nitrobenzo[d][1,3]dioxole-5-carbaldehyde (4.4 g, 73%). ¹H NMR (400 MHz, CDCl₃): δ 10.12 (s, 1H), 7.50 (s, 1H), 6.28 (s, 2H).

[00192] **Step B:** To a solution of 4-bromo-6-nitrobenzo[d][1,3]dioxole-5-carbaldehyde (2.4 g, 8.8 mmol, 1.0 eq) in THF (40.0 mL) was added (2-chloro-5-fluorophenyl)magnesium bromide (26.2 mL, 13.1 mmol, 0.5 M, 1.5 eq) dropwise at -78 °C under N₂ atmosphere. Then the reaction mixture was stirred at room temperature for 30 mins. The mixture was added water (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic phases were washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by column chromatography on silica gel (eluted with petroleum ether / EtOAc = 15 / 1) to give (4-bromo-6-nitrobenzo[d][1,3]dioxol-5-yl)(2-chloro-5-fluorophenyl)methanol (2.0 g, 57%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.50-7.47 (m, 2H), 7.25-7.20 (m, 1H), 7.15-7.11 (m, 1H), 6.62 (d, *J* = 14.8 Hz, 1H), 6.29 (d, *J* = 4.4 Hz, 2H), 6.18 (d, *J* = 5.6 Hz, 1H).

[00193] **Step C:** To a solution of (4-bromo-6-nitrobenzo[d][1,3]dioxol-5-yl)(2-chloro-5-fluorophenyl)methanol (2.0 g, 4.9 mmol, 1.0 eq) in DCM (40 mL) was added Dess-Martin (2.5 g, 5.88 mmol, 1.2 eq) at 0 °C. Then the reaction mixture was stirred at room temperature for 2 h.

The mixture was added with water (40 mL) and extracted with DCM (40 mL x 3). The combined organic phases were washed with brine (40 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel chromatography (petroleum ether / EtOAc = 15 / 1) to give product (4-bromo-6-nitrobenzo[d][1,3]dioxol-5-yl)(2-chloro-5-fluorophenyl)methanone (1.2 g, 60%). ¹H NMR (400 MHz, CDCl₃): δ 7.69-7.67 (m, 2H), 7.44-7.41 (m, 1H), 7.24-7.19 (m, 1H), 6.29 (s, 2H).

[00194] **Step D:** To a solution of (4-bromo-6-nitrobenzo[d][1,3]dioxol-5-yl)(2-chloro-5-fluorophenyl)methanone (270 mg, 0.67 mmol, 1.0 eq) in *N,N*-Dimethylacetamide (4 mL) was added Zn(CN)₂ (79 mg, 0.67 mmol, 1.0 eq) and Pd(PPh₃)₄ (231 mg, 0.2 mmol, 0.3 eq). Then the reaction mixture was stirred at 160 °C for 20 min with M.W. The mixture was added with water (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic phases were washed with brine (5 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by column chromatography on silica gel (eluted with petroleum ether / EtOAc = 5:1) to give 5-(2-chloro-5-fluorobenzoyl)-6-nitrobenzo[d][1,3]dioxole-4-carbonitrile (100 mg, 43%). ¹H NMR (300 MHz, CDCl₃): δ 7.78 (s, 1H), 7.73-7.70 (m, 1H), 7.44-7.41 (m, 1H), 6.41 (s, 2H).

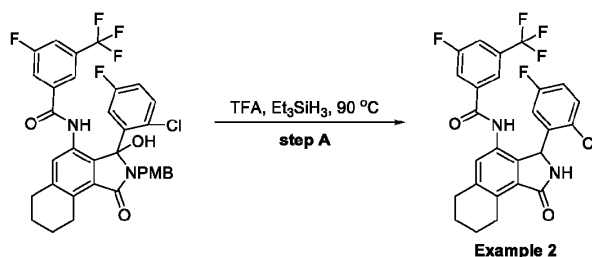
[00195] **Step E:** To a solution of 5-(2-chloro-5-fluorobenzoyl)-6-nitrobenzo[d][1,3]dioxole-4-carbonitrile (100 mg, 0.29 mmol, 1.0 eq) in *can* (5 mL) and H₂O (0.5 mL) was added KOH (5.0 mg, 0.086 mmol, 0.3 eq). Then the reaction mixture was stirred at room temperature for 2 h. The mixture was dried over Na₂SO₄ and concentrated to give crude. The residue was purified by column chromatography on silica gel (eluted with petroleum ether / EtOAc = 15 / 1) to give 6-(2-chloro-5-fluorophenyl)-6-hydroxy-5-nitro-6,7-dihydro-8H-[1,3]dioxolo[4,5-*e*]isoindol-8-one (50 mg, 48%) confirmed by LCMS. LCMS: *m/z* 365.0 ([M-H]⁻).

[00196] **Step F:** To a solution of 6-(2-chloro-5-fluorophenyl)-6-hydroxy-5-nitro-6,7-dihydro-8H-[1,3]dioxolo[4,5-*e*]isoindol-8-one (100 mg, 0.273 mmol, 1.0 eq) in TFA (4 mL) was added Triethylsilane (127 mg, 1.1 mmol, 4.0 eq). Then the reaction mixture was stirred at 100 °C for 4 h. The mixture was concentrated to afford the crude product. The residue was triturated with DCM / MeOH = 10 / 1 and filtered to afford 6-(2-chloro-5-fluorophenyl)-5-nitro-6,7-dihydro-8H-[1,3]dioxolo[4,5-*e*]isoindol-8-one (50 mg, 25%) as a yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.39 (s, 1H), 7.93 (m, 1H), 7.56 (s, 1H), 7.23-7.17 (m, 1H), 6.61-6.45 (m, 4H). LCMS: *m/z* 351.0 ([M+H]⁺).

[00197] **Step G:** To a solution of 6-(2-chloro-5-fluorophenyl)-5-nitro-6,7-dihydro-8H-[1,3]dioxolo[4,5-e]isoindol-8-one (12 mg, 0.034 mmol, 1.0 eq) in EtOH (0.5 mL) and was added Fe (9 mg, 0.17 mmol, 5.0 eq). The reaction was heated to 45 °C was added NH₄Cl (1 mg, 0.017 mmol, 0.5 eq) and H₂O (0.2 mL). Then the reaction mixture was stirred at 90 °C for 12 h. The mixture was filtered through a Celite pad, and the filtrate was concentrated to give 5-amino-6-(2-chloro-5-fluorophenyl)-6,7-dihydro-8H-[1,3]dioxolo[4,5-e]isoindol-8-one (7 mg, 63.6%). LCMS: m/z 321.0 ([M+H]⁺).

[00198] **Step H:** To a solution of 5-amino-6-(2-chloro-5-fluorophenyl)-6,7-dihydro-8H-[1,3]dioxolo[4,5-e]isoindol-8-one (7 mg, 0.022 mmol, 1.0 eq) in ACN (0.5 mL) was added Pyridine (4 mg, 0.044 mmol, 2.0 eq) and 3-fluoro-5-(trifluoromethyl)benzoyl chloride (4 mg, 0.018 mmol, 0.8 eq). Then the reaction mixture was stirred at room temperature for 2 h. The mixture was added water (0.5 mL) and extracted with EtOAc (1 mL x 3). The combined organic phases were washed with brine (1.0 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by Prep-TLC (EtOAc) to give final N-(6-(2-chloro-5-fluorophenyl)-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (2.5 mg, 23%). LCMS: m/z 509.0 ([M+H]⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.20 (s, 1H), 9.00 (brs, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.77-7.64 (m, 2H), 7.30-7.27 (m, 1H), 7.10-7.04 (m, 2H), 6.27 (d, *J* = 14.8 Hz, 2H), 5.91-5.89 (m, 1H).

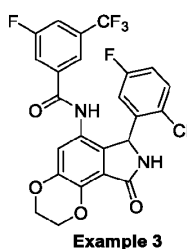
Example 2 N-(3-(2-chloro-5-fluorophenyl)-1-oxo-2,3,6,7,8,9-hexahydro-1H-benzo[e]isoindol-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00199] To a solution of N-(3-(2-chloro-5-fluorophenyl)-3-hydroxy-2-(4-methoxybenzyl)-1-oxo-2,3,6,7,8,9-hexahydro-1H-benzo[e]isoindol-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (15 mg, 0.02 mmol, 1.0 eq) in TFA (0.5 mL) was added Et₃SiH (11.6 mg, 0.1 mmol, 5.0 eq). The reaction mixture was heated to reflux and stirred for 5 h. Then the reaction mixture was by prep-HPLC (acetonitrile with 0.1% FA in water) to give N-(3-(2-chloro-5-fluorophenyl)-1-oxo-

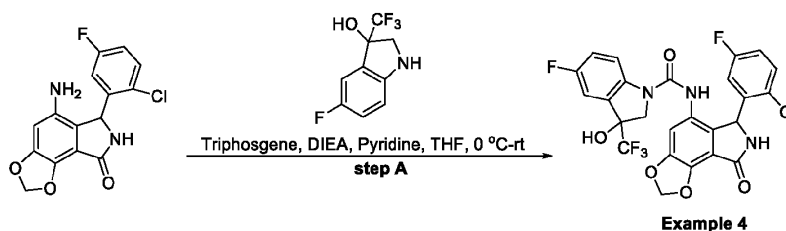
2,3,6,7,8,9-hexahydro-1H-benzo[e]isoindol-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (2.0 mg, 19.2%). LCMS: m/z 519.0 ($[M-H]^-$). 1H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.39-7.33 (m, 2H), 7.04-7.00 (m, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.31 (s, 1H), 6.10 (s, 1H), 5.35 (s, 1H), 3.35 (s, 2H), 2.89 (s, 2H), 1.87 (m, 4H).

Example 3 N-(7-(2-chloro-5-fluorophenyl)-9-oxo-2,3,8,9-tetrahydro-7H-[1,4]dioxino[2,3-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide was synthesized via general route I:



[00200] LCMS: m/z 525.0 ($[M+H]^+$). 1H NMR (300 MHz, $DMSO-d_6$): δ 10.16 (s, 1H), 8.82 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.70-7.63 (m, 2H), 7.30-7.26 (q, J_1 = 8.7, J_2 = 5.1, 1H), 7.10-7.04 (m, 1H), 5.83 (s, 1H), 4.37 (t, J = 3.6 Hz, 4H).

Example 4 N-(6-(2-chloro-5-fluorophenyl)-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluoro-3-hydroxy-3-(trifluoromethyl)indoline-1-carboxamide



[00201] **Step A:** To a solution of **8** (50 mg, 0.16 mmol, 1.0 eq) in THF (1 mL) was added Triphosgene (47 mg, 0.16 mmol, 1.0 eq) and DIEA (20 mg, 0.16 mmol, 1.0 eq) at 0 °C under N_2 atmosphere. Then the reaction mixture was stirred at 0 °C for 30 min. After a solution of 5-fluoro-3-(trifluoromethyl)indolin-3-ol (69 mg, 0.32 mmol, 2.0 eq) in Pyridine (0.2 mL) was added. The mixture was stirred for 2 h at room temperature. The reaction mixture was quenched by the addition of the saturated aqueous NH_4Cl (2 mL) and the mixture was extracted with EtOAc (2 mL x 3), the combined organic layers were washed with brine (2 mL), dried over sodium sulfate and concentrated. The residue was purified by Prep-HPLC to give N-(6-(2-

chloro-5-fluorophenyl)-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluoro-3-hydroxy-3-(trifluoromethyl)indoline-1-carboxamide (32.3 mg, 37%). LCMS: m/z 568.0 ($[M+H]^+$). 1H NMR (300 MHz, DMSO- d_6): δ 8.95 (s, 1H), 8.44 (d, J = 17.4 Hz, 1H), 7.90-7.76 (m, 1H), 7.39-7.01 (m, 5H), 6.97 (d, J = 25.2 Hz, 1H), 6.66 (brs, 1H), 6.24 (d, J = 10.5 Hz, 2H), 5.98-5.92 (m, 1H), 4.13-3.89 (m, 1H), 3.56-3.50 (m, 1H).

[00202] **Example 4** was separated to **Example 6, 7, 8 and 9** via the chiral prep-SFC separation method below:

Instrument: Waters 150 preparative SFC(SFC-26)

Column: (S, S) Whelk O1, 250×30mm I.D., 10 μ m

Mobile phase: A for CO₂ and B for Ethanol

Gradient: B 40%

Flow rate: 80 mL /min

Back pressure: 100 bar

Column temperature: 38°C

Wavelength: 220nm

Cycle time: ~25 min

Sample preparation: Compound was dissolved in ~9 ml methanol/DCM

Injection: 3 ml per injection.

Work up: After separation, the fractions were dried off via rotary evaporator at bath temperature 40°C to get the P3 and P4, the mixture of P1&P2 was then further separated with the method below.

Instrument: Waters 150 preparative SFC(SFC-26)

Column: ChiralPak AD , 250×30mm I.D., 10 μ m

Mobile phase: A for CO₂ and B for Ethanol

Gradient: B 35%

Flow rate: 80 mL /min

Back pressure: 100 bar

Column temperature: 38°C

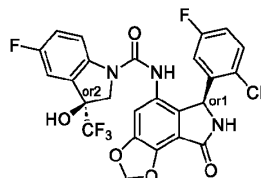
Wavelength: 220nm

Cycle time: ~6 min

Sample preparation: Compound was dissolved in ~32 ml methanol/DCM

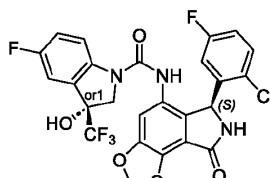
Injection: 4 ml per injection.

Work up: After separation, the fractions were dried off via rotary evaporator at bath temperature 40°C to get the P1 and P2.



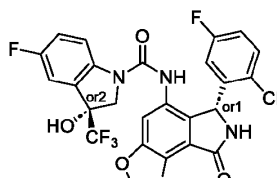
P1 Example 6

[00203] ^1H NMR (400 MHz, CD_3OD) δ 7.82 (dd, $J = 9.0, 4.5$ Hz, 1H), 7.28 (dd, $J = 9.0, 5.0$ Hz, 1H), 7.18 (d, $J = 8.0$ Hz, 1H), 7.15-7.05 (m, 1H), 7.02 – 6.89 (m, 2H), 6.65 (br, 1H), 6.30-6.10 (m, 3H), 4.20 (d, $J = 11.8$ Hz, 1H), 3.60-3.40 (m, 1H).



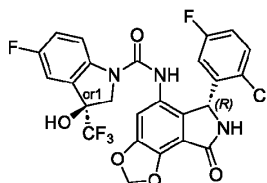
P2 Example 7

[00204] ^1H NMR (400 MHz, CD_3OD) δ 7.98-7.80 (m, 1H), 7.28 (dd, $J = 8.8, 5.0$ Hz, 1H), 7.22 – 7.05 (m, 2H), 6.99 (td, $J = 8.4, 3.0$ Hz, 1H), 6.91 (s, 1H), 6.65 (br, 1H), 6.30 – 6.10 (m, 3H), 3.90 (d, $J = 11.4$ Hz, 1H), 3.69 – 3.72 (m, 1H).



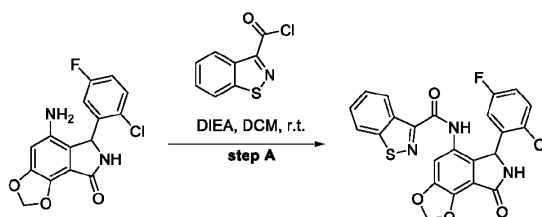
P3 Example 8

[00205] ^1H NMR (400 MHz, CD_3OD) δ 7.82 (dd, $J = 9.0, 4.5$ Hz, 1H), 7.28 (dd, $J = 9.0, 5.0$ Hz, 1H), 7.18 (d, $J = 8.0$ Hz, 1H), 7.15-7.05 (m, 1H), 7.02 – 6.89 (m, 2H), 6.65 (br, 1H), 6.30 – 6.10 (m, 3H), 4.20 (d, $J = 11.8$ Hz, 1H), 3.60-3.40 (m, 1H).

**P4 Example 9**

[00206] ^1H NMR (400 MHz, CD_3OD) δ 7.98-7.80 (m, 1H), 7.28 (dd, J = 8.8, 5.0 Hz, 1H), 7.22 – 7.05 (m, 2H), 6.99 (td, J = 8.4, 3.0 Hz, 1H), 6.91 (s, 1H), 6.65 (br, 1H), 6.30 – 6.10 (m, 3H), 3.90 (d, J = 11.4 Hz, 1H), 3.69 – 3.72 (m, 1H).

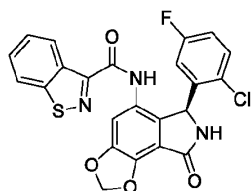
Example 5 N-(6-(2-chloro-5-fluorophenyl)-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)benzo[d]isothiazole-3-carboxamide was synthesized via general route II from intermediate 5-amino-6-(2-chloro-5-fluorophenyl)-6,7-dihydro-8H-[1,3]dioxolo[4,5-e]isoindol-8-one:

**Example 5**

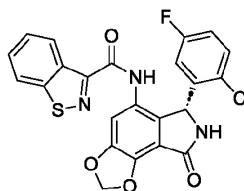
[00207] **Step A:** To a solution of 5-amino-6-(2-chloro-5-fluorophenyl)-6,7-dihydro-8H-[1,3]dioxolo[4,5-e]isoindol-8-one (50 mg, 0.16 mmol, 1.0 eq) in DCM (2 mL) was added benzo[d]isothiazole-3-carbonyl chloride (62 mg, crude) and DIEA (101 mg, 0.780 mmol, 5.0 eq) dropwise at 0 °C. Then the reaction mixture was stirred at room temperature for 2 h. The mixture was added water (2 mL) and extracted with DCM (2 mL x 3). The combined organic phases were washed with brine (2 mL), dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by Prep-HPLC to give N-(6-(2-chloro-5-fluorophenyl)-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)benzo[d]isothiazole-3-carboxamide (5.2 mg, 3.5%). LCMS: m/z 482.0 ($[\text{M}+\text{H}]^+$). ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 10.17 (s, 1H), 8.99 (s, 1H), 8.60 (d, J = 8.1 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 7.70-7.56 (m, 2H), 7.21-7.17 (m, 2H), 7.00-6.93 (m, 1H), 6.26 (d, J = 9.0 Hz, 2H), 6.07 (s, 1H).

Example 11 (S)-N-(6-(2-chloro-5-fluorophenyl)-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)benzo[d]isothiazole-3-carboxamide and **Example 12** (R)-N-(6-(2-chloro-

5-fluorophenyl)-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)benzo[d]isothiazole-3-carboxamide were separated from **Example 5** with the prep-SFC method below:



P1 Example 11



P2 Example 12

Instrument: MG II preparative SFC(SFC-14)

Column: ChiralCel OD, 250×30mm I.D., 10μm

Mobile phase: A for CO₂ and B for Ethanol

Gradient: B 30%

Flow rate: 80 mL /min

Back pressure: 100 bar

Column temperature: 38°C

Wavelength: 220nm

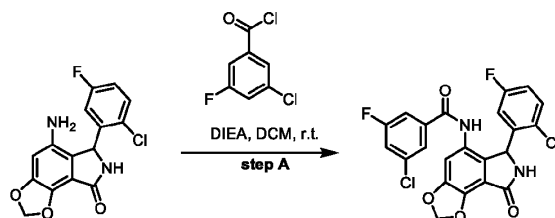
Cycle time: ~5.5min

Sample preparation: Compound was dissolved in ~120 ml methanol/DCM

Injection: 4 ml per injection.

Work up: After separation, the fractions were dried off via rotary evaporator at bath temperature 40°C to get the desired isomers.

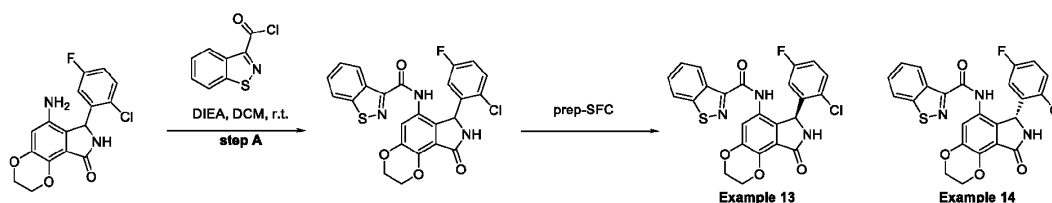
Example 10 3-chloro-N-(6-(2-chloro-5-fluorophenyl)-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluorobenzamide was synthesized via General Synthesis route II from intermediate **5-amino-6-(2-chloro-5-fluorophenyl)-6,7-dihydro-8H-[1,3]dioxolo[4,5-e]isoindol-8-one**



Example 10

[00208] **Step A:** To a solution of 5-amino-6-(2-chloro-5-fluorophenyl)-6,7-dihydro-8H-[1,3]dioxolo[4,5-e]isoindol-8-one (30 mg, 0.10 mmol, 1.0 eq) in DCM (1.0 mL) was added 3-chloro-5-fluorobenzoyl chloride (36 mg, 0.20 mmol, 2.0 eq) and DIEA (60 mg, 0.50 mmol, 5.0 eq) at room temperature. Then the mixture was stirred for 2 h at the same temperature. The mixture was added water (2 mL) and extracted with DCM (2 mL x 3). The combined organic phases were washed with brine (2 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by Prep-HPLC (acetonitrile with 0.1% FA in water 35% to 47%) to afford 2.2 mg, 5% as a white solid. LCMS: m/z 476.9 ([M+H]⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 10.08 (s, 1H), 9.10 (brs, 1H), 7.73 - 7.60 (m, 1H), 7.55 - 7.28 (m, 3H), 7.20 - 7.09 (m, 1H), 7.04 (s, 1H), 6.90 - 6.50 (m, 1H), 6.36 - 6.15 (m, 2H), 6.05 - 5.80 (m, 1H).

Example 13 (S)-N-(7-(2-chloro-5-fluorophenyl)-9-oxo-2,3,8,9-tetrahydro-7H-[1,4]dioxino[2,3-e]isoindol-6-yl)benzo[d]isothiazole-3-carboxamide and Example 14 (R)-N-(7-(2-chloro-5-fluorophenyl)-9-oxo-2,3,8,9-tetrahydro-7H-[1,4]dioxino[2,3-e]isoindol-6-yl)benzo[d]isothiazole-3-carboxamide were synthesized via **General Synthesis route II** from intermediate **6-amino-7-(2-chloro-5-fluorophenyl)-2,3,7,8-tetrahydro-9H-[1,4]dioxino[2,3-e]isoindol-9-one**



[00209] **Step A:** To a solution of 6-amino-7-(2-chloro-5-fluorophenyl)-3,7,8,9-tetrahydro-2H-[1,4]dioxino[3,2-e]isoindol-9-one (102 mg, 0.304 mmol) and TEA (92.2 mg, 0.911 mmol) in DCM (2 mL) was added benzo[d][1,2]thiazole-3-carbonyl chloride (60 mg, 0.304 mmol). The mixture was stirred at rt for 2h. The solvent was removed and the residue was purified by prep-HPLC to afforded N-[7-(2-chloro-5-fluorophenyl)-9-oxo-3,7,8,9-tetrahydro-2H-[1,4]dioxino[3,2-e]isoindol-6-yl]benzo[d][1,2]thiazole-3-carboxamide (25 mg, 50 μmol, 16.6%) as a white solid. The solid was separated by prep-SFC to afforded P1 Example 13 (S)-N-((S)-7-(2-chloro-5-fluorophenyl)-9-oxo-2,3,8,9-tetrahydro-7H-[1,4]dioxino[2,3-e]isoindol-6-yl)-5-fluoro-3-hydroxy-3-(trifluoromethyl)indoline-1-carboxamide (2.2 mg) as a pale solid. LCMS: ESI m/z 496 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.11 (s, 1H), 8.81 (s, 1H), 8.60 (d, *J* =

8.2 Hz, 1H), 8.28 (d, $J = 8.2$ Hz, 1H), 7.66 – 7.58 (m, 2H), 7.31 – 7.09 (m, 3H), 6.97 (t, $J = 7.0$ Hz, 1H), 6.66 (s, 1H), 6.01 (s, 1H), 4.36 (s, 4H). and P2 Example 14 (R)-N-(7-(2-chloro-5-fluorophenyl)-9-oxo-2,3,8,9-tetrahydro-7H-[1,4]dioxino[2,3-e]isoindol-6-yl)benzo[d]isothiazole-3-carboxamide (2.0 mg) as a pale solid. LCMS: ESI m/z 496 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.11 (s, 1H), 8.81 (s, 1H), 8.60 (d, $J = 8.2$ Hz, 1H), 8.28 (d, $J = 8.2$ Hz, 1H), 7.66 – 7.58 (m, 2H), 7.31 – 7.09 (m, 3H), 6.97 (t, $J = 7.0$ Hz, 1H), 6.66 (s, 1H), 6.01 (s, 1H), 4.36 (s, 4H).

[00210] Preparative SFC separation method:

Instrument: Waters Thar 80 preparative SFC

Column: ChiralPak IB, 250×21.2 mm I.D., 5 μ m

Mobile phase: A for CO₂ and B for ETOH + 0.1%NH₃H₂O

Gradient: B 40 %

Flow rate: 40 mL/min

Back pressure: 100 bar

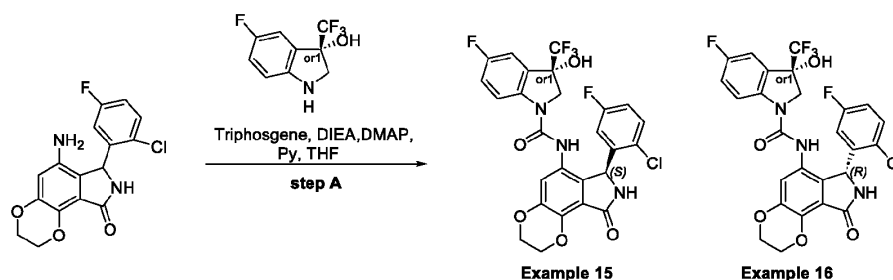
Column temperature: 35 °C

Wavelength: 220 nm

Cycle-time: 20 min

Eluted time: 2 H

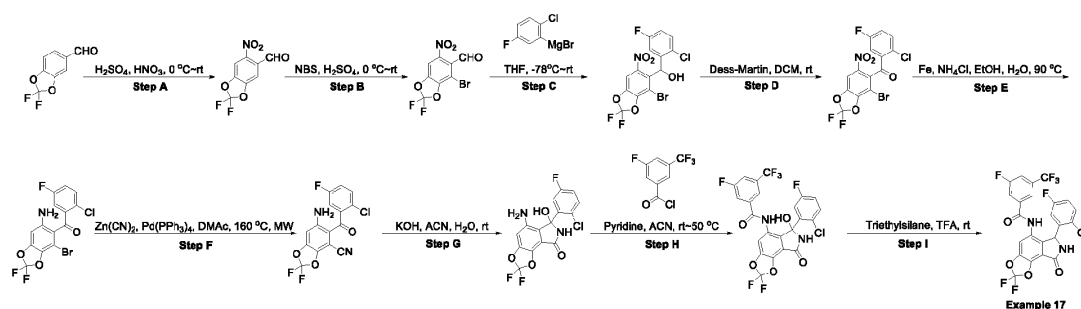
Example 15 (R*)-N-((S)-7-(2-chloro-5-fluorophenyl)-9-oxo-2,3,8,9-tetrahydro-7H-[1,4]dioxino[2,3-e]isoindol-6-yl)-5-fluoro-3-hydroxy-3-(trifluoromethyl)indoline-1-carboxamide and **Example 16** (R*)-N-((R)-7-(2-chloro-5-fluorophenyl)-9-oxo-2,3,8,9-tetrahydro-7H-[1,4]dioxino[2,3-e]isoindol-6-yl)-5-fluoro-3-hydroxy-3-(trifluoromethyl)indoline-1-carboxamide



[00211] **Step A:** To a solution of 6-amino-7-(2-chloro-5-fluorophenyl)-2,3,7,8-tetrahydro-9H-[1,4]dioxino[2,3-e]isoindol-9-one (25 mg, 0.075 mmol, 1.0 eq) in anhydrous THF (0.5 mL) was

added DIEA (9.7 mg, 0.075 mmol, 1.0 eq). The mixture was stirred and cooled to 0 °C. A solution of triphosgene (22.4 mg, 0.076 mmol, 1.01 eq) in anhydrous THF (0.5 mL) was added dropwise at 0 °C. The mixture was stirred for 0.5 h at 0 °C. Then the solution was added to a solution of (S)-5-fluoro-3-(trifluoromethyl)indolin-3-ol (33.1 mg, 0.15 mmol, 2.0 eq) in pyridine (0.5 mL) and DMAP (catalytic amount). The resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was diluted with aqueous NH₄Cl (10 mL) and extracted with DCM (10 mL x 3). The organic layers were washed with brine (5 mL x 3), dried over Na₂SO₄, filtered, and concentrated to give the crude, which was purified by Prep-HPLC (acetonitrile with 0.1% FA in water) to afford a mixture (13 mg). Then the mixture was separated by chiral separation to afford P1 Example 15 (R*)-N-((S)-7-(2-chloro-5-fluorophenyl)-9-oxo-2,3,8,9-tetrahydro-7H-[1,4]dioxino[2,3-e]isoindol-6-yl)-5-fluoro-3-hydroxy-3-(trifluoromethyl)indoline-1-carboxamide (2.9 mg, white solid, yield for 7%). LCMS: m/z 582.0 ([M+H]⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 8.77 (brs, 1H), 8.36 (s, 1H), 7.78 (dd, *J* = 8.8, 4.4 Hz, 1H), 7.34 (s, 1H), 7.30 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.27 - 7.14 (m, 2H), 7.14 - 7.02 (m, 1H), 6.94 (s, 1H), 5.91 (brs, 1H), 4.60 - 4.22 (m, 4H), 4.11 (d, *J* = 12.0 Hz, 1H), 3.51 (d, *J* = 11.6 Hz, 1H). And P2 Example 16 (R*)-N-((R)-7-(2-chloro-5-fluorophenyl)-9-oxo-2,3,8,9-tetrahydro-7H-[1,4]dioxino[2,3-e]isoindol-6-yl)-5-fluoro-3-hydroxy-3-(trifluoromethyl)indoline-1-carboxamide (3.5 mg, white solid, yield for 8%). LCMS: m/z 582.0 ([M+H]⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 8.75 (brs, 1H), 8.42 (s, 1H), 8.00 - 7.80 (m, 1H), 7.35 (s, 1H), 7.34 - 7.00 (m, 5H), 6.86 (s, 1H), 5.86 (brs, 1H), 4.60 - 4.24 (m, 4H), 3.91 (d, *J* = 12.0 Hz, 1H), 3.54 (d, *J* = 11.6 Hz, 1H).

Example 17 N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide was synthesized with the General Synthetic Route I



[00212] **Step A:** To a solution of 2,2-difluorobenzo[d][1,3]dioxole-5-carbaldehyde (10.0 g, 53.7 mmol, 1.0 eq) in H₂SO₄ (50 mL) was added dropwise HNO₃ (5 mL) at 0 °C. Then the reaction mixture was warm to room temperature and stirred for 2 h. The mixture was poured into ice water (500 mL) and extracted with DCM (250 mL x 3). The combined organic phases were washed with brine (250 mL), dried over Na₂SO₄ and concentrated to give 2,2-difluoro-6-nitrobenzo[d][1,3]dioxole-5-carbaldehyde (11.0 g, 89%) as a yellow liquid. ¹H NMR (300 MHz, CDCl₃): δ ppm 10.35 (s, 1H), 7.87 (s, 3H), 7.67 (s, 1H).

[00213] **Step B:** To a solution of 2,2-difluoro-6-nitrobenzo[d][1,3]dioxole-5-carbaldehyde (5.0 g, 21.6 mmol, 1.0 eq) in H₂SO₄ (50 mL) was added portion wise NBS (5.8 g, 32.4 mmol, 1.5 eq) at 0 °C. Then the mixture was stirred for 12 h at room temperature. The mixture was poured into ice water (200 mL) and extracted with DCM (100 mL x 3). The combined organic phases were washed with brine (100 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by Prep-HPLC (acetonitrile with 0.1% FA in water 55% to 60%) to afford 4-bromo-2,2-difluoro-6-nitrobenzo[d][1,3]dioxole-5-carbaldehyde (1.0 g, 14.9%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ ppm 10.17 (s, 1H), 7.84 (s, 1H).

[00214] **Step C:** To a solution of 4-bromo-2,2-difluoro-6-nitrobenzo[d][1,3]dioxole-5-carbaldehyde (1.0 g, 3.2 mmol, 1.0 eq) in THF (10 mL) was added Magnesium reagent (2-chloro-5-fluorophenyl)magnesium bromide (9.6 mL, 4.8 mmol, 1.5 eq, 0.5 M) at -78 °C under N₂ atmosphere. Then the reaction mixture was stirred at room temperature for 1 h. The reaction mixture quenched by the addition of the saturated aqueous NH₄Cl (20 mL), and the mixture was extracted with EtOAc (20 mL). The combined organic phases were washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give (4-bromo-2,2-difluoro-6-nitrobenzo[d][1,3]dioxol-5-yl)(2-chloro-5-fluorophenyl)methanol (1.6 g, crude) as a yellow liquid. LCMS: m/z 437.9 ([M-H]).

[00215] ¹H NMR (400 MHz, CDCl₃): δ ppm 7.38 (s, 1H), 7.34 - 7.22 (m, 2H), 7.12 - 6.90 (m, 1H), 6.42 (s, 1H), 3.37 (brs, 1H).

[00216] **Step D:** To a solution of (4-bromo-2,2-difluoro-6-nitrobenzo[d][1,3]dioxol-5-yl)(2-chloro-5-fluorophenyl)methanol (1.6 g, 3.6 mmol, 1.0 eq, crude) in DCM (20 mL) was added Dess-Martin (1.8 g, 4.3 mmol, 1.2 eq). Then the reaction mixture was stirred at room temperature for 2 h. The mixture was added with water (50 mL) and extracted with DCM (50 mL x 3). The combined organic phases were washed with brine (50 mL), dried over Na₂SO₄ and

concentrated to give a residue. The residue was purified by silica gel chromatography (petroleum ether / EtOAc = 5:1) to afford (4-bromo-2,2-difluoro-6-nitrobenzo[d][1,3]dioxol-5-yl)(2-chloro-5-fluorophenyl)methanone (1.0 g, 70.7% yield for 2 steps) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ ppm 7.99 (s, 1H), 7.75 (dd, *J* = 8.8, 3.2 Hz, 1H), 7.52 - 7.40 (m, 1H), 7.35 - 7.22 (m, 1H).

[00217] **Step E:** To a solution of (4-bromo-2,2-difluoro-6-nitrobenzo[d][1,3]dioxol-5-yl)(2-chloro-5-fluorophenyl)methanone (250 mg, 0.57 mmol, 1.0 eq) in EtOH (5.0 mL) was added Fe (159 mg, 2.85 mmol, 5.0 eq). After the reaction mixture was heated to 65 °C, a solution of NH₄Cl (15 mg, 0.9 mmol, 0.5 eq) in H₂O (1.5 mL) was added. Then the reaction mixture was heated to reflux and stirred for 2 h. The mixture was filtered through a Celite pad, and the filtrate was concentrated to give the crude product. The residue was purified by Prep-TLC (petroleum ether / EtOAc = 3:1) to give (6-amino-4-bromo-2,2-difluorobenzo[d][1,3]dioxol-5-yl)(2-chloro-5-fluorophenyl)methanone (230 mg, 98.7%) as a yellow solid. LCMS: *m/z* 407.9, 409.9 ([*M*+*H*]⁺).

[00218] **Step F:** To a solution of (6-amino-4-bromo-2,2-difluorobenzo[d][1,3]dioxol-5-yl)(2-chloro-5-fluorophenyl)methanone (230 mg, 0.56 mmol, 1.0 eq) in DMAc (5 mL) was added Zn(CN)₂ (79 mg, 0.67 mmol, 1.2 eq) and Pd(PPh₃)₄ (195 mg, 0.17 mmol, 0.3 eq). Then the reaction mixture was stirred at 160 °C for 30 min in the microwave. The mixture was added with water (20 mL) and extracted with EtOAc (10 mL x 3). The combined organic phases were washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether / EtOAc = 3:1) to give 6-amino-5-(2-chloro-5-fluorobenzoyl)-2,2-difluorobenzo[d][1,3]dioxole-4-carbonitrile (110 mg, 55.0%) as a yellow solid.

[00219] ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 8.17 (s, 2H), 7.65 - 7.57 (m, 1H), 7.52 - 7.38 (m, 2H), 7.18 (s, 1H).

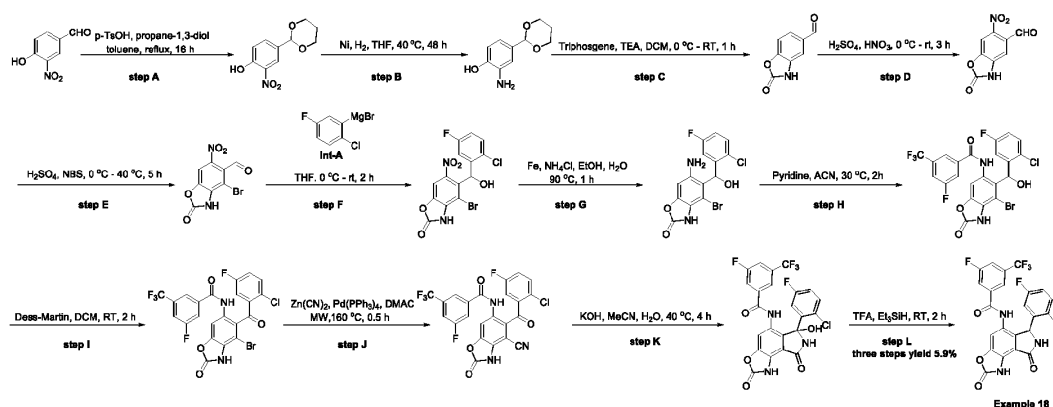
[00220] **Step G:** To a solution of 6-amino-5-(2-chloro-5-fluorobenzoyl)-2,2-difluorobenzo[d][1,3]dioxole-4-carbonitrile (110 mg, 0.31 mmol, 1.0 eq) in ACN (1.0 mL) and H₂O (0.1 mL) was added KOH (5 mg, 0.093 mmol, 0.3 eq) at room temperature. Then the reaction mixture was stirred at same temperature for 2 h. The mixture was dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by Prep-TLC (petroleum ether / EtOAc = 2:1) to give 5-amino-6-(2-chloro-5-fluorophenyl)-2,2-difluoro-6-hydroxy-6,7-dihydro-

8H-[1,3]dioxolo[4,5-e]isoindol-8-one (80 mg, 69.2%) as a yellow solid. LCMS: m/z 371.0 ([M-H]).

[00221] **Step H:** To a solution of 5-amino-6-(2-chloro-5-fluorophenyl)-2,2-difluoro-6-hydroxy-6,7-dihydro-8H-[1,3]dioxolo[4,5-e]isoindol-8-one (80 mg, 0.22 mmol, 1.0 eq) in ACN (1.0 mL) was added Acyl chloride (49 mg, 0.22 mmol, 1.0 eq) and Pyridine (34 mg, 0.44 mmol, 2.0 eq). Then the reaction mixture was stirred at 50 °C for 12 h. The mixture was added with water (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic phases were washed with brine (5 mL), dried over Na₂SO₄ and concentrated to give N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-6-hydroxy-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (160 mg, crude) as a yellow solid. LCMS: m/z 560.9 ([M-H]).

[00222] **Step I:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-6-hydroxy-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (160 mg, 0.28 mmol, 1.0 eq, crude) in TFA (2.0 mL) was added Triethylsilane (132 mg, 1.14 mmol, 4.0 eq). Then the reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated to give a residue. The residue was purified by Prep-HPLC (acetonitrile with 0.1% FA in water 45% to 64%) to give N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (18 mg, 15.3% yield for 2 steps) as a white solid. LCMS: m/z 547.0 ([M+H]⁺). ¹H NMR (300 MHz, DMSO-*d*₆): δ ppm 10.48 (brs, 1H), 9.38 (s, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.83 - 7.50 (m, 3H), 7.40 - 7.20 (m, 1H), 7.20 - 7.00 (m, 2H), 6.03 (s, 1H).

Example 18 N-(6-(2-chloro-5-fluorophenyl)-2,8-dioxo-1,6,7,8-tetrahydro-2H-oxazolo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide was synthesized via **General Synthetic Route I** from intermediate **6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazole-5-carbaldehyde**



[00223] **Step A:** To a solution of 4-hydroxy-3-nitrobenzaldehyde (45.0 g, 269.3 mmol, 1.0 eq) and propane-1,3-diol (30.7 g, 403.9 mmol, 1.5 eq) in Toluene (500 mL) was added p-TsOH (5.1 g, 26.9 mmol, 0.1 eq) at 25 °C. The reaction mixture was heated to reflux for 16 h. The mixture was concentrated, added with water (300 mL) and extracted with EtOAc (200 mL x 2). The combined organic phase was washed with brine (200 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel chromatography (eluted with petroleum ether : EtOAc = 5:1) to give 4-(1,3-dioxan-2-yl)-2-nitrophenol (42 g, 69.3%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 10.58 (s, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 7.69 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 5.46 (s, 1H), 4.37 – 4.10 (m, 2H), 4.09 – 3.70 (m, 2H), 2.30 – 2.10 (m, 1H), 1.57 – 1.40 (m, 1H). LCMS: *m/z* 224.1 ([M-H]).

[00224] **Step B:** To a solution of 4-(1,3-dioxan-2-yl)-2-nitrophenol (40.0 g, 177.6 mmol, 1.0 eq) in THF (500 mL) was added dropwise a solution of Nickel (15 g) at 25 °C under H₂ atmosphere. The reaction mixture was stirred at 40 °C for 48 h. Then the mixture was filtered and concentrated to give 2-amino-4-(1,3-dioxan-2-yl)phenol (33 g, 95.2%) as a black solid. LCMS: *m/z* 196.1 ([M+H]⁺).

[00225] **Step C:** A solution of 2-amino-4-(1,3-dioxan-2-yl)phenol (26.0 g, 133.2 mmol, 1.0 eq) and TEA (29.6 g, 293.0 mmol, 2.2 eq) in DCM (500 mL) was added portion-wise Triphosgene (51.4 g, 173.1 mmol, 1.3 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then the mixture was stirred at room temperature for 1 h. The mixture was added with water (300 mL) and extracted with DCM (200 mL x 2). The combined organic phase was washed with brine (300 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel chromatography (eluted with petroleum ether : EtOAc = 2 : 1) to give

2-oxo-2,3-dihydrobenzo[d]oxazole-5-carbaldehyde (11.2 g, 51.5%) as a white solid. LCMS: m/z 162.1 ($[M-H]^+$).

[00226] **Step D:** To a solution of 2-oxo-2,3-dihydrobenzo[d]oxazole-5-carbaldehyde (11.2 g, 68.6 mmol, 1.0 eq) in H_2SO_4 (98%, 120 mL) was added dropwise HNO_3 (5.2 g, 82.4 mmol, 1.2 eq) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The product was then precipitated by pouring the solution over ice-water (600 mL) and collected by vacuum filtration to give 6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazole-5-carbaldehyde (10.0 g, 70.0%) as a red solid. 1H NMR (300 MHz, $DMSO-d_6$): δ 12.83 (brs, 1H), 8.55 (s, 1H), 8.43 (s, 1H), 7.76 (s, 1H). LCMS: m/z 207.1 ($[M-H]^+$).

[00227] **Step E:** To a solution of 6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazole-5-carbaldehyde (10.0 g, 48.0 mmol, 1.0 eq) in H_2SO_4 (110 mL) was added NBS (12.8 g, 72.1 mmol, 1.5 eq) at 0 °C. The reaction mixture was stirred at 40 °C for 5 h. The product was then precipitated by pouring the solution over ice-water (400 mL) and collected by vacuum filtration to give 4-bromo-6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazole-5-carbaldehyde (8.6 g, 62.4%) as a yellow solid. 1H NMR (300 MHz, $DMSO-d_6$): δ 10.17 (s, 1H), 8.24 (s, 1H). LCMS: m/z 284.9, 286.9 ($[M-H]^+$).

[00228] **Step F:** To a solution of 4-bromo-6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazole-5-carbaldehyde (5.5 g, 19.2 mmol, 1.0 eq) in THF (70 mL) was added **Int-A** (2-chloro-5-fluorophenyl)magnesium bromide (191.6 mL, 0.5 M in THF, 95.8 mmol, 5.0 eq) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 2 h. Then the mixture was added water (200 mL), extracted with ethyl acetate (100 mL x 2). The combined organic phases were washed with brine (200 mL), dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by silica gel (eluted with petroleum ether / EtOAc = 1: 1) to give 4-bromo-5-((2-chloro-5-fluorophenyl)(hydroxy)methyl)-6-nitrobenzo[d]oxazol-2(3H)-one (3.2 g, 40.0%) as a yellow oil. LCMS: m/z 414.9, 416.9 ($[M-H]^+$). 1H NMR (300 MHz, $DMSO-d_6$): δ 12.61 (brs, 1H), 7.92 (s, 1H), 7.50 (dd, J = 8.8, 5.2 Hz, 1H), 7.42 -7.00 (m, 2H), 6.73 (d, J = 6.0 Hz, 1H), 6.27 (d, J = 5.4 Hz, 1H).

[00229] **Step G:** To a solution of 4-bromo-5-((2-chloro-5-fluorophenyl)(hydroxy)methyl)-6-nitrobenzo[d]oxazol-2(3H)-one (3.0 g, 7.2 mmol, 1.0 eq) and Fe (2.0 g, 35.9 mmol, 5.0 eq) in EtOH (60 mL) was added NH_4Cl (192.1 mg, 3.6 mmol, 0.5 eq) in H_2O (10 mL) dropwise at 50 °C. The reaction mixture was heated to 90 °C and stirred for 1 h. Then the mixture was added

water (80 mL) and ethyl acetate (30 mL), filtered, then the filtrate was extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated to give 6-amino-4-bromo-5-((2-chloro-5-fluorophenyl)(hydroxy)methyl)benzo[d]oxazol-2(3H)-one (2.3 g, 82.4%) as a yellow solid.

LCMS: m/z 384.9, 386.9 ($[\text{M}-\text{H}]^-$).

[00230] **Step H:** To a solution of 6-amino-4-bromo-5-((2-chloro-5-fluorophenyl)(hydroxy)methyl)benzo[d]oxazol-2(3H)-one (700 mg, 1.8 mmol, 1.0 eq) in ACN (10 mL) were added 3-fluoro-5-(trifluoromethyl) benzoyl chloride (818.3 mg, 3.6 mmol, 2.0 eq) and Pyridine (428.6 mg, 5.4 mmol, 3.0 eq). The reaction mixture was stirred at 30 °C for 2 h. The product was then precipitated by pouring the solution over ice-water (30 mL) and collected by vacuum filtration to give N-(4-bromo-5-((2-chloro-5-fluorophenyl)(hydroxy)methyl)-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (600 mg, 57.7%) as a yellow solid. **LCMS:** m/z 574.9, 576.8 ($[\text{M}-\text{H}]^-$).

[00231] **Step I:** To a solution of N-(4-bromo-5-((2-chloro-5-fluorophenyl)(hydroxy)methyl)-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (200 mg, 0.35 mmol, 1.0 eq) in DCM (6 mL) was added DMP (440 mg, 1.05 mmol, 3.0 eq) at 25 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was added with water (10 mL) and extracted with DCM (10 mL x 2). The combined organic phase was washed with NaHCO_3 (10 mL x 2), $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL x 2) and brine (20 mL), dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by silica gel chromatography (eluted with petroleum ether : EtOAc = 5:1) to give N-(4-bromo-5-(2-chloro-5-fluorobenzoyl)-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (70 mg, 34.7%) as a yellow solid. **LCMS:** m/z 572.8, 574.9 ($[\text{M}-\text{H}]^-$).

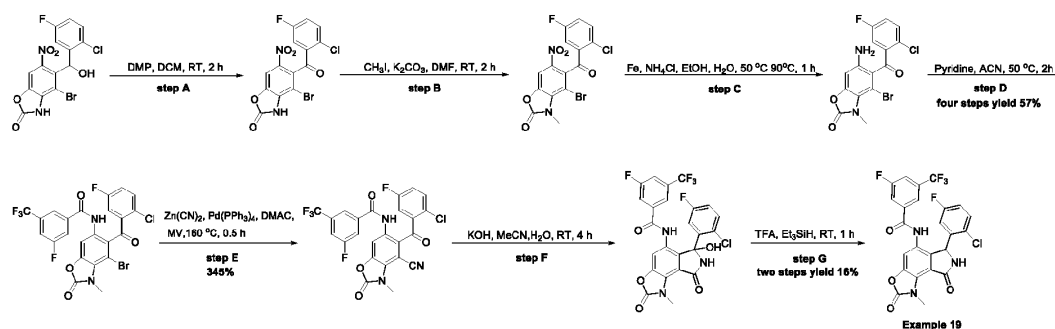
[00232] **Step J:** A sealed vial was charged with N-(4-bromo-5-(2-chloro-5-fluorobenzoyl)-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (50 mg, 0.09 mmol, 1.0 eq), $\text{Zn}(\text{CN})_2$ (15.4 mg, 0.13 mmol, 1.5 eq), $\text{Pd}(\text{PPh}_3)_4$ (30.0 mg, 0.03 mmol, 0.3 eq) and DMAC (1 mL). The sealed vial was irradiated in the microwave at 160 °C for 0.5 h. The mixture was added water (3 mL) and extracted with EtOAc (2 mL x 2). The combined organic phases were washed with brine (3 mL x 2), dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by silica gel (eluted with petroleum ether/ EtOAc = 2: 1) to

give N-(5-(2-chloro-5-fluorobenzoyl)-4-cyano-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (40 mg, crude) as a yellow oil. LCMS: m/z 520.0 ([M-H]⁻).

[00233] **Step K:** To a solution of N-(5-(2-chloro-5-fluorobenzoyl)-4-cyano-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (40.0 mg, 0.08 mmol, 1.0 eq) in MeCN (1 mL) / H₂O (0.1 mL) was added KOH (1.3 mg, 0.02 mmol, 0.3 eq) at room temperature. The reaction mixture was stirred at 40 °C for 4 h. The mixture was added water (3 mL) and extracted with EtOAc (3 mL x 2). The combined organic phases were washed with brine (3 mL x 2), dried over Na₂SO₄ and concentrated to give N-(6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-1,6,7,8-tetrahydro-2H-oxazolo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (50 mg, crude) as a yellow oil. LCMS: m/z 537.9 ([M-H]⁻).

[00234] **Step L:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-1,6,7,8-tetrahydro-2H-oxazolo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (50 mg, 0.09 mmol, 1.0 eq) in TFA (5 mL) was added Et₃SiH (104.7 mg, 0.9 mmol, 10.0 eq). The reaction mixture was stirred at room temperature for 4 h. Then the reaction mixture was concentrated to give a residue. The residue was purified by prep-HPLC (acetonitrile with 0.1% FA in water) to give N-(6-(2-chloro-5-fluorophenyl)-2,8-dioxo-1,6,7,8-tetrahydro-2H-oxazolo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (2.8 mg, three steps yield 5.9%) as a white solid. LCMS: m/z 522.0 ([M-H]⁻). ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.59 (brs, 1H), 10.35 (s, 1H), 9.18 (brs, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.86 – 7.60 (m, 2H), 7.43 (s, 1H), 7.36 – 7.22 (m, 1H), 7.15 – 7.00 (m, 1H), 6.90 – 5.80 (m, 1H).

Example 19 N-(4-bromo-5-(2-chloro-5-fluorobenzoyl)-3-methyl-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00235] **Step A:** To a solution of 4-bromo-5-(2-chloro-5-fluorophenyl)(hydroxy)methyl)-6-nitrobenzo[d]oxazol-2(3H)-one (100 mg, 0.24 mmol, 1.0 eq) in DCM (4 mL) was added DMP

(152 mg, 0.36 mmol, 1.5 eq) at 25 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated to give 4-bromo-5-(2-chloro-5-fluorobenzoyl)-6-nitrobenzo[d]oxazol-2(3H)-one (230 mg, crude) as a yellow solid.

[00236] **Step B:** A solution of 4-bromo-5-(2-chloro-5-fluorobenzoyl)-6-nitrobenzo[d]oxazol-2(3H)-one (230 mg, 0.55 mmol, 1.0 eq) and K₂CO₃ (764.3 mg, 5.5 mmol, 10.0 eq) in DMF (10 mL) was added CH₃I (392.5 mg, 2.9 mmol, 5.0 eq) at 25 °C. The reaction mixture was stirred at 25 °C for 2 h. The mixture was added water (20 mL) and extracted with EtOAc (10 mL x 2). The combined organic phases were washed with brine (10 mL x 2), dried over Na₂SO₄ and concentrated to give 4-bromo-5-(2-chloro-5-fluorobenzoyl)-3-methyl-6-nitrobenzo[d]oxazol-2(3H)-one (120 mg, crude) as a yellow oil.

[00237] **Step C:** To a solution of 4-bromo-5-(2-chloro-5-fluorobenzoyl)-3-methyl-6-nitrobenzo[d]oxazol-2(3H)-one (120 mg, 0.28 mmol, 1.0 eq) and Fe (78 mg, 1.4 mmol, 5.0 eq) in EtOH (3 mL) was added NH₄Cl (7.5 mg, 0.14 mmol, 0.5 eq) in H₂O (0.3 mL) dropwise at 50 °C. The reaction mixture was heated to 90 °C and stirred for 1 h. Then the mixture was added water (3 mL) and ethyl acetate (5 mL), filtered, then the filtrate was extracted with ethyl acetate (5 mL). The combined organic phases were washed with brine (5 mL), dried over Na₂SO₄ and concentrated to give 6-amino-4-bromo-5-(2-chloro-5-fluorobenzoyl)-3-methylbenzo[d]oxazol-2(3H)-one (100 mg, crude) as a yellow solid. LCMS: m/z 398.9, 400.9 ([M+H]⁺).

[00238] **Step D:** To a solution of 6-amino-4-bromo-5-(2-chloro-5-fluorobenzoyl)-3-methylbenzo[d]oxazol-2(3H)-one (100 mg, 0.25 mmol, 1.0 eq) in ACN (2 mL) were added 3-fluoro-5-(trifluoromethyl) benzoyl chloride (86.1 mg, 0.38 mmol, 1.5 eq) and Pyridine (59.3 mg, 0.75 mmol, 3.0 eq). The reaction mixture was stirred at 50 °C for 2 h. Then the mixture was added water (3 mL) and extracted with ethyl acetate (5 mL x 2). The combined organic phases were washed with brine (5 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by Pre-TLC (eluted with petroleum ether / EtOAc = 3: 1) to give N-(4-bromo-5-(2-chloro-5-fluorobenzoyl)-3-methyl-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (80 mg, four steps yield 56.5%) as a yellow solid. LCMS: m/z 586.8, 588.9 ([M-H]⁻).

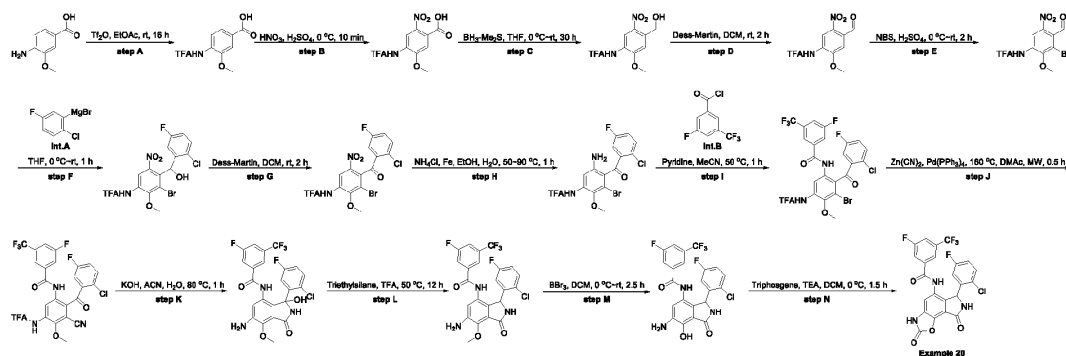
[00239] **Step E:** A sealed vial was charged with N-(4-bromo-5-(2-chloro-5-fluorobenzoyl)-3-methyl-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (60 mg, 0.1 mmol, 1.0 eq), Zn(CN)₂ (18.1 mg, 0.15 mmol, 1.5 eq), Pd(PPh₃)₄ (36.2 mg, 0.03 mmol, 0.3

eq) and DMAc (1.8 mL). The sealed vial was irradiated in the microwave at 160 °C for 0.5 h. The mixture was added water (3 mL) and extracted with EtOAc (2 mL x 2). The combined organic phases were washed with brine (3 mL x 2), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel (eluted with petroleum ether/ EtOAc = 3: 1) to give N-(5-(2-chloro-5-fluorobenzoyl)-4-cyano-3-methyl-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (18.7 mg, 34.9%) as a yellow solid. LCMS: m/z 534.0 ([M-H]⁻).

[00240] **Step F:** To a solution of N-(5-(2-chloro-5-fluorobenzoyl)-4-cyano-3-methyl-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (25 mg, 0.05 mmol, 1.0 eq) in MeCN (1 mL) / H₂O (0.1 mL) was added KOH (5.6 mg, 0.1 mmol, 2.0 eq) at room temperature. The reaction mixture was stirred at room temperature for 4 h. The mixture was added water (2 mL) and extracted with EtOAc (2 mL x 2). The combined organic phases were washed with brine (2 mL), dried over Na₂SO₄ and concentrated to give N-(6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-2,8-dioxo-1,6,7,8-tetrahydro-2H-oxazolo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (25 mg, crude) as a yellow oil. LCMS: m/z 551.9 ([M-H]⁻).

[00241] **Step G:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-2,8-dioxo-1,6,7,8-tetrahydro-2H-oxazolo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (25 mg, 0.04 mmol, 1.0 eq) in TFA (2 mL) was added Et₃SiH (23.2 mg, 0.2 mmol, 5.0 eq). The reaction mixture was stirred at room temperature for 1 h. Then the reaction mixture was concentrated to give a residue. The residue was purified by prep-HPLC (acetonitrile with 0.1% FA in water) to give N-(6-(2-chloro-5-fluorophenyl)-1-methyl-2,8-dioxo-1,6,7,8-tetrahydro-2H-oxazolo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (4.4 mg, two steps yield 16.4%) as a white solid. LCMS: m/z 535.9 ([M-H]⁻). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.37 (s, 1H), 9.30 (brs, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.84 - 7.62 (m, 2H), 7.52 (s, 1H), 7.40 - 7.22 (m, 1H), 7.18 - 7.00 (m, 1H), 6.90 - 5.80 (m, 1H), 3.86 (s, 3H).

Example 20 N-(6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3,6,7,8-tetrahydro-2H-oxazolo[5,4-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00242] **Step A:** To a solution of 4-amino-3-methoxybenzoic acid (50.0 g, 299.1 mmol, 1.0 eq) in EtOAc (2000 mL) was added TFAA (50 mL, 358.92 mmol, 1.2 eq), which was mixed with EtOAc (500 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 16 h. The mixture was concentrated to give 3-methoxy-4-(2,2,2-trifluoroacetamido)benzoic acid (82.0 g, crude) as a yellow solid. LCMS: m/z 262.1 ($[M-H]^-$).

[00243] **Step B:** To a solution of 3-methoxy-4-(2,2,2-trifluoroacetamido)benzoic acid (82.0 g, crude, 0.31 mol, 1.0 eq) in H₂SO₄ (98%, 4100 mL) was added dropwise a solution of HNO₃ (27.1 g) and H₂SO₄ (98%, 197 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. Then the mixture was slowly poured into ice water (7.0 L) and filtered to give 5-methoxy-2-nitro-4-(2,2,2-trifluoroacetamido)benzoic acid (64.0 g, 69.5% yield for 2 steps) as a brown solid. LCMS: m/z 307.0 ($[M-H]^-$). ¹H NMR (300 MHz, DMSO-*d*₆): δ ppm 11.13 (s, 1H), 8.27 (s, 1H), 7.46 (s, 1H), 3.99 (s, 3H).

[00244] **Step C:** To the solution of 5-methoxy-2-nitro-4-(2,2,2-trifluoroacetamido)benzoic acid (32.0 g, 103.8 mmol, 1.0 eq) in THF (400 mL) was added portion-wise BH₃-Me₂S (2M) (155.8 mL, 311.5 mmol, 3.0 eq) at 0 °C. The reaction mixture was stirred at room temperature for 20 h and then the mixture was stirred at room temperature for 1 h. The mixture was added water (300 mL) and extracted with EtOAc (200 mL x 2). The combined organic phase was washed with brine (300 mL), dried over Na₂SO₄ and concentrated to give 2,2,2-trifluoro-N-(4-(hydroxymethyl)-2-methoxy-5-nitrophenyl)acetamide (25.0 g, crude) as a yellow solid. LCMS: m/z 293.0 ($[M-H]^-$).

[00245] **Step D:** To a solution of 2,2,2-trifluoro-N-(4-(hydroxymethyl)-2-methoxy-5-nitrophenyl)acetamide (15.0 g, 50.9 mmol, 1.0 eq) in DCM (750 mL) was added DMP (32.4 g, 76.49 mmol, 1.5 eq) at 25 °C. The reaction mixture was stirred at room temperature for 2 h. The

mixture was added water (300 mL) and extracted with EtOAc (200 mL x 2). The combined organic phase was washed with brine (300 mL), dried over Na₂SO₄ and concentrated to give residue. The residue was purified by silica gel chromatography (petroleum ether / EtOAc = 3:1) to give 2,2,2-trifluoro-N-(4-formyl-2-methoxy-5-nitrophenyl)acetamide (11.0 g, 60.4% yield for 2 steps) as a yellow solid. LCMS: m/z 291.0 ([M-H]⁻).

[00246] **Step E:** To a solution of 2,2,2-trifluoro-N-(4-(hydroxymethyl)-2-methoxy-5-nitrophenyl)acetamide (11.0 g, 37.6 mmol, 1.0 eq) in H₂SO₄ (98%, 190 mL) was added NBS (10.0 g, 56.4 mmol, 1.5 eq) at 0 °C. The reaction mixture was stirred at 25 °C for 2 h. The mixture was poured into ice-water (400 mL) and filtered to give the residue, which was triturated with petroleum ether / EtOAc (3:1, 60 mL) to give N-(3-bromo-4-formyl-2-methoxy-5-nitrophenyl)-2,2,2-trifluoroacetamide (12.1 g, 86.6%) as a yellow solid. LCMS: m/z 368.9, 370.9 ([M-H]⁻). ¹H NMR (300 MHz, DMSO-*d*₆): δ ppm 11.62 (s, 1H), 10.18 (s, 1H), 8.47 (s, 1H), 3.86 (s, 3H).

[00247] **Step F:** To a solution of N-(3-bromo-4-formyl-2-methoxy-5-nitrophenyl)-2,2,2-trifluoroacetamide (12.1 g, 32.6 mmol, 1.0 eq) in THF (121 mL) was added **Int-A** (2-chloro-5-fluorophenyl)magnesium bromide (326.0 mL, 0.5 M in THF, 163.0 mmol, 5.0 eq) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 1 h. Then the mixture was added water (200 mL) and extracted with EtOAc (200 mL x 2). The combined organic phases were washed with brine (200 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel chromatography (petroleum ether / EtOAc = 3:1) to give N-(3-bromo-4-((2-chloro-5-fluorophenyl)(hydroxy)methyl)-2-methoxy-5-nitrophenyl)-2,2,2-trifluoroacetamide (11.0 g, 67.3%) as a yellow solid. LCMS: m/z 498.9, 500.9 ([M-H]⁻). ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 11.46 (s, 1H), 8.06 (s, 1H), 7.60 - 7.51 (m, 1H), 7.32 - 7.20 (m, 1H), 7.04 (dd, *J* = 9.6, 3.2 Hz, 1H), 6.82 (d, *J* = 6.0 Hz, 1H), 6.29 (d, *J* = 5.2 Hz, 1H), 3.76 (s, 3H).

[00248] **Step G:** To a solution of N-(3-bromo-4-((2-chloro-5-fluorophenyl)(hydroxy)methyl)-2-methoxy-5-nitrophenyl)-2,2,2-trifluoroacetamide (11.0 g, 21.9 mmol, 1.0 eq) in DCM (440 mL) was added DMP (13.9 g, 32.9 mmol, 1.5 eq) at 25 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was added water (200 mL) and extracted with DCM (200 mL x 2). The combined organic phase was washed with aqueous solution NaHCO₃ (200 mL x 2), aqueous solution Na₂S₂O₃ (100 mL x 2) and brine (200 mL), dried over Na₂SO₄ and

concentrated to give a residue. The residue was purified by silica gel chromatography (petroleum ether / EtOAc = 3:1) to give N-(3-bromo-4-(2-chloro-5-fluorobenzoyl)-2-methoxy-5-nitrophenyl)-2,2,2-trifluoroacetamide (6.6 g, 59.9%) as a yellow solid. LCMS: m/z 496.8, 498.8 ([M-H]⁻).

[00249] **Step H:** To a solution of N-(3-bromo-4-(2-chloro-5-fluorobenzoyl)-2-methoxy-5-nitrophenyl)-2,2,2-trifluoroacetamide (2.0 g, 4.0 mmol, 1.0 eq) and Fe (1.2 g, 20.0 mmol, 5.0 eq) in EtOH (40 mL) was added NH₄Cl (107.0 mg, 2.0 mmol, 0.5 eq) in H₂O (20 mL) dropwise at 50 °C. The reaction mixture was heated to 90 °C and stirred for 1 h. Then the mixture was added water (80 mL), EtOAc (30 mL) and filtered, then the filtrate was extracted with EtOAc (50 mL x 2). The combined organic phases were washed with brine (50 mL), dried over Na₂SO₄ and concentrated to give N-(5-amino-3-bromo-4-(2-chloro-5-fluorobenzoyl)-2-methoxyphenyl)-2,2,2-trifluoroacetamide (0.9 g, 47.9%) as a yellow solid. LCMS: m/z 466.8, 468.9 ([M-H]⁻).

[00250] **Step I:** To a solution of N-(5-amino-3-bromo-4-(2-chloro-5-fluorobenzoyl)-2-methoxyphenyl)-2,2,2-trifluoroacetamide (900 mg, 1.9 mmol, 1.0 eq) in ACN (10 mL) was added **Int.B** 3-fluoro-5-(trifluoromethyl)benzoyl chloride (516.6 mg, 2.3 mmol, 1.2 eq) and Pyridine (300.6 mg, 5.4 mmol, 2.0 eq). The reaction mixture was stirred at 50 °C for 1 h. The residue was purified by silica gel chromatography (petroleum ether / EtOAc = 3:1) to give N-(3-bromo-2-(2-chloro-5-fluorobenzoyl)-4-methoxy-5-(2,2,2-trifluoroacetamido)phenyl)-3-fluoro-5-(trifluoromethyl)benzamide (800 mg, 57.7%) as a yellow solid. LCMS: m/z 656.8, 658.9 ([M-H]⁻).

[00251] **Step J:** A sealed vial was charged with N-(3-bromo-2-(2-chloro-5-fluorobenzoyl)-4-methoxy-5-(2,2,2-trifluoroacetamido)phenyl)-3-fluoro-5-(trifluoromethyl)benzamide (100 mg, 0.15 mmol, 1.0 eq), Zn(CN)₂ (26.4 mg, 0.23 mmol, 1.5 eq), Pd(PPh₃)₄ (52.0 mg, 0.05 mmol, 0.3 eq) and DMAc (3 mL). The sealed vial was irradiated in the microwave at 160 °C for 0.5 h. The mixture was added water (9 mL) and extracted with EtOAc (5 mL x 2). The combined organic phases were washed with brine (4 mL x 2), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel chromatography (petroleum ether / EtOAc = 3:1) to give N-(2-(2-chloro-5-fluorobenzoyl)-3-cyano-4-methoxy-5-(2,2,2-trifluoroacetamido)phenyl)-3-fluoro-5-(trifluoromethyl)benzamide (47 mg, 51.2%) as a yellow solid. LCMS: m/z 603.9 ([M-H]⁻).

[00252] **Step K:** To a solution of N-(2-(2-chloro-5-fluorobenzoyl)-3-cyano-4-methoxy-5-(2,2,2-trifluoroacetamido)phenyl)-3-fluoro-5-(trifluoromethyl)benzamide (191 mg, 0.32 mmol, 1.0 eq) in MeCN (12 mL) / H₂O (1.2 mL) was added KOH (35.9 mg, 0.64 mmol, 2.0 eq) at room temperature. The reaction mixture was stirred at 80 °C for 1 h. The mixture was added water (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic phases were washed with brine (30 mL x 2), dried over Na₂SO₄ and concentrated to give N-(6-amino-3-(2-chloro-5-fluorophenyl)-3-hydroxy-7-methoxy-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (144 mg, 86.5%) as a brown solid. LCMS: m/z 526.0 ([M-H]⁻).

[00253] **Step L:** To a solution of N-(6-amino-3-(2-chloro-5-fluorophenyl)-3-hydroxy-7-methoxy-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (160 mg, 0.30 mmol, 1.0 eq) in TFA (2 mL) was added Et₃SiH (174 mg, 1.5 mmol, 5.0 eq). The reaction mixture was stirred at 50 °C for 12 h. Then the reaction mixture was concentrated to give a residue, which was purified by Prep-TLC (EtOAc) to obtain N-(6-amino-3-(2-chloro-5-fluorophenyl)-7-methoxy-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (80 mg, 52.1%) as a white solid. LCMS: m/z 512.0 ([M+H]⁺).

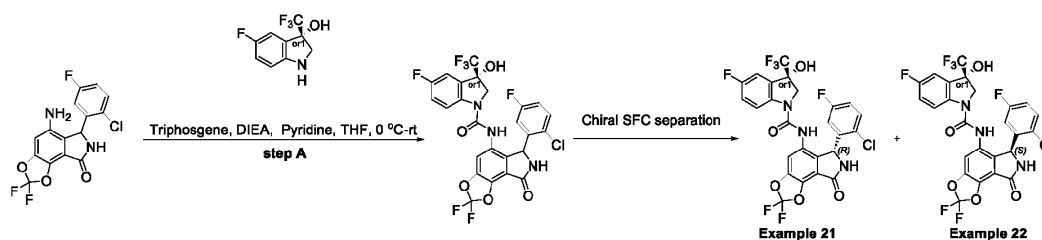
[00254] **Step M:** To a solution of N-(6-amino-3-(2-chloro-5-fluorophenyl)-7-methoxy-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (10 mg, 0.02 mmol, 1.0 eq) in DCM (1 mL) was added BBr₃ (7.5 mg, 0.03 mmol, 1.5 eq) dropwise at under N₂ at 0 °C. The reaction mixture was stirred at room temperature for 2.5 h. Then the reaction mixture was quenched by MeOH (0.5 mL) and concentrated to obtain the N-(6-amino-3-(2-chloro-5-fluorophenyl)-7-hydroxy-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (10 mg, crude) as yellow oil. LCMS: m/z 498.0 ([M+H]⁺).

[00255] **Step N:** To a solution of N-(6-amino-3-(2-chloro-5-fluorophenyl)-7-hydroxy-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (10 mg, 0.02 mmol, 1.0 eq) in DCM (2 mL) was added TEA (44 mg, 0.44 mmol, 2.2 eq). Then the mixture was added Triphosgene (71 mg, 0.24 mmol, 1.2 eq) at 0 °C under N₂. The reaction mixture was stirred at 0 °C for 1.5 h. Then the reaction mixture was concentrated to give a residue, which was purified by prep-HPLC (acetonitrile with 0.1% FA in water 30% to 70%) to give N-(6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3,6,7,8-tetrahydro-2H-oxazolo[5,4-e]isindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (2.8 mg, 26.7% yield for 2 steps) as a white solid. LCMS: m/z 522.0 ([M-H]⁻). ¹H NMR (300 MHz, DMSO-*d*₆): δ ppm 10.22 (s, 1H), 9.00 (s, 1H), 8.35 - 8.20 (m, 1H), 7.91 (d, *J* = 8.4 Hz,

1H), 7.78 - 7.55 (m, 2H), 7.38 - 7.22 (m, 1H), 7.15 - 6.93 (m, 2H), 6.80 - 6.50 (m, 1H), 6.10 - 5.80 (m, 1H).

Example 21 (R*)-N-((R)-6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluoro-3-hydroxy-3-(trifluoromethyl)indoline-1-carboxamide

Example 22 (R*)-N-((S)-6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluoro-3-hydroxy-3-(trifluoromethyl)indoline-1-carboxamide



[00256] **Step A:** To a solution of 5-amino-6-(2-chloro-5-fluorophenyl)-2,2-difluoro-6,7-dihydro-8H-[1,3]dioxolo[4,5-e]isoindol-8-one (200 mg, 0.56 mmol, 1.0 eq) in THF (2 mL) was added Triphosgene (168 mg, 0.56 mmol, 1.0 eq) and DIEA (73 mg, 0.56 mmol, 1.0 eq) at 0 °C under N₂ atmosphere. Then the reaction mixture was stirred at 0 °C for 30 min. A solution of rel-(R)-5-fluoro-3-(trifluoromethyl)indolin-3-ol (248 mg, 1.12 mmol, 2.0 eq) in Pyridine (1.0 mL) was added. The mixture was stirred for 2 h at room temperature. The reaction mixture was quenched by the addition of the saturated aqueous NH₄Cl (2 mL) and the mixture was extracted with EtOAc (2 mL x 3), the combined organic layers were washed with brine (2 mL), dried over sodium sulfate and concentrated. The residue was purified by Prep-HPLC (acetonitrile with 0.1% FA in water 40% to 57%) to give rel-(3R)-N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluoro-3-hydroxy-3-(trifluoromethyl)indoline-1-carboxamide (170 mg, 50.3%) as a white solid. LCMS: m/z 602.0 ([M-H]⁻). It (170 mg) was separated through chiral SFC separation to provide P1 (R*)-N-((R)-6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluoro-3-hydroxy-3-(trifluoromethyl)indoline-1-carboxamide (50.0 mg, 29.4%) as a white solid LCMS: m/z 602.0 ([M-H]⁻). ¹H NMR (300 MHz, DMSO-*d*₆): δ ppm 9.32 (s, 1H), 8.79 (s, 1H), 7.99 - 7.80 (m, 1H), 7.60 - 7.37 (m, 2H), 7.37 - 7.07 (m, 4H), 6.82 (brs, 1H), 6.06 (s, 1H), 3.91 (d, *J*=12.0 Hz, 1H), 3.55 (d, *J*=12.0 Hz, 1H). And P2 (R*)-N-((S)-6-(2-chloro-5-

fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluoro-3-hydroxy-3-(trifluoromethyl)indoline-1-carboxamide (41.6 mg, 24.5%) as a white solid. LCMS: m/z 601.9 ($[M-H]^-$). 1H NMR (400 MHz, DMSO- d_6): δ ppm 9.33 (s, 1H), 8.70 (s, 1H), 7.80 (dd, $J = 8.8, 4.4$ Hz, 1H), 7.54 (s, 1H), 7.39 (d, $J = 2.0$ Hz, 1H), 7.33 (dd, $J = 8.8, 4.2$ Hz, 1H), 7.30 - 7.16 (m, 2H), 7.15 - 7.04 (m, 1H), 6.77 (brs, 1H), 6.12 (s, 1H), 4.20 - 4.00 (m, 1H), 3.51 (d, $J = 12.0$ Hz, 1H).

[00257] The prep-SFC separation is below:

Chiral purity by SFC (area normalization)

Principle NP HPLC with UV detection, Assessment in area %

MeOH: HPLC grade, J&K

CO₂: 99.999%

Solvent: ACN

Equipment: apparatus Waters SFC

Column: CHIRALCEL OD-H 20 mm*250 mm, 5 μ m

Chromatographic conditions:

Mobile phase A: CO₂

Mobile phase B: MeOH

Gradient: B 20%

Flow rate: 30 ml/min

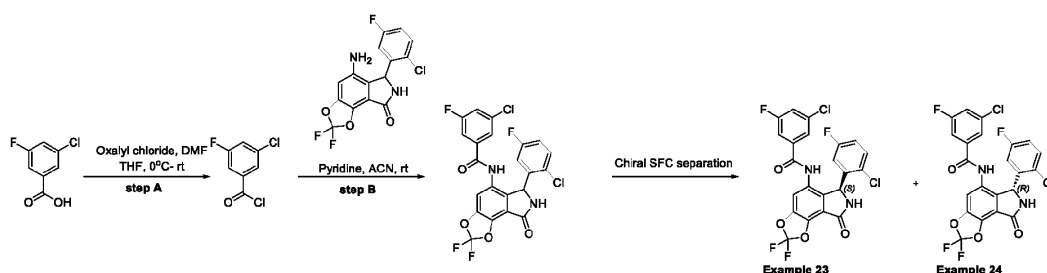
Injection volume: 0.5 ml

Injection concentration: 20 mg/ml

Column temperature: 35°C

Prep SFC Cycle time 11 min

Example 23 (S)-3-chloro-N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluorobenzamide and **Example 24 (R)-3-chloro-N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluorobenzamide**



[00258] **Step A:** To a solution of 3-chloro-5-fluorobenzoic acid (5.0 g, 28.6 mmol, 1.0 eq) in THF (50 mL) was added dropwise $(\text{COCl})_2$ (10.9 g, 85.8 mmol, 3.0 eq) and DMF (0.1 mL) at room temperature. Then the reaction mixture was stirred for 2 h at the same temperature. The mixture was concentrated to give 3-chloro-5-fluorobenzoyl chloride (5.5 g, crude) as a yellow solid and was used directly.

[00259] **Step B:** To a solution of 5-amino-6-(2-chloro-5-fluorophenyl)-2,2-difluoro-6,7-dihydro-8H-[1,3]dioxolo[4,5-e]isoindol-8-one (200 mg, 0.56 mmol, 1.0 eq) in ACN (2 mL) was added 3-chloro-5-fluorobenzoyl chloride (130 mg, 0.67 mmol, 1.2 eq) and Pyridine (89 mg, 1.12 mmol, 2.0 eq) at room temperature. Then the mixture was stirred for 2 h at the same temperature. The mixture was added water (2 mL) and extracted with EtOAc (2 mL $\times$ 3). The combined organic phases were washed with brine (2 mL), dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by Prep-HPLC (acetonitrile with 0.1% FA in water 35% to 47%) to afford 3-chloro-N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluorobenzamide (100.0 mg, 34.8%) as a white solid. LCMS: m/z 510.9 ($[\text{M}-\text{H}]^-$). It was separated via chiral SFC with the condition below to provide P1 (S)-3-chloro-N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluorobenzamide (20.0 mg, 20.0%) as a white solid. LCMS: m/z 510.9 ($[\text{M}-\text{H}]^-$). ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ ppm 10.33 (s, 1H), 9.37 (s, 1H), 7.77 - 7.63 (m, 1H), 7.60 (s, 1H), 7.48 - 7.23 (m, 3H), 7.23 - 7.05 (m, 1H), 6.85 (brs, 1H), 6.04 (s, 1H). And P2 CAN-3-chloro-N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluorobenzamide (30.0 mg, 30.0%), as a white solid. LCMS: m/z 510.9 ($[\text{M}-\text{H}]^-$). ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ ppm 10.33 (s, 1H), 9.37 (s, 1H), 7.77 - 7.63 (m, 1H), 7.60 (s, 1H), 7.45 - 7.25 (m, 3H), 7.24 - 7.05 (m, 1H), 6.86 (brs, 1H), 6.04 (s, 1H).

[00260] Chiral SFC Separation Method:

Chiral purity by SFC (area normalization)

Principle NP HPLC with UV detection, Assessment in area %

Reagents:

MeOH: HPLC grade, J&K

CO₂: 99.999%

Solvent: MeOH+CAN

Equipment: apparatus Waters SFC

Column: CHIRALCEL AS-H 20 mm*250 mm, 5 μm

Chromatographic conditions:

Mobile phase A: CO₂

Mobile phase B: MeOH

Gradient: B 30%

Flow rate: 30 ml/min

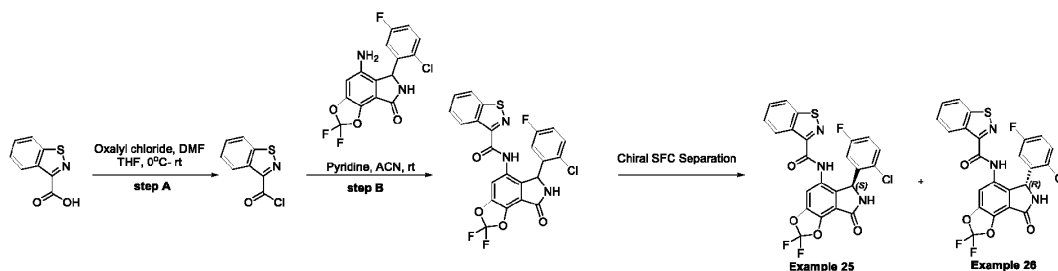
Injection volume: 1.0 ml

Injection concentration: 20 mg/ml

Column temperature: 35°C

Example 25 (S)-N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)benzo[d]isothiazole-3-carboxamide

Example 26 (R)-N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)benzo[d]isothiazole-3-carboxamide



[00261] **Step A:** To a solution of 3-chloro-5-fluorobenzoic acid (200 mg, 1.12 mmol, 1.0 eq) in THF (2.0 mL) was added dropwise (COCl)₂ (0.425 g, 3.35 mmol, 3.0 eq) and DMF (0.1 mL) at room temperature. Then the reaction mixture was stirred for 2 h at the same temperature. The mixture was concentrated to give 3-chloro-5-fluorobenzoyl chloride (250 mg, crude) as a yellow solid and it was used as crude directly for next step.

[00262] **Step B:** To a solution of 5-amino-6-(2-chloro-5-fluorophenyl)-2,2-difluoro-6,7-dihydro-8H-[1,3]dioxolo[4,5-e]isoindol-8-one (200 mg, 0.56 mmol, 1.0 eq) in ACN (2 mL) was added 3-chloro-5-fluorobenzoyl chloride (133 mg, 0.67 mmol, 1.2 eq) and Pyridine (89 mg, 1.12 mmol, 2.0 eq) at room temperature. Then the mixture was stirred for 2 h at the same temperature. The mixture was added water (2 mL) and extracted with EtOAc (2 mL x 3). The combined organic phases were washed with brine (2 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by Prep-HPLC (acetonitrile with 0.1% FA in water 35% to 47%) to afford 3-chloro-N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluorobenzamide (~ 60 mg, 20.7%) as a white solid. LCMS: m/z 515.9 ([M-H]⁻). It was separated via chiral prep-SFC separation with the method below to provide P1 (S)-3-chloro-N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluorobenzamide (15.7 mg, 39.3%) as a white solid. LCMS: m/z 515.9 ([M-H]⁻). ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 10.43 (s, 1H), 9.37 (s, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.90 - 7.52 (m, 3H), 7.50 - 6.60 (m, 3H), 6.22 (brs, 1H). And P2 (R)-3-chloro-N-(6-(2-chloro-5-fluorophenyl)-2,2-difluoro-8-oxo-7,8-dihydro-6H-[1,3]dioxolo[4,5-e]isoindol-5-yl)-5-fluorobenzamide (17.9 mg, 44.8%), as a white solid. LCMS: m/z 515.9 ([M-H]⁻). ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 10.43 (s, 1H), 9.37 (s, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.90 - 7.52 (m, 3H), 7.50 - 6.70 (m, 3H), 6.22 (brs, 1H).

[00263] Chiral prep-SFC Separation Method:

Chiral purity by UPCC (area normalization)

Principle NP HPLC with UV detection, Assessment in area %

Reagents:

MeOH: HPLC grade, MREDA

CO₂: 99.999%

Solvent: MeOH

Equipment: apparatus Waters UPCC

Column: CHIRALPAK AS-3, 4.6mm*150mm, 3um

Chromatographic conditions

Mobile phase A: CO₂

Mobile phase B: MeOH

Gradient: B 30%

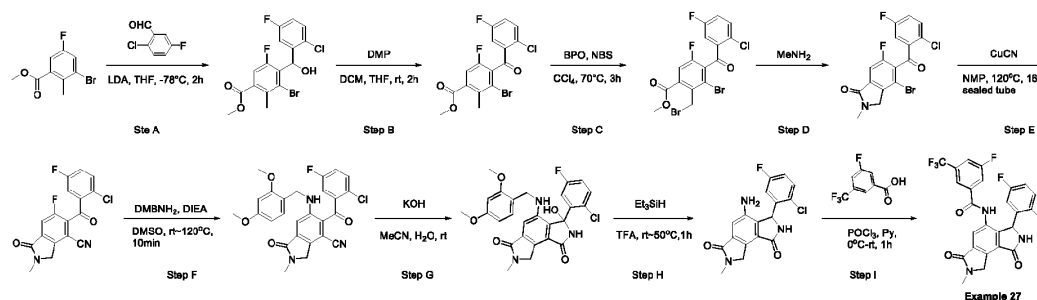
Flow rate: 2.0ml/min

Detection UV: 210nm

Column temperature: 35°C

Injection volume: 2.0ul

Example 27 N-(3-(2-chloro-5-fluorophenyl)-7-methyl-1,6-dioxo-1,2,3,6,7,8-hexahydropyrrolo[3,4-e]isoindol-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00264] **Step A:** To a stirred mixture of methyl 3-bromo-5-fluoro-2-methylbenzoate (5 g, 20.2 mmol) in dry THF (30 mL) cooled to -78 °C was added dropwise a solution of LDA (20.2 mL, 40.5 mmol, 2M) for 0.5 h. The reaction mixture was stirred at -78 °C for 20 min. A solution of 2-chloro-5-fluorobenzene-1-carbaldehyde (4.17 g, 26.3 mmol) in THF (10 mL) was added dropwise at -78 °C for 0.1 h. The resulting mixture was stirred at -78 °C for 2 h. The reaction mixture was quenched by addition of aqueous saturated NH₄Cl solution. The following mixture was extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (0-30% EA in PE) to give methyl 3-bromo-4-[(2-chloro-5-fluorophenyl)(hydroxy)methyl]-5-fluoro-2-methylbenzoate (2.2 g, 5.42 mmol, 26.8%) as yellow oil.

[00265] **Step B:** To a solution of methyl 3-bromo-4-[(2-chloro-5-fluorophenyl)(hydroxy)methyl]-5-fluoro-2-methylbenzoate (2.2 g, 5.42 mmol) in DCM (22 mL) at 0 °C under N₂ was added 1,1,1-triacetoxy-1,3-dihydro-1λ⁵-benzo[d][1,2]iodoxol-3-one (4.6 g, 10.8 mmol). The reaction mixture was stirred at rt for 1 hour. The mixture was treated with H₂O (100 mL) and extracted with EA (3 x 300 mL). The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography (0-30% EA in PE) followed to give methyl 3-bromo-4-[(2-chloro-5-

fluorophenyl)carbonyl]-5-fluoro-2-methylbenzoate (1.7 g, 4.21 mmol, 77.6%) as a yellow oil.

LCMS: ESI m/z 403/405 [M + H]⁺.

[00266] **Step C:** To a stirred mixture of methyl 3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-5-fluoro-2-methylbenzoate (1 g, 2.47 mmol) in CCl₄ (15 mL) was added NBS (572 mg, 3.23 mmol) and 2-[(1E)-(2-cyanoprop-2-yl)diazanyl]-2-methylpropanenitrile (110 mg, 0.74 mmol). The reaction mixture was stirred at reflux for 2 h. The cooled reaction mixture diluted with water and extracted with DCM. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (PE: EA=2: 1) to give methyl 3-bromo-2-(bromomethyl)-4-[(2-chloro-5-fluorophenyl)carbonyl]-5-fluorobenzoate (1.1 g, 2.27 mmol, 91.9%) as a white solid.

[00267] **Step D:** A stirred solution of methyl 3-bromo-2-(bromomethyl)-4-[(2-chloro-5-fluorophenyl)carbonyl]-5-fluorobenzoate (1.1 g, 2.28 mmol) in methanamine (10 mL) was stirred for 0.5 h. The reaction was concentrated under reduced pressure give 4-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-6-fluoro-2-methyl-2,3-dihydro-1H-isoindol-1-one (650 mg, 1.62 mmol, 71.2%). LCMS: ESI m/z 400/402 [M + H]⁺.

[00268] **Step E:** To a solution of 4-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-6-fluoro-2-methyl-2,3-dihydro-1H-isoindol-1-one (450 mg, 1.12 mmol) in NMP (5 mL) was added CuCN (100 mg, 1.12 mmol). The reaction mixture was stirred at 120 °C under N₂ for 1 hour. The cooled reaction mixture was treated with H₂O (100 mL) and extracted with EA (3 x 300 mL). The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography (PE: EA=2: 1) followed to give 5-[(2-chloro-5-fluorophenyl)carbonyl]-6-fluoro-2-methyl-1-oxo-2,3-dihydro-1H-isoindole-4-carbonitrile (350 mg, 1.01 mmol, 89.9%) as a yellow oil. LCMS: ESI m/z 347 [M + H]⁺.

[00269] **Step F:** To a solution of 5-[(2-chloro-5-fluorophenyl)carbonyl]-6-fluoro-2-methyl-1-oxo-2,3-dihydro-1H-isoindole-4-carbonitrile (300 mg, 0.87 mmol) in DMSO (4 mL) was added DIEA (112 mg, 0.87 mmol) in sealed tube. The mixture was refluxed under N₂ for 30 minutes until the starting material was consumed completely. The cooled reaction mixture was poured into water (6 mL) and extracted with EtOAc (6 mL). The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated. The crude product was purified by silica gel chromatography eluted with PE: EA = 3: 1 to give 5-[(2-chloro-5-fluorophenyl)carbonyl]-6-

{[(2,4-dimethoxyphenyl)methyl]amino}-2-methyl-1-oxo-2,3-dihydro-1H-isoindole-4-carbonitrile (80 mg, 0.16 mmol, 18.7%) as a yellow solid.

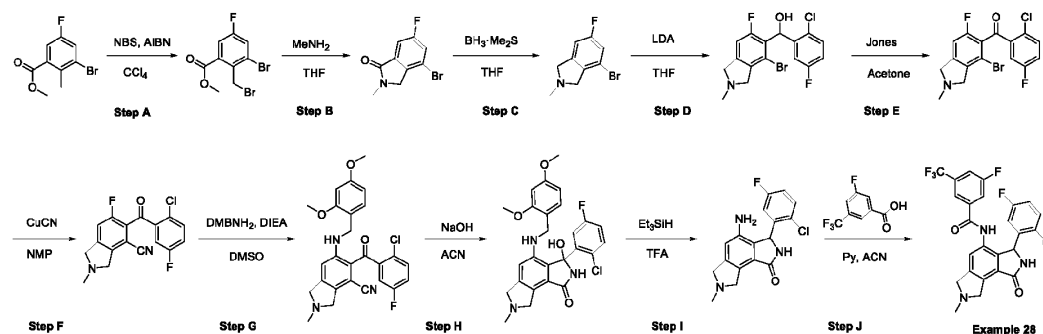
[00270] **Step G:** To a stirred mixture of 5-[(2-chloro-5-fluorophenyl)carbonyl]-6-{[(2,4-dimethoxyphenyl)methyl]amino}-2-methyl-1-oxo-2,3-dihydro-1H-isoindole-4-carbonitrile (80 mg, 0.16 mmol) in acetonitrile (4 mL) was added dropwise a solution of KOH (45.5 mg, 0.81 mmol) in H₂O (1 mL). The solution was stirred at room temperature for an additional 2 h. The reaction was then extracted with DCM (3 × 5.0 mL). The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography eluting with a solvent mixture composed of PE: EA=3:1 to afford 3-(2-chloro-5-fluorophenyl)-4-{[(2,4-dimethoxyphenyl)methyl]amino}-3-hydroxy-7-methyl-1,2,3,6,7,8-hexahydropyrrolo[4,3-e]isoindole-1,6-dione (40 mg, 0.08 mmol, 48.2%) as a yellow oil. LCMS: ESI m/z 512 [M + H]⁺.

[00271] **Step H:** To a solution of 3-(2-chloro-5-fluorophenyl)-4-{[(2,4-dimethoxyphenyl)methyl]amino}-3-hydroxy-7-methyl-1,2,3,6,7,8-hexahydropyrrolo[4,3-e]isoindole-1,6-dione (40 mg, 0.08 mmol) in TFA (2 mL) was added triethylsilane (90.7 mg, 0.78 mmol). The reaction mixture was stirred at 50 °C for 1 hour. The cooled mixture was concentrated. The residue was diluted with H₂O (50 mL), adjusted pH=8 with saturated aqueous NaHCO₃ and extracted with EA. The organic layer was washed with brine (50 mL), dried over Na₂SO₄ and concentrated. The residue was purified by column (PE: EA=1: 1) to give 4-amino-3-(2-chloro-5-fluorophenyl)-7-methyl-1,2,3,6,7,8-hexahydropyrrolo[4,3-e]isoindole-1,6-dione (30 mg, 0.09 mmol, 100%) as a yellow solid. LCMS: ESI m/z 346 [M + H]⁺.

[00272] **Step I:** To a stirred mixture of 4-amino-3-(2-chloro-5-fluorophenyl)-7-methyl-1,2,3,6,7,8-hexahydropyrrolo[4,3-e]isoindole-1,6-dione (20 mg, 0.06 mmol) and 5-fluoro-3-(trifluoromethyl)benzoic acid (12 mg, 0.06 mmol) in dry pyridine (1 mL) was added dropwise POCl₃ (8.87 mg, 0.06 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. The reaction mixture was extracted with EA (15 mL). The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give N-[3-(2-chloro-5-fluorophenyl)-7-methyl-1,6-dioxo-1,2,3,6,7,8-hexahydropyrrolo[4,3-e]isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (3.5 mg, 0.007 mmol, 11.3%) as a white solid. LCMS: ESI m/z 536 [M + H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.82 (s, 1H), 7.66 (dd, J = 16.2, 8.7 Hz, 3H),

7.27 (dd, $J = 9.0, 5.0$ Hz, 1H), 7.00 (td, $J = 8.4, 3.0$ Hz, 1H), 6.28 (s, 2H), 4.88 (d, $J = 2.6$ Hz, 2H), 3.27 (s, 3H).

Example 28 N-[3-(2-chloro-5-fluorophenyl)-7-methyl-1-oxo-1,2,3,6,7,8-hexahydropyrrolo[4,3-c]isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide



[00273] **Step A:** To a solution of methyl 3-bromo-5-fluoro-2-methylbenzoate (1 g, 4.05 mmol) in CCl_4 (10 mL) was added 1-bromotetrahydropyrrole-2,5-dione (1.08 g, 6.071 mmol) and benzoic peroxyanhydride (0.39 g, 1.619 mmol). The reaction mixture was stirred at 90°C overnight. The cooled mixture was diluted with water, extracted with EA, and the organic phase was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by column chromatography eluted with ethyl acetate in petroleum ether (0~5% gradient) to give methyl 3-bromo-2-(bromomethyl)-5-fluorobenzoate (1.2 g, 3.68 mmol, 90.95%) as a colorless oil.

[00274] **Step B:** To a solution of methyl 3-bromo-2-(bromomethyl)-5-fluorobenzoate (1 g, 3.07 mmol) in THF (10 mL) was added methanamine (7.7 mL, 15.3 mmol, 2M in THF). The reaction mixture was stirred at 25°C for 1 h. The reaction mixture was diluted with water, extracted with EA. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by column chromatography eluted with ethyl acetate in petroleum ether (35% gradient) to give 4-bromo-6-fluoro-2-methyl-2,3-dihydro-1H-isoindol-1-one (500 mg, 2.049 mmol, 66.78%) as a white solid. LCMS: ESI m/z 244 $[\text{M} + \text{H}]^+$.

[00275] **Step C:** To a solution of 4-bromo-6-fluoro-2-methyl-2,3-dihydro-1H-isoindol-1-one (1 g, 4.09 mmol) in THF (7.5 mL) was added borane dimethylsulfane (5 mL, 50.0 mmol) at 25°C , and the reaction mixture was stirred at 60°C for 4 h. The cooled reaction solution was quenched with methanol and 6 M HCl was added to adjusted pH to 1-2. Then the mixture was

heated to 80 °C and stirred for 1 h. The reaction was cooled to room temperature and adjusted pH to 7-8 with 6 M NaOH. The reaction solution was extracted with EA. The organic layer was separated, washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with MeOH in DCM (0~5% gradient) to afford compound 4-bromo-6-fluoro-2-methyl-2,3-dihydro-1H-isoindole (650 mg, 2.825 mmol, 68.95%) as a colorless oil. LCMS: ESI m/z 230 [M + H]⁺.

[00276] **Step D:** To a solution of 4-bromo-6-fluoro-2-methyl-2,3-dihydro-1H-isoindole (1.5 g, 6.519 mmol) in dry THF (15 mL) was added dropwise lithium di(prop-2-yl)azanide (4.890 mL, 9.779 mmol) at -65 °C. The reaction mixture was stirred at -65 °C under N₂ atmosphere for 0.5 h. A solution of 2-chloro-5-fluorobenzene-1-carbaldehyde (1.55 g, 9.779 mmol) in THF (8 mL) was added dropwise. The reaction mixture was stirred at -65 °C for 1 h. The reaction mixture was quenched by adding sat. aq. NH₄Cl solution, extracted with EA. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel with MeOH in DCM (0→4%, V/V) to give diethyl (4-bromo-6-fluoro-2-methyl-2,3-dihydro-1H-isoindol-5-yl)(2-chloro-5-fluorophenyl)methanol (1 g, 2.573 mmol, 39.47%) as a white solid. LCMS: ESI m/z 388 [M + H]⁺.

[00277] **Step E:** To a solution of (4-bromo-6-fluoro-2-methyl-2,3-dihydro-1H-isoindol-5-yl)(2-chloro-5-fluorophenyl)methanol (800 mg, 2.058 mmol) in propan-2-one (10 mL) was added 65272-70-0 (0.5 mL, 2.058 mmol) at 0 °C. The reaction mixture was stirred 0 °C for 2 hr. After 2 h, the reaction mixture was quenched with isopropyl alcohol (10 mL). The isopropyl alcohol was removed under vacuum then was extracted with EA, combined all organic phases, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel with MeOH in DCM (0→5%, V/V) to give (4-bromo-6-fluoro-2-methyl-2,3-dihydro-1H-isoindol-5-yl)(2-chloro-5-fluorophenyl)methanone (700 mg, 1.811 mmol, 87.96%) as a white solid. LCMS: ESI m/z 386 [M + H]⁺.

[00278] **Step F:** To a solution of (4-bromo-6-fluoro-2-methyl-2,3-dihydro-1H-isoindol-5-yl)(2-chloro-5-fluorophenyl)methanone (600 mg, 1.55 mmol) in 1-methyltetrahydropyrrol-2-one (10 mL) was added CuCN (278 mg, 3.10 mmol) at 25 °C. The reaction mixture was stirred at 120 °C under N₂ atmosphere for 4 hr. The cooled reaction mixture was diluted water, extracted with EA. The organic phase was washed with water and brine, dried over anhydrous Na₂SO₄ and

concentrated. The residue was purified by flash chromatography eluted with MeOH in DCM (0~3% gradient) to afford 5-[(2-chloro-5-fluorophenyl)carbonyl]-6-fluoro-2-methyl-2,3-dihydro-1H-isoindole-4-carbonitrile (250 mg, 0.751 mmol, 48.4%) as a yellow solid. LCMS: ESI m/z 333 $[M + H]^+$.

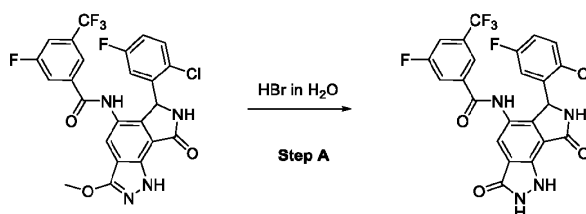
[00279] **Step G:** To a solution of 5-[(2-chloro-5-fluorophenyl)carbonyl]-6-fluoro-2-methyl-2,3-dihydro-1H-isoindole-4-carbonitrile (250 mg, 0.751 mmol) in DMSO (6 mL) was added (2,4-dimethoxyphenyl)methanamine (125 mg, 0.751 mmol) and ethyl[di(prop-2-yl)]amine (194 mg, 1.503 mmol) at 25 °C. The reaction mixture was stirred at 120 °C for 1 hr. The reaction solution was diluted with EA, washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography eluted with MeOH in DCM (0~4% gradient) to afford 5-[(2-chloro-5-fluorophenyl)carbonyl]-6-[(2,4-dimethoxyphenyl)methyl]amino}-2-methyl-2,3-dihydro-1H-isoindole-4-carbonitrile (160 mg, 0.333 mmol, 44.37%) as a yellow solid. LCMS: ESI m/z 480 $[M + H]^+$.

[00280] **Step H:** To a solution of 5-[(2-chloro-5-fluorophenyl)carbonyl]-6-[(2,4-dimethoxyphenyl)methyl]amino}-2-methyl-2,3-dihydro-1H-isoindole-4-carbonitrile (140 mg, 0.292 mmol) in ACN (5 mL) and H_2O (0.5 mL) was added NaOH (23.34 mg, 0.583 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 0.5 h. The reaction solution was diluted with EA, washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography eluted with MeOH in DCM (0~8% gradient) to afford 3-(2-chloro-5-fluorophenyl)-4-[(2,4-dimethoxyphenyl)methyl]amino}-3-hydroxy-7-methyl-1,2,3,6,7,8-hexahydropyrrolo[4,3-e]isoindol-1-one (114 mg, 0.229 mmol, 78.5%) as a yellow solid. LCMS: ESI m/z 498 $[M + H]^+$.

[00281] **Step I:** To a solution of 3-(2-chloro-5-fluorophenyl)-4-[(2,4-dimethoxyphenyl)methyl]amino}-3-hydroxy-7-methyl-1,2,3,6,7,8-hexahydropyrrolo[4,3-e]isoindol-1-one (100 mg, 0.201 mmol) in 2,2,2-trifluoroacetic acid (3 mL) was added triethylsilane (0.3 mL) at rt. The reaction mixture was stirred at rt for 0.5 h. After 0.5 h, the reaction mixture was diluted with H_2O . The aqueous layer was extracted with EA. Combined the EA layer and washed with brine, dried by Na_2SO_4 , filtered and concentrated in vacuo to afford 4-amino-3-(2-chloro-5-fluorophenyl)-7-methyl-1,2,3,6,7,8-hexahydropyrrolo[4,3-e]isoindol-1-one (85 mg, 0.154 mmol, 76.54%) as a yellow oil. LCMS: ESI m/z 332 $[M + H]^+$.

[00282] **Step J:** To a solution of 4-amino-3-(2-chloro-5-fluorophenyl)-7-methyl-1,2,3,6,7,8-hexahydropyrrolo[4,3-e]isoindol-1-one (80 mg, 0.145 mmol) in ACN (5 mL) was added pyridine (0.117 mL, 1.447 mmol) and 3-fluoro-5-(trifluoromethyl)benzoyl chloride (98 mg, 0.434 mmol) at room temperature. The reaction mixture was stirred at 25 °C for 10 min and then concentrated. The residue was purified by silica gel column chromatography eluted with EA and further purified by prep-HPLC to afford N-[3-(2-chloro-5-fluorophenyl)-7-methyl-1-oxo-1,2,3,6,7,8-hexahydropyrrolo[4,3-e]isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide (19.1 mg, 0.037 mmol, 25.3%) as a white solid. LCMS: ESI m/z 522 $[M + H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.58 (s, 1H), 9.26 (s, 1H), 7.96 (d, $J = 7.6$ Hz, 1H), 7.75 (d, $J = 8.8$ Hz, 1H), 7.67 (s, 1H), 7.51 (s, 1H), 7.36 – 7.28 (m, 1H), 7.10 (s, 1H), 6.05 (s, 1H), 4.74 (s, 2H), 4.51 (s, 2H), 2.97 (s, 3H).

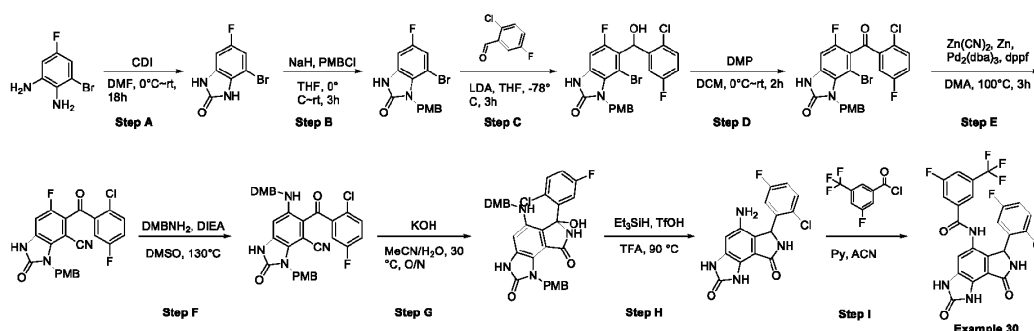
Example 29 N-(6-(2-chloro-5-fluorophenyl)-3,8-dioxo-1,2,3,6,7,8-hexahydropyrrolo[3,4-g]indazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



Example 29

[00283] **Step A:** A solution of N-[6-(2-chloro-5-fluorophenyl)-3-methoxy-8-oxo-1,6,7,8-tetrahydropyrrolo[4,3-g]indazol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (30 mg, 0.056 mmol) in HBr (3 mL, 30% HBr in H₂O) was stirred at 50 °C overnight. The cooled reaction mixture was diluted with H₂O, extracted with EA, washed with brine, dried over Na₂SO₄ and concentrated. The residue purified by prep-HPLC to afford compound N-(6-(2-chloro-5-fluorophenyl)-3,8-dioxo-1,2,3,6,7,8-hexahydropyrrolo[3,4-g]indazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (2.0 mg, 0.004 mmol, 6.84%) as a white solid. LCMS: ESI m/z 523 $[M + H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 12.43 (s, 1H), 10.82 (s, 1H), 10.28 (s, 1H), 9.07 (s, 1H), 7.93 (d, $J = 8.2$ Hz, 1H), 7.70 (d, $J = 14.8$ Hz, 4H), 7.29 (dd, $J = 8.8, 5.1$ Hz, 1H), 7.10 (d, $J = 7.8$ Hz, 1H), 6.13 (s, 1H).

Example 30 N-[6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3,6,7,8-tetrahydro-1H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide



[00284] **Step A:** To a stirred solution of 3-bromo-5-fluorobenzene-1,2-diamine (18 g, 87.8 mmol) in DMF (180 mL) under argon atmosphere was added CDI (10.9 mL, 87.8 mmol) at 0 °C. The reaction mixture was stirred at rt for 18 h. The reaction was monitored by TLC. The mixture was treated with H₂O (100 mL) and extracted with EA (3 x 300 mL). The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was triturated with DCM (100 mL) and filtered to afford 4-bromo-6-fluoro-2,3-dihydro-1H-benzo[d]imidazol-2-one (16.5 g, 71.4 mmol, 81.4%) as a yellow oil.

[00285] **Step B:** To the suspension of NaH (8.31 g, 208 mmol, 60% in mineral) in dry THF (60 mL) was added batchwise 4-bromo-6-fluoro-2,3-dihydro-1H-benzo[d]imidazol-2-one (16 g, 69.3 mmol) at 0 °C. After the completion of addition, the reaction mixture was stirred for additional 1.5 hours at 0 °C. 4-Methoxybenzylchloride (28.3 mL, 208 mmol) was added slowly, the mixture was stirred at 0 °C for 0.5 hr and stirred at rt for 2 hrs. The reaction mixture was quenched by addition of aqueous saturated NH₄Cl solution. The following mixture was extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (0-30% EA in PE) to give 7-bromo-5-fluoro-1-[(4-methoxyphenyl)methyl]-2,3-dihydro-1H-benzo[d]imidazol-2-one (7.2 g, 20.5 mmol, 29.6%) as a yellow oil. LCMS: ESI m/z 351/353 [M + H]⁺.

[00286] **Step C:** To a stirred mixture of 7-bromo-5-fluoro-1-[(4-methoxyphenyl)methyl]-2,3-dihydro-1H-benzo[d]imidazol-2-one (7 g, 19.9 mmol) in dry THF (70 mL) cooled to -78 °C was added dropwise a solution of LDA (39.9 mL, 79.7 mmol, 2M) for 0.5 h. The reaction mixture was stirred at -78 °C for 20 min. A solution of 2-chloro-5-fluorobenzene-1-carbaldehyde (4.74 g, 29.9 mmol) in THF (20 mL) was added dropwise at -78 °C for 0.1 h. The resulting mixture was stirred at -78 °C for 2 h. The reaction mixture was quenched by addition of aqueous saturated NH₄Cl solution. The following mixture was extracted with EA. The organic layer was washed

with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (0-30% EA in PE) to give 7-bromo-6-[(2-chloro-5-fluorophenyl)(hydroxy)methyl]-5-fluoro-1-[(4-methoxyphenyl)methyl]-2,3-dihydro-1H-benzo[d]imidazol-2-one (3.2 g, 6.28 mmol, 31.5%) as a yellow oil.

[00287] **Step D:** To a solution of 7-bromo-6-[(2-chloro-5-fluorophenyl)(hydroxy)methyl]-5-fluoro-1-[(4-methoxyphenyl)methyl]-2,3-dihydro-1H-benzo[d]imidazol-2-one (3.2 g, 6.28 mmol) in DCM (40 mL) at 0 °C under N₂ was added 1,1,1-triacetoxy-1,3-dihydro-1H-benzo[d][1,2]iodoxol-3-one (832 mg, 1.96 mmol). The reaction mixture was stirred at rt for 1 hour. The mixture was treated with H₂O (100 mL) and extracted with EA (3 x 300 mL). The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography (0-30% EA in PE) followed to give 7-bromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-5-fluoro-1-[(4-methoxyphenyl)methyl]-2,3-dihydro-1H-benzo[d]imidazol-2-one (1.9 g, 3.74 mmol, 59.6%) as a yellow oil. LCMS: ESI m/z 507/509 [M + H]⁺.

[00288] **Step E:** To a solution of 4-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-6-fluoro-1-[(4-methoxyphenyl)methyl]-2,3-dihydro-1H-benzo[d]imidazol-2-one (1.7 g, 3.35 mmol) and Zn(CN)₂ (0.47 g, 4.02 mmol) in DMA (20 mL) was added Zn (0.04 g, 0.67 mmol) followed by Pd₂(dba)₃ (0.31 g, 0.34 mmol), bis(cyclopentyl)diphenylphosphane) iron(0) (0.38 g, 0.67 mmol) under N₂ with stirred. The mixture was refluxed for 3 hours until the starting material was consumed completely. The cooled reaction mixture was treated with H₂O (100 mL) and extracted with EA (3 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography (0-30% EA in PE) followed to give 5-[(2-chloro-5-fluorophenyl)carbonyl]-6-fluoro-1-[(4-methoxyphenyl)methyl]-2-oxo-3H-benzo[d]imidazole-4-carbonitrile (1.2 g, 2.64 mmol, 78.9%) as a yellow oil.

[00289] **Step F:** To a solution of 5-[(2-chloro-5-fluorophenyl)carbonyl]-6-fluoro-3-[(4-methoxyphenyl)methyl]-2-oxo-1H-benzo[d]imidazole-4-carbonitrile (200 mg, 0.308 mmol) in DMSO (5 mL) was added (2,4-dimethoxyphenyl)methanamine (51.5 mg, 0.308 mmol) and DIEA (80 mg, 0.617 mmol) at 25 °C. The reaction mixture was stirred at 130 °C for 5 hr. The reaction solution was purified by flash chromatography eluted with ACN in H₂O (0~65% gradient) to afford 5-[(2-chloro-5-fluorophenyl)carbonyl]-6-[(2,4-

dimethoxyphenyl)methyl]amino}-3-[(4-methoxyphenyl)methyl]-2-oxo-1H-benzo[d]imidazole-4-carbonitrile (60 mg, 0.100 mmol, 32.4%) as a yellow solid. LCMS: ESI m/z 601 $[M + H]^+$.

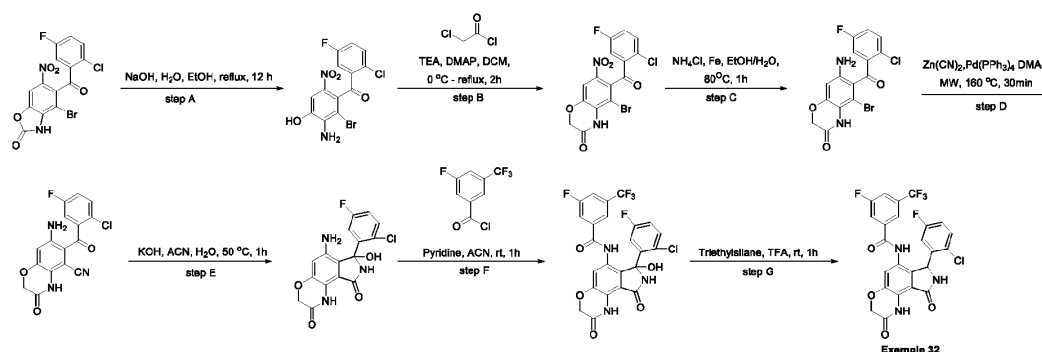
[00290] **Step G:** To a solution of 5-[(2-chloro-5-fluorophenyl)carbonyl]-6-{[(2,4-dimethoxyphenyl)methyl]amino}-3-[(4-methoxyphenyl)methyl]-2-oxo-1H-benzo[d]imidazole-4-carbonitrile (60 mg, 0.100 mmol) in ACN (5 mL) and H₂O (1 mL) was added KOH (28.0 mg, 0.499 mmol) at 25 °C. The reaction mixture was stirred at 30 °C for overnight. The reaction solution was diluted with EA, washed with water and brine, dried over anhydrous Na₂SO₄, concentrated. The residue was purified by flash chromatography eluted with MeOH in DCM (0~8% gradient) to afford 6-(2-chloro-5-fluorophenyl)-5-{[(2,4-dimethoxyphenyl)methyl]amino}-6-hydroxy-1-[(4-methoxyphenyl)methyl]-1,2,3,6,7,8-hexahydroimidazo[5,4-e]isoindole-2,8-dione (15 mg, 0.024 mmol, 24.27%) as a yellow solid. LCMS: ESI m/z 619 $[M + H]^+$.

[00291] **Step H:** To a solution of 6-(2-chloro-5-fluorophenyl)-5-{[(2,4-dimethoxyphenyl)methyl]amino}-6-hydroxy-1-[(4-methoxyphenyl)methyl]-1,2,3,6,7,8-hexahydroimidazo[5,4-e]isoindole-2,8-dione (15 mg, 0.024 mmol) in 2,2,2-trifluoroacetic acid (2 mL) was added triethylsilane (5.64 mg, 0.048 mmol) and trifluoromethanesulfonic acid (0.2 mL, 2.260 mmol) at room temperature. The reaction mixture was stirred at 90 °C for 2 h. The TFE and TfOH were removed under vacuum. Then the mixture was adjusted pH to 8 by NaHCO₃(aqueous), extracted with EA. The organic layer was separated, washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to afford 5-amino-6-(2-chloro-5-fluorophenyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindole-2,8-dione (10 mg, 0.021 mmol, 86.85%) as a yellow solid and used into next step without further purification. LCMS: ESI m/z 333 $[M + H]^+$.

[00292] **Step I:** To a solution of 5-amino-6-(2-chloro-5-fluorophenyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindole-2,8-dione (10 mg, 0.021 mmol) in acetonitrile (1 mL) was added Py (0.005 mL, 0.063 mmol) and 3-fluoro-5-(trifluoromethyl)benzoyl chloride (9.52 mg, 0.042 mmol) at room temperature. The reaction mixture was stirred at 25 °C for 10 min. The ACN and pyridine were removed under vacuum to give a crude product which was purified by prep-HPLC to afford N-[6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3,6,7,8-tetrahydro-1H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (2.2 mg, 0.004 mmol, 20.0%) as a white solid. LCMS: ESI m/z 523 $[M + H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.38

(s, 1H), 11.00 (s, 1H), 10.21 (s, 1H), 8.99 (s, 1H), 7.92 (d, $J = 8.2$ Hz, 1H), 7.71 (d, $J = 9.4$ Hz, 1H), 7.66 (s, 1H), 7.29 (dd, $J = 8.8, 5.2$ Hz, 1H), 7.07 (t, $J = 6.8$ Hz, 1H), 7.03 (s, 1H), 5.98 (s, 1H).

Example 32 N-(7-(2-chloro-5-fluorophenyl)-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00293] **Step A:** To a solution of 4-bromo-5-(2-chloro-5-fluorobenzoyl)-6-nitrobenzo[d]oxazol-2(3H)-one (2.0 g, 4.81 mmol, 1.0 eq) in EtOH (20 mL) were added NaOH (770 mg, 19.25 mmol, 4.0 eq) in H₂O (20 mL). The reaction mixture was refluxed for 12 h. The reaction mixture was concentrated and added with DCM: MeOH=10:1 (50 mL). Then the mixture was filtered and the filtrate was concentrated to give (3-amino-2-bromo-4-hydroxy-6-nitrophenyl)(2-chloro-5-fluorophenyl)methanone (2.3 g, crude) as a brown solid. LCMS: m/z 387.0, 388.9([M-H]).

[00294] **Step B:** To a solution of (3-amino-2-bromo-4-hydroxy-6-nitrophenyl)(2-chloro-5-fluorophenyl)methanone (1.0 g, 2.57 mmol, 1.0 eq) in DCM (8.5 mL) were added TEA (546 mg, 5.39 mmol, 2.1 eq) and DMAP (63 mg, 0.51 mmol, 0.2 eq) at 0 °C under N₂ atmosphere. Then the chloroacetyl chloride (304 mg, 2.70 mmol, 1.05 eq) was added to the system. The reaction mixture was refluxed for 2 h. The reaction mixture was cooled to 25 °C and the chloroacetyl chloride (434 mg, 3.85 mmol, 1.5 eq) was added. The reaction mixture was heated to reflux for 4 h. The reaction mixture was cooled to 25 °C, quenched with aqueous solution NaHSO₄ (30 mL) and extracted with EtOAc (20 mL x 3). The combined organic phases were washed with brine (30 mL), dried over Na₂SO₄ and concentrated to give 5-bromo-6-(2-chloro-5-fluorobenzoyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (1.1 g, crude) as a brown solid. LCMS: m/z 426.9, 428.8 ([M-H]).

[00295] **Step C:** To a solution of 5-bromo-6-(2-chloro-5-fluorobenzoyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (1.1 g, 2.45 mmol, 1.0 eq) in EtOH (10 mL) was added NH₄Cl (520 mg, 9.77 mmol, 4 eq) in H₂O (3.5 mL). Then Fe (410 mg, 7.33 mmol, 3.0 eq) was added to the system at 50 °C. The reaction mixture was heated to 90 °C and stirred for 1 h. Then water (15 mL) and ethyl acetate (5 mL) were added, filtered, the filtrate was extracted with ethyl acetate (10 mL x 2). The combined organic phases were washed with brine (10 mL), dried over Na₂SO₄ and concentrated to give a curde. The residue was purified by Pre-TLC (eluted with petroleum ether/ EtOAc = 3 : 1) to give 7-amino-5-bromo-6-(2-chloro-5-fluorobenzoyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (110 mg) as a yellow solid. LCMS: m/z 398.9, 400.9 ([M+H]⁺).

[00296] **Step D:** A sealed vial was charged with 7-amino-5-bromo-6-(2-chloro-5-fluorobenzoyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (50 mg, 0.13 mmol, 1.0 eq), Zn(CN)₂ (15 mg, 0.13 mmol, 1.0 eq), Pd(PPh₃)₄ (44 mg, 0.04 mmol, 0.3 eq) and DMAc (0.5 mL). The sealed vial was irradiated in the microwave at 160 °C for 30 min. The mixture was added water (3 mL) and extracted with EtOAc (3 mL x 2). The combined organic phases were washed with brine (5 mL x 2), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by Pre-TLC (eluted with petroleum ether/ EtOAc = 1: 1) to give 7-amino-6-(2-chloro-5-fluorobenzoyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-5-carbonitrile (18 mg, 41.5 %) as a yellow solid. LCMS: m/z 344.1 ([M-H]⁻).

[00297] **Step E:** To a solution of 7-amino-6-(2-chloro-5-fluorobenzoyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-5-carbonitrile (150 mg, 0.43 mmol, 1.0 eq) in ACN (5 mL) / H₂O (0.5 mL) was added KOH (72.4 mg, 1.29 mmol, 3.0 eq) at room temperature. The reaction mixture was stirred at 50 °C for 1 h. The mixture was added water (5 mL) and extracted with EtOAc (5 mL x 2). The combined organic phases were washed with brine (5 mL), dried over Na₂SO₄ and concentrated to give 6-amino-7-(2-chloro-5-fluorophenyl)-7-hydroxy-7,8-dihydro-[1,4]oxazino[3,2-e]isoindole-2,9(1H,3H)-dione (150 mg, crude) as a yellow oil. LCMS: m/z 362.0 ([M-H]⁻).

[00298] **Step F:** To a solution of 6-amino-7-(2-chloro-5-fluorophenyl)-7-hydroxy-7,8-dihydro-[1,4]oxazino[3,2-e]isoindole-2,9(1H,3H)-dione (150 mg, 0.41 mmol, 1.0 eq) in ACN (5 mL) were added 3-fluoro-5-(trifluoromethyl) benzoyl chloride (278 mg, 1.23 mmol, 3 eq) and Pyridine (162.2 mg, 2.05 mmol, 5.0 eq). The reaction mixture was stirred at room temperature for 1 h. Then the mixture was diluted with water (10 mL) and extracted with ethyl acetate (5 mL

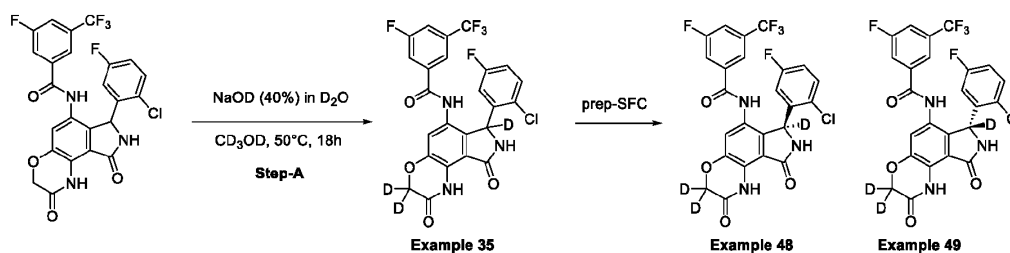
x 2). The combined organic phases were washed with brine (5 mL) and aqueous solution Na_2CO_3 (5 mL), dried over Na_2SO_4 and concentrated to give N-(7-(2-chloro-5-fluorophenyl)-7-hydroxy-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (240 mg, crude) as a yellow oil. LCMS: m/z 551.9 ($[\text{M}-\text{H}]^-$).

[00299] **Step G:** To a solution of N-(7-(2-chloro-5-fluorophenyl)-7-hydroxy-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (240 mg, 0.41 mmol, 1.0 eq) in TFA (5 mL) was added Et_3SiH (238 mg, 2.05 mmol, 5.0 eq). The reaction mixture was stirred at room temperature for 1 h. Then the reaction mixture was concentrated to give a residue. The residue was purified by prep-HPLC (acetonitrile with 0.1% FA in water) to give N-(7-(2-chloro-5-fluorophenyl)-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (19 mg, three steps yield ~ 8.2%) as a white solid. LCMS: m/z 535.9 ($[\text{M}-\text{H}]^-$). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.34 (brs, 1H), 9.51 (brs, 1H), 9.28 (s, 1H), 7.93 (d, $J = 8.0$ Hz, 1H), 7.70 (d, $J = 8.8$ Hz, 1H), 7.63 (s, 1H), 7.33 – 7.30 (m, 1H), 7.12 – 7.07 (m, 2H), 6.90 – 6.76 (m, 1H), 5.95 (s, 1H), 4.81 (s, 2H).

Example 35 N-(7-(2-chloro-5-fluorophenyl)-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3,3,7-d₃-3-fluoro-5-(trifluoromethyl)benzamide

Example 48 (S)-N-(7-(2-chloro-5-fluorophenyl)-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3,3,7-d₃-3-fluoro-5-(trifluoromethyl)benzamide

Example 49 (R)-N-(7-(2-chloro-5-fluorophenyl)-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3,3,7-d₃-3-fluoro-5-(trifluoromethyl)benzamide



[00300] **Step A:** To a solution of N-[7-(2-chloro-5-fluorophenyl)-2,9-dioxo-1,2,3,7,8,9-hexahydro[1,4]oxazino[3,2-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (7 mg, 0.01 mmol) in CD_3OD (0.5 mL) was added 40% NaOD in D_2O (0.26 mg, 0.0026 mmol). The reaction mixture was stirred at 50°C for 18 h. To the cooled mixture was added 1N HCl and the pH was

adjusted to about 7. The reaction mixture was pre-purified by prep-HPLC purification to give N-[7-(2-chloro-5-fluorophenyl)-3,3-dideuterio-2,9-dioxo-1,2,3,7,8,9-hexahydro[1,4]oxazino[3,2-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (2.9 mg, 0.01 mmol, 41.3%) as a white solid. LCMS: ESI m/z 541 $[M + H]^+$. 1H NMR (400 MHz, CD_3OD) 7.67 – 7.58 (m, 3H), 7.25 (dd, $J = 8.8, 5.0$ Hz, 1H), 7.08 (s, 1H), 7.02 – 6.94 (m, 1H), 6.68 (s, 1H). Another batch of 200 mg of N-[7-(2-chloro-5-fluorophenyl)-3,3-dideuterio-2,9-dioxo-1,2,3,7,8,9-hexahydro[1,4]oxazino[3,2-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide was then subjected to chiral prep-SFC separation with the method below to afford P1 Example 48 (S)-N-(7-(2-chloro-5-fluorophenyl)-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl-3,3,7-d₃)-3-fluoro-5-(trifluoromethyl)benzamide (51.8 mg, 0.096 mmol, 52%) as a white solid. LCMS: ESI m/z 541 $[M + H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 10.40 (s, 1H), 9.52 (s, 1H), 9.26 (s, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 7.72 (s, 1H), 7.66 (s, 1H), 7.31 (dd, $J = 8.8, 5.2$ Hz, 1H), 7.11 (d, $J = 6.4$ Hz, 1H), 7.08 (dd, $J = 8.6, 2.9$ Hz, 1H), 6.86 (brs, 1H). And P2 Example 49 (R)-N-(7-(2-chloro-5-fluorophenyl)-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl-3,3,7-d₃)-3-fluoro-5-(trifluoromethyl)benzamide (62.7 mg, 0.116 mmol, 62%) as a white solid (R)-N-(7-(2-chloro-5-fluorophenyl)-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl-3,3,7-d₃)-3-fluoro-5-(trifluoromethyl)benzamide. LCMS: ESI m/z 541 $[M + H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 10.40 (s, 1H), 9.52 (s, 1H), 9.26 (s, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 7.72 (s, 1H), 7.66 (s, 1H), 7.31 (dd, $J = 8.8, 5.2$ Hz, 1H), 7.11 (d, $J = 6.4$ Hz, 1H), 7.08 (dd, $J = 8.6, 2.9$ Hz, 1H), 6.86 (brs, 1H).

[00301] Preparative separation method:

Instrument: SHIMADZU PREP SOLUTION SFC

Column: ChiralPak IH, 250×20mm I.D., 5 μ m

Mobile phase: A for CO₂ and B for MEOH

Gradient: B 20%

Flow rate: 40mL/min

Back pressure: 100 bar

Column temperature: 35°C

Wavelength: 220 nm

Cycle-time: 6min

Eluted time: 2 h

Example 36 N-[7-(2-chloro-5-fluorophenyl)-3-methyl-2,9-dioxo-1,2,3,7,8,9-

hexahydro[1,4]oxazino[3,2-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide

Example 37 N-((3R*,7R)-7-(2-chloro-5-fluorophenyl)-3-methyl-2,9-dioxo-1,2,3,7,8,9-

hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 38 N-((3R*,7R)-7-(2-chloro-5-fluorophenyl)-3-methyl-2,9-dioxo-1,2,3,7,8,9-

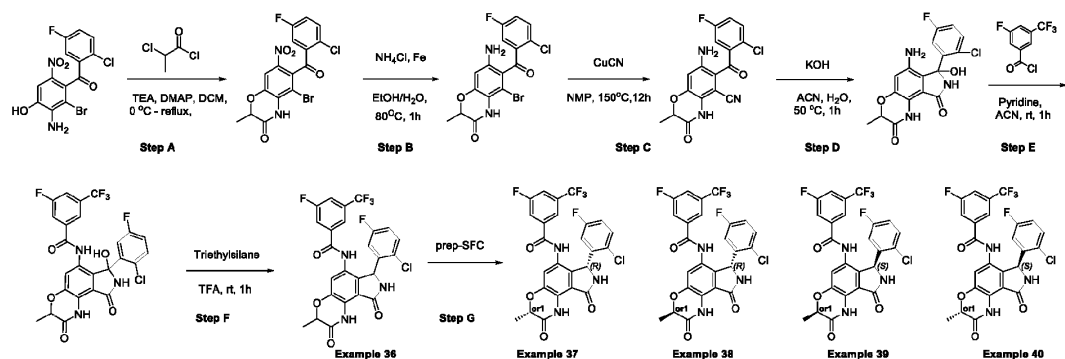
hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 39 N-((3R*,7S)-7-(2-chloro-5-fluorophenyl)-3-methyl-2,9-dioxo-1,2,3,7,8,9-

hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 40 N-((3R*,7S)-7-(2-chloro-5-fluorophenyl)-3-methyl-2,9-dioxo-1,2,3,7,8,9-

hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00302] **Step A:** To a stirred mixture of (3-amino-2-bromo-4-hydroxy-6-nitrophenyl)(2-chloro-5-fluorophenyl)methanone (500 mg, 1.28 mmol) in DCM (5 mL) was added dropwise TEA (0.357 mL, 2.56 mmol), DMAP (31 mg, 0.257 mmol) and 2-chloropropanoyl chloride (325 mg, 2.57 mmol) at RT. The reaction mixture was stirred at 50 °C for additional 2h. The cooled reaction was quenched with aqueous solution NaHSO₄ (10 mL), extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with MeOH in DCM [Gradient: 5%] to afford 5-bromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-2-methyl-7-nitro-3,4-dihydro-2H-benzo[1,4]oxazin-3-one (450 mg, 1.014 mmol, 78.9%) as a white solid. LCMS: ESI m/z 442 [M+H]⁺.

[00303] **Step B:** To a stirred mixture of 5-bromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-2-methyl-7-nitro-3,4-dihydro-2H-benzo[1,4]oxazin-3-one (420 mg, 0.947 mmol) in EtOH/H₂O (20 mL) was added dropwise NH₄Cl (152 mg, 2.84 mmol) and Fe (158 mg, 2.84 mmol). The

reaction mixture was stirred at 75 °C for an additional 1h. Water and ethyl acetate were added, filtered, the filtrate was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with MeOH in DCM [Gradient: 6%] to afford 7-amino-5-bromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-2-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-3-one (380 mg, 0.919 mmol, 97.4%) as a white solid. LCMS: ESI m/z 412[M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.79 (s, 1H), 7.60 (dd, *J* = 8.8, 4.9 Hz, 1H), 7.44 (dd, *J* = 8.2, 3.0 Hz, 1H), 7.24 (dd, *J* = 8.6, 3.0 Hz, 1H), 6.54 (s, 1H), 6.25 (s, 2H), 4.69 (d, *J* = 6.8 Hz, 1H), 1.42 (d, *J* = 6.8 Hz, 3H).

[00304] **Step C:** To a stirred mixture of 7-amino-5-bromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-2-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-3-one (700 mg, 1.69 mmol) in NMP (8 mL) was added dropwise CuCN (303 mg, 3.38 mmol). The reaction mixture was stirred at 150 °C for 1h with microwave. The cooled resulting mixture was filtered, the filtrate was washed with EA. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified using silica gel column chromatography eluting with MeOH in DCM [Gradient: 4%] to afford compound 7-amino-6-[(2-chloro-5-fluorophenyl)carbonyl]-2-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-5-carbonitrile (480 mg, 1.33mmol, 78.8%) as a white solid. LCMS: ESI m/z 360 [M+H]⁺.

[00305] **Step D:** To a solution of 7-amino-6-[(2-chloro-5-fluorophenyl)carbonyl]-2-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-5-carbonitrile (350 mg, 0.973 mmol) in CH₃CN/H₂O (8 mL) were added potassium hydroxide (273 mg, 4.86 mmol). The reaction mixture was stirred at 50 °C for 30 min. The cooled reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried by Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with MeOH in DCM [Gradient: 4%] to afford 6-amino-7-(2-chloro-5-fluorophenyl)-7-hydroxy-3-methyl-1,2,3,7,8,9-hexahydro[1,4]oxazino[3,2-*e*]isoindole-2,9-dione (270 mg, 0.715 mmol, 72.9%) as a white solid. LCMS: ESI m/z 376 [M+H]⁺.

[00306] **Step E:** To a solution of 6-amino-7-(2-chloro-5-fluorophenyl)-7-hydroxy-3-methyl-1,2,3,7,8,9-hexahydro[1,4]oxazino[3,2-*e*]isoindole-2,9-dione (200 mg, 0.529 mmol) in ACN (5 mL) were added pyridine (0.086 mL, 1.06 mmol) and 3-fluoro-5-(trifluoromethyl)benzoyl

chloride (144 mg, 0.635 mmol). The reaction mixture was stirred at RT for 30 min. The reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried by Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with MeOH in DCM [Gradient: 5%] to afford N-[7-(2-chloro-5-fluorophenyl)-7-hydroxy-3-methyl-2,9-dioxo-1,2,3,7,8,9-hexahydro[1,4]oxazino[3,2-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (150 mg, 0.264 mmol, 49.9%) as a white solid.

LCMS: ESI m/z 567 [M+H]⁺

[00307] **Step F:** To a solution of N-[7-(2-chloro-5-fluorophenyl)-7-hydroxy-3-methyl-2,9-dioxo-1,2,3,7,8,9-hexahydro[1,4]oxazino[3,2-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (200 mg, 0.352 mmol) in TFA (4 mL) were added Et₃SiH (204 mg, 1.76 mmol). The reaction mixture was stirred at 50 °C for 1h. The reaction mixture was stirred at RT for 30 min. The reaction mixture was diluted with aqueous NaHCO₃, extracted with EA. The organic phase was washed with brine, dried by Na₂SO₄ and concentrated. The residue was purified by prep-HPLC afford Example 36: N-[7-(2-chloro-5-fluorophenyl)-3-methyl-2,9-dioxo-1,2,3,7,8,9-hexahydro[1,4]oxazino[3,2-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (100 mg, 0.181 mmol, 68.6%) as a white solid. LCMS: ESI m/z 552 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.34 (s, 1H), 9.52 (s, 0.5H), 9.48 (s, 0.5H), 9.27 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.66 (m, 2H), 7.41 – 7.25 (m, 1H), 7.17 – 7.00 (m, 2H), 6.78 (s, 1H), 5.88 (brs, 1H), 5.02 – 4.84 (m, 1H), 1.52 (d, *J* = 6.8 Hz, 3H).

[00308] **Step G:** Example 36 (100 mg, 0.181 mmol) was separated by chiral prep-SFC (Waters Thar 80 preparative SFC-Chiral Cel OD, 250×21.2mm I.D., 5μm, 20%, phase A: CO₂, phase B: MeOH) to afford: P-1 Example 37 (15 mg, 0.027 mmol, 10.3%) as a white solid. LCMS: ESI m/z 552 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.34 (s, 1H), 9.52 (s, 1H), 9.27 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.66 (m, 2H), 7.41 – 7.25 (m, 1H), 7.17 – 7.00 (m, 2H), 6.78 (s, 1H), 5.88 (brs, 1H), 4.96 (q, *J* = 6.8 Hz, 1H), 1.51 (d, *J* = 6.8 Hz, 3H).

[00309] P-2 Example 38 (15.8 mg, 0.028 mmol, 10.8%) as a white solid. LCMS: ESI m/z 552 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.34 (s, 1H), 9.48 (s, 0.5H), 9.27 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.69 – 7.66 (m, 2H), 7.41 – 7.25 (m, 1H), 7.17 – 7.00 (m, 2H), 6.78 (s, 1H), 5.88 (brs, 1H), 4.94 (q, *J* = 6.8 Hz, 1H), 1.52 (d, *J* = 6.8 Hz, 3H).

[00310] P-3 Example 39 (16.9 mg, 0.031 mmol, 11.6%) as a white solid. LCMS: ESI m/z 552 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.34 (s, 1H), 9.52 (s, 1H), 9.27 (s, 1H), 7.93 (d, *J*

= 8.4 Hz, 1H), 7.70 – 7.66 (m, 2H), 7.41 – 7.25 (m, 1H), 7.17 – 7.00 (m, 2H), 6.78 (s, 1H), 5.88 (brs, 1H), 4.96 (q, $J = 6.8$ Hz, 1H), 1.51 (d, $J = 6.8$ Hz, 3H).

[00311] P-4 Example 40 (12.2 mg, 0.021 mmol, 8.34%) as a white solid. LCMS: ESI m/z 552 $[M + H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.34 (s, 1H), 9.48 (s, 0.5H), 9.27 (s, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.69 – 7.66 (m, 2H), 7.41 – 7.25 (m, 1H), 7.17 – 7.00 (m, 2H), 6.78 (s, 1H), 5.88 (brs, 1H), 4.94 (q, $J = 6.8$ Hz, 1H), 1.52 (d, $J = 6.8$ Hz, 3H).

[00312] Preparative separation method:

Instrument: Waters Thar 80 preparative SFC

Column: ChiralPak IH, 250×21.2 mm I.D., 5 μ m

Mobile phase: A for CO₂ and B for MEOH

Gradient: B 20 %

Flow rate: 40 mL/min

Back pressure: 100 bar

Column temperature: 35 °C

Wavelength: 220 nm

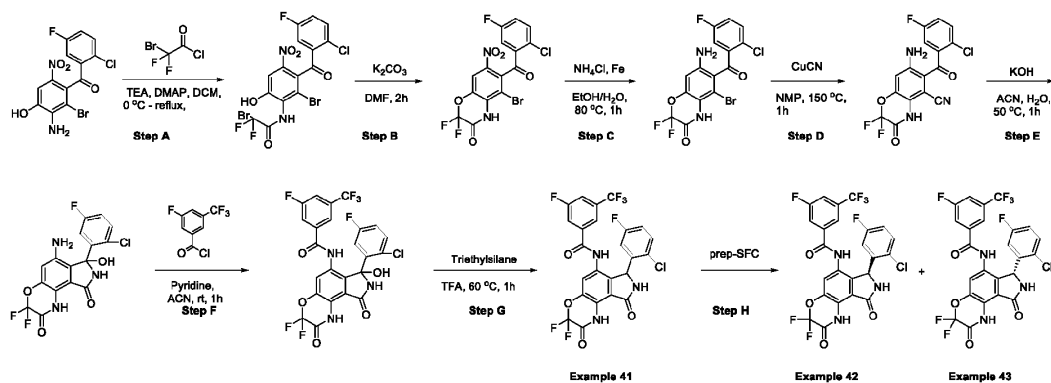
Cycle-time: 6 min

Eluted time: 2 H

Example 41 N-(7-(2-chloro-5-fluorophenyl)-3,3-difluoro-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 42 (S)-N-(7-(2-chloro-5-fluorophenyl)-3,3-difluoro-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 43 (R)-N-(7-(2-chloro-5-fluorophenyl)-3,3-difluoro-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00313] **Step A:** To a stirred mixture of (3-amino-2-bromo-4-hydroxy-6-nitrophenyl)(2-chloro-5-fluorophenyl)methanone (800 mg, 2.05 mmol) in DCM (10 mL) was added dropwise TEA (0.571 mL, 4.10 mmol), DMAP (50 mg, 0.411 mmol) and 2-bromo-2,2-difluoroacetyl chloride (794 mg, 4.10 mmol) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at 50 °C for an additional 2h. The cooled reaction was quenched with aqueous solution NaHSO₄ (10 mL), extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 35%] to afford compound 2-bromo-N-(2-bromo-3-(2-chloro-5-fluorobenzoyl)-6-hydroxy-4-nitrophenyl)-2,2-difluoroacetamide (650 mg, 1.19 mmol, 58%) as a white solid. LCMS: ESI m/z 545 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.86 (s, 1H), 11.10 (s, 1H), 7.82 (s, 1H), 7.75 – 7.65 (m, 2H), 7.65 – 7.55 (m, 1H).

[00314] **Step B:** To a solution of 2-bromo-N-(2-bromo-3-(2-chloro-5-fluorobenzoyl)-6-hydroxy-4-nitrophenyl)-2,2-difluoroacetamide (650 mg, 1.19 mmol) in DMF (10 mL) were added potassium carbonate (493 mg, 3.57 mmol), (2-methylprop-2-yl)oxidanecarboxylic anhydride (51 mg, 0.237 mmol) and DMAP (1.45 mg, 0.012 mmol). The reaction mixture was stirred at 50 °C under N₂ overnight. The cooled reaction mixture was diluted with H₂O, extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 25%] to afford compound 5-bromo-6-(2-chloro-5-fluorobenzoyl)-2,2-difluoro-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (500 mg, 1.07 mmol, 90%) as a white solid. LCMS: ESI m/z 465 [M+H]⁺

[00315] **Step C:** To a stirred mixture of 5-bromo-6-(2-chloro-5-fluorobenzoyl)-2,2-difluoro-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (500 mg, 1.074 mmol) in EtOH/H₂O (20 mL) was added dropwise NH₄Cl (172 mg, 3.222 mmol) and iron(0) (179 mg, 3.22 mmol) at rt under N₂ atmosphere. The reaction mixture was stirred at 80 °C for 1h. The cooled reaction mixture was quenched with water at rt. The resulting mixture was extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 30%] to afford compound 7-amino-5-bromo-6-(2-chloro-5-fluorobenzoyl)-2,2-difluoro-2H-benzo[b][1,4]oxazin-3(4H)-one (410 mg, 0.941 mmol, 88%) as a white solid. LCMS: ESI m/z 436 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ

11.21 (s, 1H), 7.64 (dd, $J = 8.8, 4.8$ Hz, 1H), 7.49 (td, $J = 8.4, 3.2$ Hz, 1H), 7.35 (dd, $J = 8.8, 3.0$ Hz, 1H), 6.77 (s, 1H), 6.09 (s, 2H).

[00316] **Step D:** To a stirred mixture of 7-amino-5-bromo-6-(2-chloro-5-fluorobenzoyl)-2,2-difluoro-2H-benzo[b][1,4]oxazin-3(4H)-one (400 mg, 0.918 mmol) in NMP (6 mL) was added dropwise CuCN (164 mg, 1.837 mmol). The reaction mixture was stirred at 150 °C under N₂ in microwave for 1h. The cooled reaction mixture was diluted with water, extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 35%] to afford compound 7-amino-6-(2-chloro-5-fluorobenzoyl)-2,2-difluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-5-carbonitrile (220 mg, 0.576 mmol, 63%) as a white solid. LCMS: ESI m/z 380 [M+H]⁺

[00317] **Step E:** To a solution of 7-amino-6-(2-chloro-5-fluorobenzoyl)-2,2-difluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-5-carbonitrile (220 mg, 0.552 mmol) in CH₃CN/H₂O (8 mL) were added potassium hydroxide (97 mg, 1.73 mmol). The reaction mixture was stirred at 50 °C for 30min. The cooled reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried by Na₂SO₄, filtered and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 40%] to afford compound 6-amino-7-(2-chloro-5-fluorophenyl)-3,3-difluoro-7-hydroxy-7,8-dihydro-[1,4]oxazino[3,2-e]isoindole-2,9(1H,3H)-dione (120 mg, 0.30 mmol, 52%) as a white solid. LCMS: ESI m/z 398 [M+H]⁺

[00318] **Step F:** To a solution of 6-amino-7-(2-chloro-5-fluorophenyl)-3,3-difluoro-7-hydroxy-7,8-dihydro-[1,4]oxazino[3,2-e]isoindole-2,9(1H,3H)-dione (100 mg, 0.25 mmol) in CAN (5 mL) were added 3-fluoro-5-(trifluoromethyl)benzoyl chloride (68 mg, 0.300 mmol) and pyridine (0.04 mL, 0.500 mmol). The reaction mixture was stirred at RT for 1h. The reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried by Na₂SO₄, filtered and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 35%] to afford compound N-(7-(2-chloro-5-fluorophenyl)-3,3-difluoro-7-hydroxy-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (90 mg, 0.153 mmol, 61%) as a white solid. LCMS: ESI m/z 588 [M+H]⁺

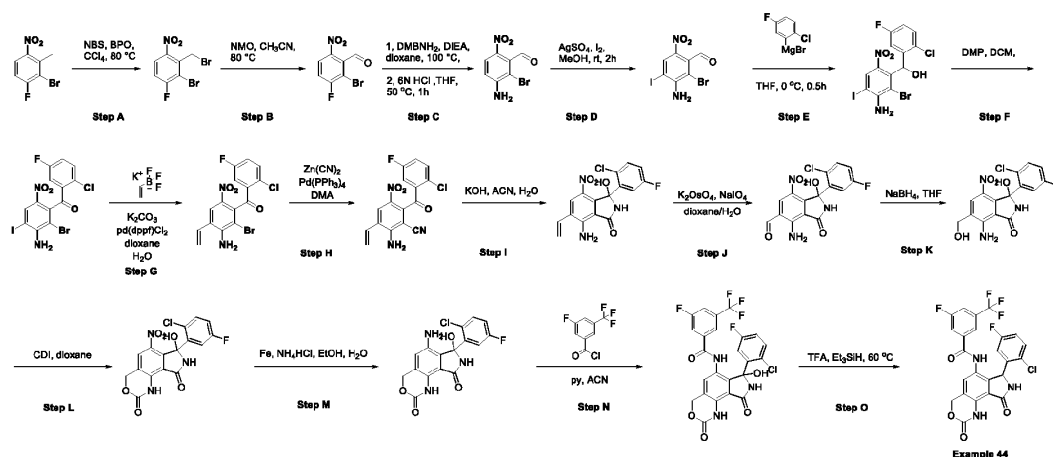
[00319] **Step G:** To a solution of N-(7-(2-chloro-5-fluorophenyl)-3,3-difluoro-7-hydroxy-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (90 mg, 0.153 mmol) in TFA (4 mL) were added Et₃SiH (88 mg, 0.763 mmol). The reaction mixture was stirred at 60 °C for 30 min. The reaction mixture was diluted with aqueous NaHCO₃, extracted with EA. The organic phase was washed with brine, dried by Na₂SO₄ and concentrated. The residue was purified by prep-HPLC afford N-(7-(2-chloro-5-fluorophenyl)-3,3-difluoro-2,9-dioxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (25.5 mg, 0.044 mmol, 29%) as a white solid. LCMS: ESI m/z 574 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.81 (s, 1H), 10.50 (s, 1H), 9.44 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.63 (s, 1H), 7.47 (s, 1H), 7.32 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.10 (td, *J* = 8.4, 2.8 Hz, 1H), 6.96 (s, 1H), 6.10 – 6.00 (brs, 1H).

[00320] **Step H:** N-[7-(2-chloro-5-fluorophenyl)-3,3-difluoro-2,9-dioxo-1,2,3,7,8,9-hexahydro[1,4]oxazino[3,2-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (25.5 mg) was purified by prep-SFC (Waters Thar 80 preparative SFC-Chiral Cel OD, 250×21.2mm I.D., 5μm, 20%, A :CO₂, phase B : IPA) to afford compound:

[00321] **P-1 Example 42** (9.3 mg, 0.016 mmol, 73%) as a white solid LCMS: ESI m/z 574 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.81 (s, 1H), 10.50 (s, 1H), 9.44 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.63 (s, 1H), 7.47 (s, 1H), 7.32 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.10 (td, *J* = 8.4, 2.8 Hz, 1H), 6.96 (s, 1H), 6.10 – 6.00 (brs, 1H).

[00322] **P-2 Example 43** (7.2 mg, 0.012 mmol, 56%) as a white solid. LCMS: ESI m/z 574 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.81 (s, 1H), 10.50 (s, 1H), 9.44 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.63 (s, 1H), 7.47 (s, 1H), 7.32 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.10 (td, *J* = 8.4, 2.8 Hz, 1H), 6.96 (s, 1H), 6.10 – 6.00 (brs, 1H).

Example 44 N-(7-(2-chloro-5-fluorophenyl)-2,9-dioxo-1,2,4,7,8,9-hexahydro-[1,3]oxazino[4,5-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00323] **Step A:** A mixture of 2-bromo-1-fluoro-3-methyl-4-nitrobenzene (1.0 g, 4.3 mmol), BPO (104 mg, 0.43 mmol) and NBS (800 mg, 4.5 mmol) in CCl_4 (15 mL) was stirred at 80 °C under N_2 atmosphere for 18h. The reaction was cooled to room temperature and filtered. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (eluted with EA/PE = 0-20%) to give a crude product 2-bromo-3-(bromomethyl)-1-fluoro-4-nitrobenzene (1.0 g, 3.2 mmol, 75%) as a colorless oil.

[00324] **Step B:** A solution of 2-bromo-3-(bromomethyl)-1-fluoro-4-nitrobenzene (1.0 g, 3.2 mmol) and NMO (560 mg, 4.8 mmol) in CH_3CN (15 mL) was stirred at 80 °C for 1 h. TLC and LCMS indicated the reaction was over. The reaction was cooled and poured into ice-water, extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography on silica gel (eluted with EA/PE = 0 ~ 40%) to give the desired product 2-bromo-3-fluoro-6-nitrobenzene-1-carbaldehyde (800 mg, 3.2 mmol, 100%) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.20 (s, 1H), 8.33 (dd, J = 9.2, 4.4 Hz, 1H), 7.89 – 7.77 (m, 1H).

[00325] **Step C:** A solution of 2-bromo-3-fluoro-6-nitrobenzene-1-carbaldehyde (800 mg, 3.2 mmol, 100%), DIEA (1.12 g, 8.9 mmol) and DMBNH₂ (1.0 g, 5.9 mmol) in 1,4-dioxane (10 mL) was stirred at 100 °C for 1 h. TLC and LCMS indicated the reaction was over. The reaction was cooled and poured into ice-water, extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was dissolved in THF (10 mL) and 6N HCl (10 mL). The solution was stirred at 60 °C for 1 h. The reaction was cooled to 0 °C, adjust pH to 7~8 with NaHCO_3 , extracted with EA. The organic layer was washed with

brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography on silica gel (eluted with EA/PE = 0 ~ 50%) to give the desired product 3-amino-2-bromo-6-nitrobenzene-1-carbaldehyde (500 mg, 2.0 mmol, 68%) as a yellow solid. LCMS: ESI m/z 246/248 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.23 (s, 1H), 8.07 (d, J = 9.2 Hz, 1H), 7.24 (s, 2H), 6.97 (d, J = 9.2 Hz, 1H).

[00326] **Step D:** To a mixture of 2-bromo-3-methyl-4-nitroaniline (800 mg, 3.2 mmol) and Ag_2SO_4 (1.4 g, 4.5 mmol) in MeOH (20 mL) was added I_2 (1.07g, 4.2 mmol). The resulting mixture was stirred at room temperature for 1 h. TLC indicated the reaction was over. The mixture was poured into H_2O . The mixture was filtered, and the filtrate was extracted with EA. The organic layer was concentrated and washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography on silica gel (eluted with EA/PE = 0 ~ 50%) to give the desired product 3-amino-2-bromo-4-iodo-6-nitrobenzene-1-carbaldehyde (700 mg, 1.9 mmol, 58%) as a yellow solid. LCMS: ESI m/z 371.9 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.13 (s, 1H), 8.47 (s, 1H), 6.87 (s, 2H).

[00327] **Step E:** To a solution of 3-amino-2-bromo-4-iodo-6-nitrobenzene-1-carbaldehyde (1.6 g, 4.31 mmol) in THF (30 mL) was added (2-chloro-5-fluorophenyl)magnesium chloride (0.5M, 30 mL) at 0 °C. The mixture was stirred at rt for 1h, then diluted with EA and aqueous NH_4Cl . The organic was separated and concentrated. The residue was purified by column chromatography on silica gel (eluted with EA/PE = 0-30%) to afford (3-amino-2-bromo-4-iodo-6-nitrophenyl)(2-chloro-4-fluorophenyl)methanol (1.7 g, 3.39 mmol, 79%) as a brown solid. LCMS: ESI m/z 503 $[\text{M}+\text{H}+2]^+$.

[00328] **Step F:** To a solution of (3-amino-2-bromo-4-iodo-6-nitrophenyl)(2-chloro-4-fluorophenyl)methanol (1.7 g, 3.39 mmol) in DCM (35 mL) was added DMP (2.88 g, 6.78 mmol). The reaction mixture was stirred at rt for 1 h. The mixture was treated with H_2O (20 mL) and extracted with DCM (2x20 mL). The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by column chromatography to give (3-amino-2-bromo-4-iodo-6-nitrophenyl)(2-chloro-4-fluorophenyl)methanone (1.5 g, 3.00 mmol, 89%) as a brown solid. LCMS: ESI m/z 501 $[\text{M}+\text{H}+2]^+$.

[00329] **Step G:** A sealed vial was charged with (3-amino-2-bromo-4-iodo-6-nitrophenyl)(2-chloro-4-fluorophenyl)methanone (500 mg, 1.00 mmol), potassium trifluoro(vinyl)- λ^5 -boranuide (161 mg, 1.21 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (73.3 mg, 100 μmol), K_2CO_3 (414 mg, 3.01 mmol), dioxane

(10 mL) and H₂O (2 mL). The mixture was stirred at 85 °C under N₂ for 2h. The mixture was diluted with water (~10 mL) and extracted with EtOAc (~20 mL x 2). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by column (eluted with (EA: PE=30%)) to give (3-amino-2-bromo-6-nitro-4-vinylphenyl)(2-chloro-4-fluorophenyl)methanone (270 mg, 0.676 mmol, 67%) as a yellow solid. LCMS: ESI m/z 401 [M+H]⁺.

[00330] **Step H:** A sealed vial was charged with (3-amino-2-bromo-6-nitro-4-vinylphenyl)(2-chloro-4-fluorophenyl)methanone (480 mg, 1.20 mmol), Zn(CN)₂ (705 mg, 6.01 mmol), Pd(PPh₃)₄ (139 mg, 0.120 mmol) and DMA (10 mL). The mixture was stirred at 170 °C (MW) under N₂ for 3h. The mixture was diluted with water (~10mL) and extracted with EtOAc (~20 mL x 2). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by column (eluted with (EA: PE=30%)) to give 6-amino-2-[(2-chloro-4-fluorophenyl)carbonyl]-3-nitro-5-vinylbenzene-1-carbonitrile (170 mg, 0.492 mmol, 41%) as a brown solid. LCMS: ESI m/z 346 [M+H]⁺.

[00331] **Step I:** To a solution of 6-amino-2-[(2-chloro-4-fluorophenyl)carbonyl]-3-nitro-5-vinylbenzene-1-carbonitrile (170 mg, 0.492 mmol) in ACN (4 mL) and H₂O (0.5 mL) was added KOH (138 mg, 2.46 mmol). The reaction mixture was stirred at 40 °C for 16 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic phases were washed with brine (20 mL x 2), dried over Na₂SO₄ and concentrated to give 7-amino-3-(2-chloro-4-fluorophenyl)-3-hydroxy-4-nitro-6-vinyl-2,3-dihydro-1H-isoindol-1-one (170 mg, 0.467 mmol, 95%) as a brown solid. LCMS: ESI m/z 364 [M+H]⁺.

[00332] **Step J:** To a solution of 7-amino-3-(2-chloro-4-fluorophenyl)-3-hydroxy-4-nitro-6-vinyl-2,3-dihydro-1H-isoindol-1-one (70 mg, 0.192 mmol) in dioxane (2 mL) and H₂O (0.2 mL) were added NaIO₄ (123 mg, 0.577 mmol) and potassium citrate (7.09 mg, 19 μmol). The mixture was stirred at rt for 3 h. The mixture was quenched with saturated NaHCO₃ solution and extracted with ethyl acetate. The organic layers were combined and concentrated to give 4-amino-1-(2-chloro-4-fluorophenyl)-1-hydroxy-7-nitro-3-oxo-2,3-dihydro-1H-isoindole-5-carbaldehyde (60 mg, 0.164 mmol, 85%) as a brown solid. LCMS: ESI m/z 366 [M+H]⁺.

[00333] **Step K:** To a solution of 4-amino-1-(2-chloro-4-fluorophenyl)-1-hydroxy-7-nitro-3-oxo-2,3-dihydro-1H-isoindole-5-carbaldehyde (50 mg, 0.137 mmol) in THF (2 mL) was added NaBH₄ (10.3 mg, 0.273 mmol). The mixture was stirred at rt for 1h. The mixture was

diluted with water (~10mL) and extracted with EtOAc (~20 mL x 2). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by column (eluted with (MeOH: DCM=10%) to give 7-amino-3-(2-chloro-4-fluorophenyl)-3-hydroxy-6-(hydroxymethyl)-4-nitro-2,3-dihydro-1H-isoindol-1-one (40 mg, 0.109 mmol, 80%) as a brown solid. LCMS: ESI m/z 368 [M+H]⁺.

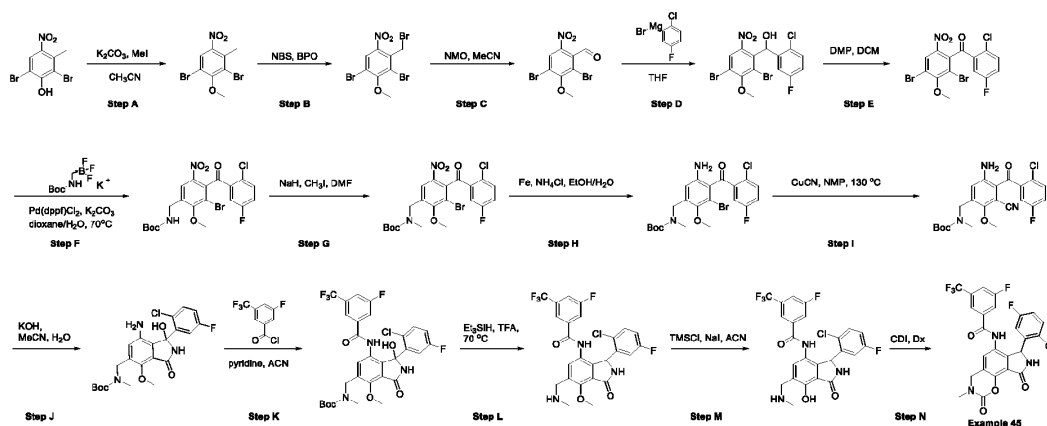
[00334] **Step L:** To a solution of 7-amino-3-(2-chloro-4-fluorophenyl)-3-hydroxy-6-(hydroxymethyl)-4-nitro-2,3-dihydro-1H-isoindol-1-one (70 mg, 0.190 mmol) in THF (1 mL) was added CDI (34.0 mg, 0.209 mmol). The mixture was stirred at 95 °C for 2 d. The cooled mixture was diluted with H₂O, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel column chromatography (MeOH: DCM = 1: 10) to give 7-amino-3-(2-chloro-4-fluorophenyl)-3-hydroxy-6-(hydroxymethyl)-4-nitro-2,3-dihydro-1H-isoindol-1-one (20 mg, 54 μmol, 29%) as a brown solid. LCMS: ESI m/z 394 [M+H]⁺.

[00335] **Step M:** To a solution of 7-amino-3-(2-chloro-4-fluorophenyl)-3-hydroxy-6-(hydroxymethyl)-4-nitro-2,3-dihydro-1H-isoindol-1-one (30 mg, 82 μmol) and Fe (21.3 mg, 0.381 mmol) in EtOH (1 mL) was added NH₄Cl (20.4 mg, 0.381 mmol) in H₂O (0.3 mL). The reaction mixture was heated to 85 °C for 2 h. Then the mixture was filtered, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (MeOH: DCM = 1:10) to give 4,7-diamino-3-(2-chloro-4-fluorophenyl)-3-hydroxy-6-(hydroxymethyl)-2,3-dihydro-1H-isoindol-1-one (20 mg, 59 μmol, 73%) as a brown solid. LCMS: ESI m/z 364 [M+H]⁺.

[00336] **Step N:** To a solution of 6-amino-7-(2-chloro-4-fluorophenyl)-7-hydroxy-1,2,4,7,8,9-hexahydro[1,3]oxazino[4,5-e]isoindole-2,9-dione (20 mg, 55 μmol) in ACN (3 mL) was added py (21.7 mg, 0.275 mmol) and 3-fluoro-5-(trifluoromethyl)benzoyl chloride (16.2 mg, 71 μmol). The reaction mixture was stirred at rt for 30min. Then the mixture was diluted with water (~20 mL) and extracted with ethyl acetate (~20mL x 2). The combined organic phases were washed with brine (20 mL), dried over Na₂SO₄ and concentrated to give N-[5-(5-chloro-2-fluorophenyl)-3-cyano-5-hydroxy-2-methyl-7-oxo-6,7-dihydro-5H-pyrrolo[4,3-f]indazol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (25 mg, 45 μmol, 82%) as a brown solid. LCMS: ESI m/z 554 [M+H]⁺.

[00337] **Step O:** To a solution of N-[7-(2-chloro-4-fluorophenyl)-7-hydroxy-2,9-dioxo-1,2,4,7,8,9-hexahydro[1,3]oxazino[4,5-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (10 mg, 18 μ mol) in TFA (1 mL) was added Et₃SiH (0.2 mL, 18 μ mol). The reaction mixture was stirred at 60 °C for 30min. The reaction mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give N-[7-(2-chloro-4-fluorophenyl)-2,9-dioxo-1,2,4,7,8,9-hexahydro[1,3]oxazino[4,5-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (3.5 mg, 7 μ mol, 36%) as a white solid. LCMS: ESI m/z 538 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.40 (s, 1H), 9.31 (s, 1H), 8.91 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.65 (s, 1H), 7.34 (d, *J* = 4.4 Hz, 1H), 7.33 – 7.25 (m, 1H), 7.10 (dd, *J* = 8.4, 5.2 Hz, 1H), 6.70 – 6.50 (s, 0.5H), 6.00 (brs, 1H), 5.52 (s, 2H).

Example 45 N-[7-(2-chloro-5-fluorophenyl)-3-methyl-2,9-dioxo-2,3,4,7,8,9-hexahydro[1,3]oxazino[6,5-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide



[00338] **Step A.** To a solution of 2,6-dibromo-3-methyl-4-nitrophenol (10 g, 32.1 mmol) in CH₃CN (100 mL) were added K₂CO₃ (8.89 g, 64.3 mmol) and CH₃I (3.9 mL, 48.2 mmol). The reaction mixture was stirred at rt overnight. The reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 0-15%] to afford 1,3-dibromo-2-methoxy-4-methyl-5-nitrobenzene (10 g, 30.7 mmol, 96%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.31 (s, 1H), 3.87 (s, 3H), 2.46 (s, 3H).

[00339] **Step B.** To a solution of 1,3-dibromo-2-methoxy-4-methyl-5-nitrobenzene (10 g, 30.7 mmol) in CCl₄ (120 mL) were added NBS (6.30 g, 36.9 mmol) and AIBN (0.25 g, 1.53

mmol). The reaction mixture was stirred at 80 °C overnight. The cooled reaction mixture was diluted with H₂O, extracted with DCM. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient : 0-20%] to afford 1,3-dibromo-4-(bromomethyl)-2-methoxy-5-nitrobenzene (10, 24.7 mmol, 80%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.43 (s, 1H), 4.80 (s, 2H), 3.90 (s, 3H).

[00340] **Step C.** To a solution of 1,3-dibromo-4-(bromomethyl)-2-methoxy-5-nitrobenzene (10g, 24.7 mmol) in CH₃CN (60 mL) was added NMO (5.80 g, 49.3 mmol). The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient : 0-30%] to afford compound 2,4-dibromo-3-methoxy-6-nitrobenzene-1-carbaldehyde (8.1 g, 24.0 mmol, 97%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.16 (s, 1H), 8.56 (s, 1H), 3.93 (s, 3H).

[00341] **Step D.** To a solution of 2,4-dibromo-3-methoxy-6-nitrobenzene-1-carbaldehyde (8.1 g, 24.0 mmol) in THF (100 mL) was added bromo(2-chloro-5-fluorophenyl)magnesium (126 mL, 126 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with NH₄Cl, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient : 0-40%] to afford compound (2-chloro-5-fluorophenyl)(2,4-dibromo-3-methoxy-6-nitrophenyl)methanol (7.1 g, 14.9 mmol, 59%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.30 (s, 1H), 7.54 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.25 (td, *J* = 8.4, 3.2 Hz, 1H), 7.06 (dd, *J* = 9.6, 3.2 Hz, 1H), 6.81 (d, *J* = 6.0 Hz, 1H), 6.24 (d, *J* = 5.6 Hz, 1H), 3.84 (s, 4H).

[00342] **Step E.** To a stirred solution of (2-chloro-5-fluorophenyl)(2,4-dibromo-3-methoxy-6-nitrophenyl)methanol (10 g, 21.3 mmol) in DCM (120 mL) was added Dess-MARTIN (9.1 g, 21.3 mmol) slowly at 0 °C. After stirred at rt for 3h, the mixture was poured into ice-water (20 mL) and extracted with DCM (10 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-50%, EtOAc in PE) to give (2-chloro-5-fluorophenyl)(2,4-dibromo-3-methoxy-6-

nitrophenyl)methanone (8.4 g, 17.9 mmol, 84%) as a yellow solid. LCMS: m/z 468 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.68 (s, 1H), 7.81 (dd, $J = 9.2, 3.2$ Hz, 1H), 7.74 (dd, $J = 8.8, 4.8$ Hz, 1H), 7.65 – 7.58 (m, 1H), 3.95 (s, 3H).

[00343] **Step F.** To a stirred solution of (2-chloro-5-fluorophenyl)(2,4-dibromo-3-methoxy-6-nitrophenyl)methanone (4.2 g, 8.9 mmol) in dioxane (16 mL)/ H₂O (4 mL) was added (2,2-dimethyl-4-oxo-5-aza-3-oxahex-6-yl)trifluoro- λ^5 -boranuide (2.6 g, 13.5 mmol), Pd(dppf)Cl₂ (660 mg, 0.89 mmol) and K₂CO₃ (3.7 g, 26.9 mmol) at rt. After stirred at 70 °C under N₂ overnight, the cooled mixture was poured into ice-water (20 mL) and extracted with DCM (10 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-50%, EtOAc in PE) to give 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl]amino]methanoate (930 mg, 1.8 mmol, 20%) as a yellow solid. LCMS: m/z 517 $[M+H]^+$.

[00344] **Step G.** To a stirred solution of 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl]amino]methanoate (900 mg, 1.7 mmol) in DMF (20 mL) was added NaH (125 mg, 5.2 mmol, 60% in mineral oil) slowly at -20 °C. After stirred at -20 °C for 1h, CH₃I (0.2 mL, 2.6 mmol) was added to the mixture. After stirred at rt for 2h, the mixture was poured into ice-water (20 mL) and extracted with EtOAc (10 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-30%, EtOAc in PE) to give 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl](methyl)amino]methanoate (430 mg, 0.81 mmol, 46%) as a yellow solid. LCMS: m/z 531 $[M+H]^+$.

[00345] **Step H.** To a stirred solution of 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl](methyl)amino]methanoate (400 mg, 0.752 mmol) in EtOH (12 mL)/ H₂O (3 mL) was added NH₄Cl (161 mg, 3.1 mmol) and Fe (420 mg, 7.5 mmol) at rt. After stirred at 80 °C for 2h, the mixture was filtered and concentrated. The residue was purified by chromatography (silica gel, 0-50 %, EtOAc in PE) to give 2-methylpropan-2-yl [(5-amino-3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-

methoxyphenyl)methyl(methylamino)methanoate (300 mg, 0.59 mmol, 79%) as a yellow solid. LCMS: m/z 502 $[M+H]^+$.

[00346] **Step I.** To a stirred solution of 2-methylpropan-2-yl [(5-amino-3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxyphenyl)methyl(methylamino)methanoate (280 mg, 0.56 mmol) in NMP (3 mL) was added CuCN (150 mg, 1.7 mmol) at rt. After stirred at 130 °C under N₂ for 2h, the cooled mixture was poured into brine (50 mL) and extracted with EtOAc (30 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated until there was no more drops. The residue was purified by prep-HPLC (C18, 40 ~ 90 % MeCN in H₂O with 0.1 % FA) to give 2-methylpropan-2-yl [(5-amino-4-[(2-chloro-5-fluorophenyl)carbonyl]-3-cyano-2-methoxyphenyl)methyl(methylamino)methanoate (230 mg, 0.51 mmol, 92%) as a yellow solid. LCMS: m/z 448 $[M+H]^+$.

[00347] **Step J.** To a stirred solution of 2-methylpropan-2-yl [(5-amino-4-[(2-chloro-5-fluorophenyl)carbonyl]-3-cyano-2-methoxyphenyl)methyl(methylamino)methanoate (230 mg, 0.51 mmol) in ACN (2 mL)/ H₂O (1 mL) was added KOH (288 mg, 5.1 mmol) slowly at rt. After stirred at rt for 1h, the mixture was poured into water (10 mL) and extracted with EtOAc (10 mL*2). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-10%, MeOH in DCM to give 2-methylpropan-2-yl ([7-amino-1-(2-chloro-5-fluorophenyl)-1-hydroxy-4-methoxy-3-oxo-2,3-dihydro-1H-isoindol-5-yl)methyl(methylamino)methanoate (170 mg, 0.36 mmol, 71%) as a white solid. LCMS: m/z 466 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81 (s, 1H), 7.96 (dd, J = 10.4, 3.2 Hz, 1H), 7.35 (d, J = 5.2 Hz, 1H), 7.29 – 7.18 (m, 1H), 6.99 (s, 1H), 6.53 (s, 1H), 4.47 (s, 2H), 4.34 (d, J = 6.0 Hz, 2H), 3.80 (s, 3H), 2.75 (s, 3H), 1.41 (d, J = 19.4 Hz, 10H).

[00348] **Step K.** To a stirred solution of 2-methylpropan-2-yl ([7-amino-1-(2-chloro-5-fluorophenyl)-1-hydroxy-4-methoxy-3-oxo-2,3-dihydro-1H-isoindol-5-yl)methyl(methylamino)methanoate (150 mg, 0.32 mmol) in ACN (2 mL) was added pyridine (76 mg, 0.97 mmol) and 3-fluoro-5-(trifluoromethyl)benzoyl chloride (145 mg, 0.64 mmol) slowly at rt. After stirred at rt for 1h, the mixture was poured into water (10 mL) and extracted with EtOAc (10 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-10%, MeOH in DCM) to give 2-methylpropan-2-yl ([1-(2-chloro-5-fluorophenyl)-7-([5-fluoro-3-(trifluoromethyl)phenyl]carbonyl)amino]-1-hydroxy-4-methoxy-3-oxo-2,3-

dihydro-1H-isoindol-5-yl)methyl}(methylamino)methanoate (180 mg, 0.27 mmol, 85%) as a brown solid. LCMS: m/z 656 $[M+H]^+$.

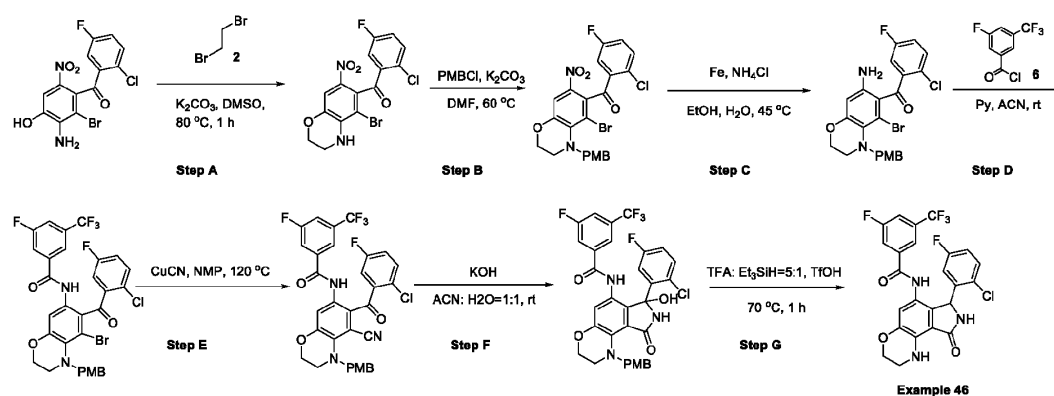
[00349] **Step L.** To a stirred solution of 2-methylpropan-2-yl ({[1-(2-chloro-5-fluorophenyl)-7-({[5-fluoro-3-(trifluoromethyl)phenyl]carbonyl}amino)-1-hydroxy-4-methoxy-3-oxo-2,3-dihydro-1H-isoindol-5-yl)methyl}(methylamino)methanoate (170 mg, 0.26 mmol) in TFA (5 mL) was added Et_3SiH (1 mL) at rt. After stirred at 70 °C for 2h, the cooled mixture was concentrated. The residue was purified by chromatography (silica gel, 0-10%, MeOH in DCM) to give N-[3-(2-chloro-5-fluorophenyl)-7-methoxy-6-[(methylamino)methyl]-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (120 mg, 0.22 mmol, 86%) as a white solid. LCMS: m/z 540 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 10.45 (s, 1H), 9.17 (s, 1H), 8.82 (s, 2H), 7.97 (d, $J = 8.4$ Hz, 1H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.68-7.60 (m, 2H), 7.32 (dd, $J = 8.8, 5.2$ Hz, 1H), 7.11 (td, $J = 8.4, 2.8$ Hz, 1H), 5.96 (brs, 1H), 4.25 (d, $J = 7.7$ Hz, 2H), 4.19 (s, 3H), 2.62 (s, 3H).

[00350] **Step M.** To a stirred solution of N-[3-(2-chloro-5-fluorophenyl)-7-methoxy-6-[(methylamino)methyl]-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (110 mg, 0.21 mmol) in ACN (6 mL) was added $TMSCl$ (110 mg, 1.1 mmol) and NaI (152 mg, 1.1 mmol) at rt. After stirred at 90 °C for 4h, the cooled mixture was poured into water (10 mL) and extracted with $EtOAc$ (10 mL*2). The combined organic phase was washed with brine, dried with Na_2SO_4 , filtered and concentrated. The residue was purified by chromatography (silica gel, 0-12%, MeOH in DCM) to give N-[3-(2-chloro-5-fluorophenyl)-7-hydroxy-6-[(methylamino)methyl]-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (90 mg, 0.17 mmol, 87%) as a white solid. LCMS: m/z 526 $[M+H]^+$.

[00351] **Step N.** To a stirred solution of N-[3-(2-chloro-5-fluorophenyl)-7-hydroxy-6-[(methylamino)methyl]-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (90 mg, 0.17 mmol) in dioxane (5 mL) was added CDI (42 mg, 0.26 mmol) at rt. After stirred at 50 °C for 1h, the mixture was poured into water (10 mL) and extracted with $EtOAc$ (10 mL*2). The combined organic phase was washed with brine, dried with Na_2SO_4 , filtered and concentrated. The residue was purified by prep-HPLC (C18, 40 ~ 90 % MeCN in H_2O with 0.1 % TFA) to give N-[7-(2-chloro-5-fluorophenyl)-3-methyl-2,9-dioxo-2,3,4,7,8,9-hexahydro[1,3]oxazino[6,5-e]isoindol-6-yl]-5-fluoro-3-

(trifluoromethyl)benzamide (24 mg, 0.04 mmol, 25%) as a white solid. LCMS: m/z 552 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 1H), 9.05 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.65 (s, 1H), 7.37 – 7.27 (m, 2H), 7.09 (td, J = 8.4, 2.8 Hz, 1H), 5.92 (brs, 1H), 4.68 – 4.55 (m, 2H), 3.03 (s, 3H).

Example 46 N-(7-(2-chloro-5-fluorophenyl)-9-oxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00352] **Step A:** To a solution of (3-amino-2-bromo-4-hydroxy-6-nitrophenyl)(2-chloro-5-fluorophenyl)methanone (450 mg, 1.15 mmol) in DMSO (5 mL) was added K_2CO_3 (319 mg, 2.31 mmol) and 1,2-dibromoethane (0.150 mL, 1.73 mmol). The reaction mixture was stirred at 80 °C under N_2 for 1 hr. The reaction was completed and monitored by TLC. The cooled reaction mixture was dissolved in EA (20 mL), washed with H_2O (20 mL) and brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography (eluting with 0~100% EA in PE) to afford (5-bromo-7-nitro-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)(2-chloro-5-fluorophenyl)methanone (200 mg, 0.481 mmol, 42%) as a yellow solid. LCMS: ESI m/z 415.6/417.6 $[M+H]^+$.

[00353] **Step B:** To a solution of (5-bromo-7-nitro-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)(2-chloro-5-fluorophenyl)methanone (200 mg, 0.481 mmol) in DMF (5 mL) was added K_2CO_3 (199 mg, 1.44 mmol) and 4-Methoxybenzylchloride (150 mg, 0.962 mmol). The reaction mixture was stirred at 60 °C under N_2 for 3 hrs. The reaction was completed and monitored by TLC. The cooled reaction mixture was dissolved in EA (20 mL), washed with H_2O (20 mL) and brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography (eluting with 0~100% EA in PE) to afford (5-bromo-4-(4-methoxybenzyl)-7-

nitro-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)(2-chloro-5-fluorophenyl)methanone (200 mg, 0.373 mmol, 78%) as a yellow oil.

[00354] **Step C:** To a solution of (5-bromo-4-(4-methoxybenzyl)-7-nitro-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)(2-chloro-5-fluorophenyl)methanone (100 mg, 0.187 mmol) in EtOH (3 mL) and H₂O (1 mL) was added NH₄Cl (29.9 mg, 0.560 mmol) and Fe (104 mg, 1.87 mmol). The reaction mixture was stirred at 45 °C under N₂ for 1 hr. The reaction was completed and monitored by TLC. The cooled reaction mixture was filtered and concentrated. Then dissolved in EA (10 mL), washed with H₂O (10 mL) and brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography (eluting with 0~50% EA in PE) to afford (7-amino-5-bromo-4-(4-methoxybenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)(2-chloro-5-fluorophenyl)methanone (55.0 mg, 0.109 mmol, 58%) as a yellow solid. LCMS: ESI m/z 505.77/507.55 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.56 (dd, J = 8.8, 4.8 Hz, 1H), 7.44 – 7.41 (m, 2H), 7.38 (dd, J = 8.8, 3.2 Hz, 1H), 7.23 – 7.19 (m, 1H), 6.88 (d, J = 8.8 Hz, 2H), 6.37 (s, 1H), 5.97 (s, 2H), 4.23 – 4.16 (m, 2H), 3.92 (s, 2H), 3.73 (s, 3H), 2.83 – 2.77 (m, 2H).

[00355] **Step D:** To a solution of (7-amino-5-bromo-4-(4-methoxybenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)(2-chloro-5-fluorophenyl)methanone (50.0 mg, 0.0990 mmol) in ACN (3 mL) was added 5-fluoro-3-(trifluoromethyl)benzoyl chloride (22.4 mg, 0.0990 mmol) and Py (0.024 mL, 0.297 mmol). The reaction mixture was stirred at room temperature for 0.5 hr. The reaction was completed and monitored by LCMS. The cooled reaction mixture was dissolved in EA (10 mL), washed with H₂O (10 mL) and brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography (eluting with 0~20% EA in PE) to afford N-(5-bromo-6-(2-chloro-5-fluorobenzoyl)-4-(4-methoxybenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-fluoro-5-(trifluoromethyl)benzamide (50.0 mg, 0.0720 mmol, 73%) as a yellow oil. LCMS: ESI m/z 695.87/697.87 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.42 (s, 1H), 8.04 – 7.98 (m, 3H), 7.93 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 11.6 Hz, 2H), 7.51 (t, J = 2.4 Hz, 1H), 7.49 (t, J = 2.4 Hz, 1H), 7.38 – 7.30 (m, 2H), 6.98 (s, 1H), 6.94 (d, J = 8.8 Hz, 2H), 4.29 – 4.23 (m, 2H), 4.14 (s, 2H), 3.76 (s, 3H), 2.98 – 2.91 (m, 2H).

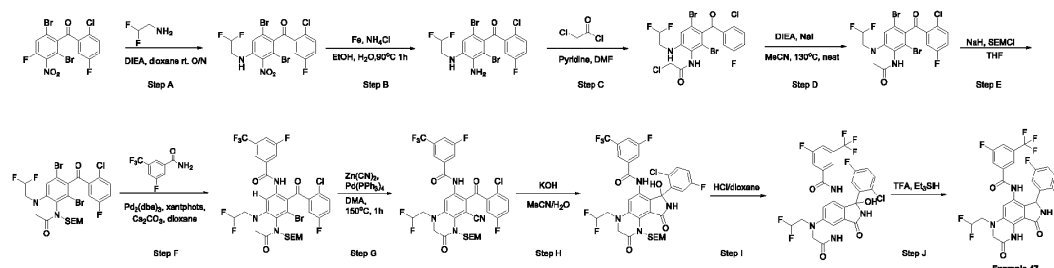
[00356] **Step E:** To a solution of N-(5-bromo-6-(2-chloro-5-fluorobenzoyl)-4-(4-methoxybenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-fluoro-5-(trifluoromethyl)benzamide (110 mg, 0.158 mmol) in NMP (5 mL) was added CuCN (21.2 mg, 0.237 mmol). The reaction mixture was stirred at 120 °C under N₂ for 3 hrs. The reaction was

completed and monitored by LCMS. The cooled reaction mixture was dissolved in EA (20 mL), washed with H₂O (15 mL) and brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography (eluting with 0-50% EA in PE) to afford N-(6-(2-chloro-5-fluorobenzoyl)-5-cyano-4-(4-methoxybenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-fluoro-5-(trifluoromethyl)benzamide (80.0 mg, 0.125 mmol, 79%) as a yellow oil. LCMS: ESI m/z 642.98 [M + H]⁺.

[00357] **Step F:** To a solution of N-(6-(2-chloro-5-fluorobenzoyl)-5-cyano-4-(4-methoxybenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-fluoro-5-(trifluoromethyl)benzamide (80.0 mg, 0.125 mmol) in ACN (3 mL) and H₂O (1 mL) was added KOH (34.9 mg, 0.623 mmol). The reaction mixture was stirred at room temperature for 2 hrs. The reaction mixture was completed and monitored by TLC. The reaction mixture was dissolved in EA (20 mL), washed with H₂O (10 mL) and brine, dried over sodium sulfate and concentrated to afford N-(7-(2-chloro-5-fluorophenyl)-7-hydroxy-1-(4-methoxybenzyl)-9-oxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (80.0 mg, 0.121 mmol, 97%) as a yellow solid. LCMS: ESI m/z 660.99 [M + H]⁺.

[00358] **Step G:** To a solution of N-(7-(2-chloro-5-fluorophenyl)-7-hydroxy-1-(4-methoxybenzyl)-9-oxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (80.0 mg, 0.121 mmol) in TFA (2 mL) was added Et₃SiH (400 μL, 2.50 mmol) and TfOH (80 μL, 0.904 mmol). The reaction mixture was stirred at 70 °C for 1 hr. The reaction mixture was completed and monitored by LCMS. The reaction mixture was concentrated and purified by prep-HPLC (C18, 30 ~ 95 % ACN in H₂O with 0.1 % TFA) to afford N-(7-(2-chloro-5-fluorophenyl)-9-oxo-1,2,3,7,8,9-hexahydro-[1,4]oxazino[3,2-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (42.3 mg, 0.0810 mmol, 67%) as a white solid. LCMS: ESI m/z 524.07 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.98 (s, 1H), 8.73 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 9.2 Hz, 1H), 7.63 (s, 1H), 7.27 (dd, J = 8.8, 5.2 Hz, 1H), 7.06 (td, J = 8.4, 2.8 Hz, 1H), 6.73 (s, 1H), 6.64 (brs, 1H), 5.82 (brs, 1H), 4.23 (dd, J = 11.2, 4.6 Hz, 2H), 3.40 – 3.36 (m, 2H).

Example 47 N-[7-(2-chloro-5-fluorophenyl)-4-(2,2-difluoroethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-f]quinoxalin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide



[00359] **Step A:** To a solution of (2-chloro-5-fluorophenyl) (2,6-dibromo-4-[(2,2-difluoroethyl)amino]-3-nitrophenyl) methanone (10 g, 22.0 mmol) in dioxane (100 mL) was added DIEA (3.8 mL, 22.0 mmol) and 2,2-difluoroethan-1-amine (1.5 mL, 22.0 mmol). The reaction was stirred at rt O/N. The reaction mixture was diluted with water, extracted with EtOAc (100 mL*3). The organic layer was separated, washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 5-8%) to afford (2-chloro-5-fluorophenyl) {2,6-dibromo-4-[(2,2-difluoroethyl)amino]-3-nitrophenyl} methanone (1.9 g, 3.7 mmol, 17 %) as a green oil. LCMS: m/z 455 [M+H]⁺.

[00360] **Step B:** To a solution of (2-chloro-5-fluorophenyl) {2,6-dibromo-4-[(2,2-difluoroethyl)amino]-3-nitrophenyl} methanone (1.9 g, 3.68 mmol) in EtOH (15 mL) was added Fe (2.05 g, 36.8 mmol) and sat. NH₄Cl (5 mL). The reaction was stirred at 80 °C for 3h. The cooled reaction mixture was filtrated and concentrated. The residue was diluted with water, extracted with EtOAc (100 mL*3). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 20%) to afford {3-amino-2,6-dibromo-4-[(2,2-difluoroethyl)amino]phenyl} (2-chloro-5-fluorophenyl) methanone (1.78 g, 3.66 mmol, 99%) as an orange solid. LCMS: m/z 487 [M+H]⁺

[00361] **Step C:** To a solution of {3-amino-2,6-dibromo-4-[(2,2-difluoroethyl)amino]phenyl} (2-chloro-5-fluorophenyl) methanone (1.26 g, 2.59 mmol) in DMF (10 mL) was added pyridine (1.05 mL, 12.9 mmol) and chloroacetyl chloride (320 mg, 2.85 mmol). The mixture was stirred at 20 °C for 1 hour. The residue was poured into water, extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The

residue was purified by a silica gel column chromatography eluted with EtOAc in PE (gradient: 0~30%) to give 2-chloro-N-{2,4-dibromo-3-[(2-chloro-5-fluorophenyl)carbonyl]-6-[(2,2-difluoroethyl)amino]phenyl}acetamide (900 mg, 1.60 mmol, 62%) as a yellow solid. LCMS: ESI m/z 563.1 $[M + H]^+$.

[00362] **Step D:** To a solution of 2-chloro-N-{2,4-dibromo-3-[(2-chloro-5-fluorophenyl)carbonyl]-6-[(2,2-difluoroethyl)amino]phenyl}acetamide (900 mg, 1.60 mmol) in CH_3CN (50 mL) was added DIEA (619 mg, 4.80 mmol) and NaI (479 mg, 3.20 mmol). The mixture was stirred at 130 °C for 30 min (neat). The cooled residue was purified by silica gel chromatography (20 g column) using 0 - 30% PE/EA to afford 6,8-dibromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-4-(2,2-difluoroethyl)-1,2,3,4-tetrahydroquinoxalin-2-one (360 mg, 0.684 mmol, 43%) as a brown solid. LCMS: ESI m/z 527.2 $[M + H]^+$.

[00363] **Step E:** To a solution of 6,8-dibromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-4-(2,2-difluoroethyl)-1,2,3,4-tetrahydroquinoxalin-2-one (240 mg, 0.456 mmol) in THF (24 mL) was added NaH (54.7 mg, 1.37 mmol, 60% in mineral oil). The mixture was stirred at 20 °C for 10 min. SEMCl (152 mg, 0.912 mmol) was added and the mixture was stirred at 20 °C for 30 min. The mixture was diluted with ice water (30 mL) and extracted with EA (30 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (3 g column) using 0 - 30% EtOAc/hexane to afford 6,8-dibromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-4-(2,2-difluoroethyl)-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-1,2,3,4-tetrahydroquinoxalin-2-one (180 mg, 0.274 mmol, 60%) as a brown oil. 1H NMR (400 MHz, $DMSO-d_6$) δ 7.85 (dd, $J = 8.9, 5.0$ Hz, 1H), 7.74 – 7.68 (m, 1H), 7.65 (s, 1H), 7.49 (dd, $J = 8.8, 2.8$ Hz, 1H), 6.25-6.42 (m, 1H), 5.64 (s, 2H), 4.12 – 4.00 (m, 4H), 3.37 – 3.32 (m, 2H), 0.80 – 0.73 (m, 2H), 0.00 (s, 9H).

[00364] **Step F:** To a solution of 6,8-dibromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-4-(2,2-difluoroethyl)-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-1,2,3,4-tetrahydroquinoxalin-2-one (180 mg, 0.274 mmol) and 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (85.1 mg, 0.411 mmol) in dioxane (9 mL) was added Cs_2CO_3 (268 mg, 0.822 mmol), Xant-PHOS (31.7 mg, 0.055 mmol) and $Pd_2(dba)_3$ (25.1 mg, 0.027 mmol). The mixture was stirred at 95 °C under N_2 for 12 hours. The cooled mixture was concentrated and the residue was purified by silica gel chromatography (5 g column) using 0 - 30% EtOAc/hexane to afford N-{8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-4-(2,2-difluoroethyl)-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-2-oxo-

1,2,3,4-tetrahydroquinoxalin-6-yl}-5-fluoro-3-(trifluoromethyl)benzamide (75 mg, 0.096 mmol, 35%) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.61 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 14.4 Hz, 2H), 7.61 (dd, J = 8.8, 4.8 Hz, 1H), 7.49 – 7.39 (m, 2H), 7.27 (s, 1H), 6.51 – 6.20 (m, 1H), 5.62 (s, 2H), 4.08 (s, 2H), 4.02 – 3.91 (m, 2H), 3.34 (d, J = 8.4 Hz, 2H), 0.81 – 0.73 (m, 2H), 0.02 – 0.02 (m, 9H).

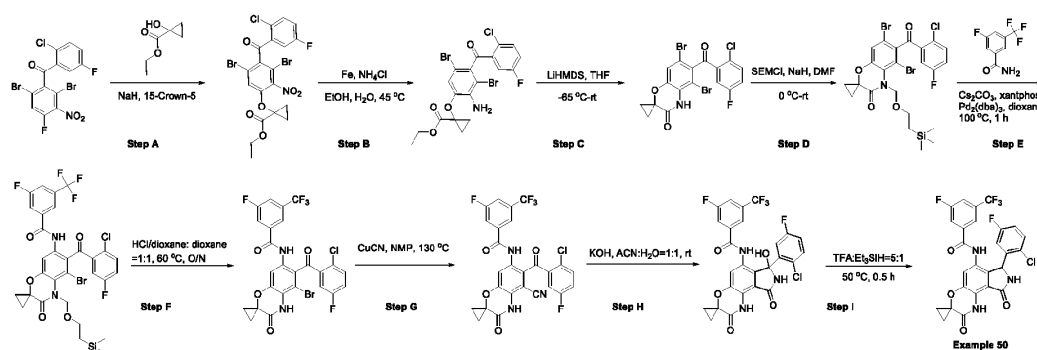
[00365] **Step G:** To a solution of N-{8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-4-(2,2-difluoroethyl)-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-2-oxo-1,2,3,4-tetrahydroquinoxalin-6-yl}-5-fluoro-3-(trifluoromethyl)benzamide (100 mg, 0.128 mmol) in DMA (4 mL) was added Zn(CN)₂ (22.5 mg, 0.192 mmol) and Pd(PPh₃)₄ (14.8 mg, 0.013 mmol). The mixture was stirred at 150 °C under N₂ for 1 hour in microwave. The mixture was purified by prep-TLC (PE/EA=7: 3) to give N-{7-[(2-chloro-5-fluorophenyl)carbonyl]-8-cyano-4-(2,2-difluoroethyl)-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-2-oxo-1,2,3,4-tetrahydroquinoxalin-6-yl}-5-fluoro-3-(trifluoromethyl)benzamide (35 mg, 0.048 mmol, 38 %) as a brown solid. LCMS: ESI m/z 727 [M - H]⁻.

[00366] **Step H:** To a solution of N-{7-[(2-chloro-5-fluorophenyl)carbonyl]-8-cyano-4-(2,2-difluoroethyl)-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-2-oxo-1,2,3,4-tetrahydroquinoxalin-6-yl}-5-fluoro-3-(trifluoromethyl)benzamide (35 mg, 0.048 mmol) in CH₃CN (3 mL) and H₂O (1 mL) was added KOH (8.08 mg, 0.144 mmol). The mixture was stirred at 20 °C for 30 min. The reaction mixture was diluted with water, extracted with EA (10 mL x 3). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated to give N-[7-(2-chloro-5-fluorophenyl)-4-(2,2-difluoroethyl)-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-7-hydroxy-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-f]quinoxalin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (35 mg, 0.042 mmol, 88%) as a brown solid. LCMS: ESI m/z 745 [M - H]⁻.

[00367] **Step I:** A solution of N-[7-(2-chloro-5-fluorophenyl)-4-(2,2-difluoroethyl)-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-7-hydroxy-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-f]quinoxalin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (30 mg, 0.040 mmol) in HCl/dioxane (3 mL) and the mixture was stirred at 20 °C for 30 min. The mixture was concentrated under vacuum to give N-[7-(2-chloro-5-fluorophenyl)-4-(2,2-difluoroethyl)-7-hydroxy-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-f]quinoxalin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (30 mg, 0.039 mmol, 97%) as a brown solid. LCMS: ESI m/z 615 [M - H]⁻.

[00368] **Step J:** To a solution of N-[7-(2-chloro-5-fluorophenyl)-4-(2,2-difluoroethyl)-7-hydroxy-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-f]quinoxalin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (30 mg, 0.049 mmol) in TFA (2 mL) was added Et₃SiH (0.5 mL, 0.008 mmol) and the mixture was stirred at 70 °C for 30 min. The cooled mixture was concentrated. The residue was purified by prep-HPLC to give N-[7-(2-chloro-5-fluorophenyl)-4-(2,2-difluoroethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-f]quinoxalin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (2 mg, 0.003 mmol, 7%) as a white solid. LCMS: ESI m/z 601 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.30 (s, 1H), 9.62 (s, 1H), 9.22 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.66 (s, 1H), 7.30 (dd, J = 8.8, 5.2 Hz, 1H), 7.09 (td, J = 8.4, 3.2 Hz, 1H), 6.91 (s, 1H), 6.76 (brs, 1H), 6.52-6.20 (m, 1H), 5.89 (brs, 1H), 4.16 (s, 2H), 3.87 – 3.71 (m, 2H).

Example 50 N-(7'-(2-chloro-5-fluorophenyl)-2',9'-dioxo-1',7',8',9'-tetrahydro-2'H-spiro[cyclopropane-1,3'-[1,4]oxazino[3,2-e]isoindol]-6'-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00369] **Step A:** To a solution of ethyl 1-hydroxycyclopropane-1-carboxylate (2.06 g, 15.8 mmol) in THF (20 mL) was added NaH (0.470 g, 19.7 mmol, 60% in mineral oil) at 0 °C. The reaction mixture was stirred at 0 °C under N₂ for 30 min. 15-crown-5 (0.580 g, 2.63 mmol) and (2-chloro-5-fluorophenyl)(2,6-dibromo-4-fluoro-3-nitrophenyl)methanone (6.00 g, 13.1 mmol) in THF (20 mL) were added. The reaction mixture was stirred at room temperature under N₂ for 1 hr. The reaction was completed and monitored by TLC. The cooled reaction mixture was quenched with water, extracted with EA (80 mL). The organic phase was washed with H₂O (50 mL) and brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (eluting with 0~30% EA in PE) to afford ethyl 1-(3,5-dibromo-4-[(2-chloro-5-

fluorophenyl)carbonyl]-2-nitrophenyl}oxy)cyclopropane-1-carboxylate (5.50 g, 9.72 mmol, 73%) as a yellow solid. LCMS: ESI m/z 564.57/566.57/568.57 $[M + H]^+$.

[00370] **Step B:** To a solution of ethyl 1-({3,5-dibromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-nitrophenyl}oxy)cyclopropane-1-carboxylate (3.00 g, 5.30 mmol) in EtOH (30 mL) and H₂O (30 mL) was added NH₄Cl (0.850 g, 15.9 mmol) and Fe (2.96 g, 53.0 mmol). The reaction mixture was stirred at 45 °C under N₂ for 1 hr. The reaction was completed and monitored by TLC. The cooled reaction mixture was filtered, concentrated, diluted with water, extracted with EA (80 mL). The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (eluting with 0~50% EA in PE) to afford ethyl 1-({2-amino-3,5-dibromo-4-[(2-chloro-5-fluorophenyl)carbonyl]phenyl}oxy)cyclopropane-1-carboxylate (1.90 g, 3.54 mmol, 66%) as a yellow solid. LCMS: ESI m/z 534.59/536.59/538.59 $[M + H]^+$.

[00371] **Step C:** To a solution of ethyl 1-({2-amino-3,5-dibromo-4-[(2-chloro-5-fluorophenyl)carbonyl]phenyl}oxy)cyclopropane-1-carboxylate (1.90 g, 3.54 mmol) in THF (20 mL) was added LiHMDS (7.09 mL, 7.09 mmol) at -78 °C. The reaction mixture was stirred at room temperature under N₂ for 1 hr. The reaction was completed and monitored by TLC. The reaction mixture was quenched with water, extracted with EA (80 mL). The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (eluting with 0~10% EA in PE) to afford 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-3,4-dihydrospiro[benzo[1,4]oxazine-2,1'-cyclopropane]-3-one (1.70 g, 3.47 mmol, 97%) as a white solid. LCMS: ESI m/z 488.52/490.52/492.52 $[M + H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.64 (s, 1H), 7.72 (dd, *J* = 8.8, 4.8 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.40 (s, 1H), 1.36 (s, 2H), 1.28 (s, 2H).

[00372] **Step D:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-3,4-dihydrospiro[benzo[1,4]oxazine-2,1'-cyclopropane]-3-one (850 mg, 1.73 mmol) in DMF (15 mL) was added NaH (208 mg, 5.20 mmol, 60% in mineral oil) at 0 °C. The reaction mixture was stirred at 0 °C under N₂ for 30 min. SEM-Cl (0.922 mL, 5.20 mmol) was added. The reaction mixture was stirred at room temperature under N₂ for 1 hr. The reaction was completed and monitored by TLC. The reaction mixture was quenched with water, extracted with EA (80 mL). The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (eluting with 0~30% EA in PE) to afford 5,7-dibromo-6-

[(2-chloro-5-fluorophenyl)carbonyl]-4-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-3,4-dihydrospiro[benzo[1,4]oxazine-2,1'-cyclopropane]-3-one (700 mg, 1.12 mmol, 64%) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.76 (dd, J = 8.8, 4.8 Hz, 1H), 7.64 (dd, J = 8.0, 3.2 Hz, 1H), 7.60 (d, J = 2.8 Hz, 1H), 7.48 (d, J = 6.0 Hz, 1H), 5.60 (s, 2H), 3.40 (t, J = 8.0 Hz, 2H), 0.90 – 0.84 (m, 2H), 0.84 – 0.76 (m, 2H), 0.74 (t, J = 8.0 Hz, 2H), 0.00 – -0.02 (m, 9H).

[00373] **Step E:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-4-{[2-(trimethylsilyl)ethyl]oxy}-3,4-dihydrospiro[benzo[1,4]oxazine-2,1'-cyclopropane]-3-one (150 mg, 0.248 mmol) in dioxane (20 mL) was added 5-fluoro-3-(trifluoromethyl)benzene-1-carboxamide (0.430 g, 2.09 mmol), Cs₂CO₃ (2.05 g, 6.29 mmol), Pd₂(dba)₃ (0.190 g, 0.210 mmol) and Xantphos (0.240 g, 0.420 mmol). The reaction mixture was stirred at 100 °C under N₂ for 1 hr. The reaction was completed and monitored by TLC. The cooled reaction mixture was diluted with water, extracted with EA (80 mL). The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (eluting with 20~100% EA in PE) to afford N-{5-bromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-4-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-3-oxo-3,4-dihydrospiro[benzo[1,4]oxazine-2,1'-cyclopropane]-7-yl}-3-fluoro-5-(trifluoromethyl)benzamide (820 mg, 1.09 mmol, 52%) as a yellow solid. LCMS: ESI m/z 744.00/746.00 [M + H]⁺.

[00374] **Step F:** To a solution of N-(5-bromo-6-(2-chloro-5-fluorobenzoyl)-3-oxo-4-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydrospiro[benzo[1,4]oxazine-2,1'-cyclopropan]-7-yl)-3-fluoro-5-(trifluoromethyl)benzamide (435 mg, 0.583 mmol) in dioxane (5 mL) was added HCl/dioxane (5 mL). The reaction mixture was stirred at 60 °C overnight. The reaction was completed and monitored by LCMS. The cooled reaction mixture was concentrated. The residue was purified by silica gel chromatography (eluting with 0-100% EA in PE) to afford N-(5-bromo-6-(2-chloro-5-fluorobenzoyl)-3-oxo-3,4-dihydrospiro[benzo[1,4]oxazine-2,1'-cyclopropan]-7-yl)-3-fluoro-5-(trifluoromethyl)benzamide (100 mg, 0.162 mmol, 27%) as a yellow solid. LCMS: ESI m/z 615.74/617.74 [M + H]⁺.

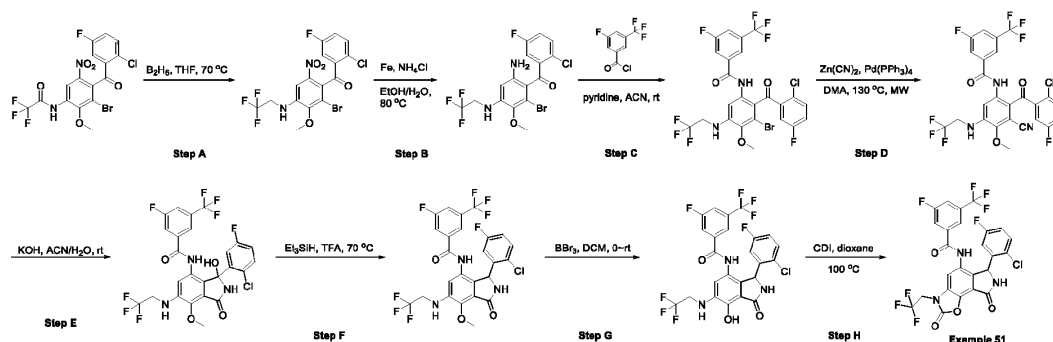
[00375] **Step G:** To a solution of N-(5-bromo-6-(2-chloro-5-fluorobenzoyl)-3-oxo-3,4-dihydrospiro[benzo[1,4]oxazine-2,1'-cyclopropan]-7-yl)-3-fluoro-5-(trifluoromethyl)benzamide (100 mg, 0.162 mmol) in NMP (3 mL) was added CuCN (21.8 mg, 0.244 mmol). The reaction mixture was stirred at 130 °C under N₂ for 3 hrs. The reaction was completed and monitored by LCMS. The cooled reaction mixture was diluted with water, extracted with EA. The organic

phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (eluting with 0-100% EA in PE) to afford N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-5-cyano-3-oxo-3,4-dihydrospiro[benzo[1,4]oxazine-2,1'-cyclopropane]-7-yl}-3-fluoro-5-(trifluoromethyl)benzamide (90.0 mg, 0.160 mmol, 98%) as a yellow oil. LCMS: ESI m/z 562.85 [M + H]⁺.

[00376] **Step H:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-5-cyano-3-oxo-3,4-dihydrospiro[benzo[1,4]oxazine-2,1'-cyclopropane]-7-yl}-3-fluoro-5-(trifluoromethyl)benzamide (90.0 mg, 0.160 mmol) in ACN (1 mL) and H₂O (1 mL) was added KOH (8.99 mg, 0.160 mmol). The reaction mixture was stirred at room temperature for 1 hr. The reaction mixture was completed and monitored by LCMS. The reaction mixture was diluted with water, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to afford N-[7-(2-chloro-5-fluorophenyl)-7-hydroxy-2,9-dioxo-2,7,8,9-tetrahydro-1H-spiro[[1,4]oxazino[3,2-e]isoindole-3,1'-cyclopropane]-6-yl]-3-fluoro-5-(trifluoromethyl)benzamide (90.0 mg, 0.155 mmol, 96%) as a yellow oil. LCMS: ESI m/z 580.86 [M + H]⁺.

[00377] **Step I:** To a solution of N-[7-(2-chloro-5-fluorophenyl)-7-hydroxy-2,9-dioxo-2,7,8,9-tetrahydro-1H-spiro[[1,4]oxazino[3,2-e]isoindole-3,1'-cyclopropane]-6-yl]-3-fluoro-5-(trifluoromethyl)benzamide (90 mg, 0.155 mmol) in TFA (1 mL) was added Et₃SiH (0.200 mL). The reaction mixture was stirred at 50 °C for 0.5 hr. The reaction mixture was completed and monitored by LCMS. The reaction mixture was concentrated and purified by prep-HPLC (C18, 30 ~ 95 % ACN in H₂O with 0.1 % TFA) to afford N-[7-(2-chloro-5-fluorophenyl)-2,9-dioxo-2,7,8,9-tetrahydro-1H-spiro[[1,4]oxazino[3,2-e]isoindole-3,1'-cyclopropane]-6-yl]-3-fluoro-5-(trifluoromethyl)benzamide (22.7 mg, 0.0402 mmol, 23%) as a yellow solid. LCMS: ESI m/z 564.87 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.36 (s, 1H), 9.60 (s, 1H), 9.32 (s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.64 (s, 1H), 7.32 (dd, J = 8.8, 5.2 Hz, 1H), 7.08 (td, J = 8.4, 3.2 Hz, 1H), 7.04 (s, 1H), 5.96 (brs, 1H), 1.41 – 1.31 (m, 4H).

Example 51 N-[6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-[1,3]oxazolo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide



[00378] **Step A:** To a stirred solution of N-{3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl}-2,2,2-trifluoroacetamide (1.2 g, 2.40 mmol) in THF (6 mL) at 0 °C under nitrogen atmosphere was added Borane-methyl sulfide complex (0.36 mL, 3.60 mmol). The reaction mixture was stirred at 70 °C for 2 hr. The cooled mixture was quenched with water (100 mL) and extracted with EA (100 mL*2). The combined organic phases were washed with brine (100 mL), dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (PE/EA = 1/100~100/1) to give {2-bromo-3-methoxy-6-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}(2-chloro-5-fluorophenyl)methanone (170 mg, 0.35 mmol, 15%) as yellow oil. LCMS: m/z 486.2 [M+H]⁺.

[00379] **Step B:** To a solution of {2-bromo-3-methoxy-6-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}(2-chloro-5-fluorophenyl)methanone (330 mg, 0.68 mmol) in EtOH/H₂O (5:1) (10 mL) were added Fe (190 mg, 3.40 mmol) and NH₄Cl (182 mg, 3.40 mmol). The reaction was stirred at 80 °C for 2 hr. The cooled reaction mixture was filtered, concentrated, diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated to afford crude compound {6-amino-2-bromo-3-methoxy-4-[(2,2,2-trifluoroethyl)amino]phenyl}(2-chloro-5-fluorophenyl)methanone (250 mg, 0.549 mmol, 81%) as a yellow oil. LCMS: m/z 457.2 [M+H]⁺.

[00380] **Step C:** To a solution of {6-amino-2-bromo-3-methoxy-4-[(2,2,2-trifluoroethyl)amino]phenyl}(2-chloro-5-fluorophenyl)methanone (200 mg, 0.439 mmol) in ACN (5 mL) were added pyridine (0.107 mL, 1.317 mmol) and 3-fluoro-5-(trifluoromethyl)benzoyl chloride (150 mg, 0.658 mmol). The reaction was stirred at rt for 1 hr. The reaction mixture was concentrated. The residue was diluted with water, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated to afford crude

compound N-{3-bromo-2-[(2-chloro-5-fluorophenyl)carbonyl]-4-methoxy-5-[(2,2,2-trifluoroethyl)amino]phenyl}-3-fluoro-5-(trifluoromethyl)benzamide (200 mg, 0.310 mmol, 71%) as a yellow oil. LCMS: m/z 646.9 [M+H]⁺.

[00381] **Step D:** To a solution of N-{3-bromo-2-[(2-chloro-5-fluorophenyl)carbonyl]-4-methoxy-5-[(2,2,2-trifluoroethyl)amino]phenyl}-3-fluoro-5-(trifluoromethyl)benzamide (180 mg, 0.279 mmol) in DMA (2 mL) was added Zn(CN)₂ (39.3 mg, 0.335 mmol) and Pd(PPh₃)₄ (32.2 mg, 0.028 mmol). The reaction mixture was degassed with N₂ and stirred at 130 °C under N₂ atmosphere for 1 hr using microwave. The cooled reaction mixture was diluted with water, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with EA/PE (1/100~2/1) to afford compound N-{2-[(2-chloro-5-fluorophenyl)carbonyl]-3-cyano-4-methoxy-5-[(2,2,2-trifluoroethyl)amino]phenyl}-3-fluoro-5-(trifluoromethyl)benzamide (130 mg, 0.22 mmol, 79%) as a yellow oil. LCMS: m/z 592.1 [M+H]⁺.

[00382] **Step E:** To a solution of N-{2-[(2-chloro-5-fluorophenyl)carbonyl]-3-cyano-4-methoxy-5-[(2,2,2-trifluoroethyl)amino]phenyl}-3-fluoro-5-(trifluoromethyl)benzamide (140 mg, 0.237 mmol) in ACN (5 mL) and H₂O (1.00 mL) was added KOH (66.4 mg, 1.18 mmol). The reaction was stirred at rt for 2 hr. The reaction mixture was diluted with water, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (1%~60%) to afford compound N-[3-(2-chloro-5-fluorophenyl)-3-hydroxy-7-methoxy-1-oxo-6-[(2,2,2-trifluoroethyl)amino]-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide (140 mg, 0.23 mmol, 97%) as a white solid. LCMS: m/z 608.0 [M-H]⁻.

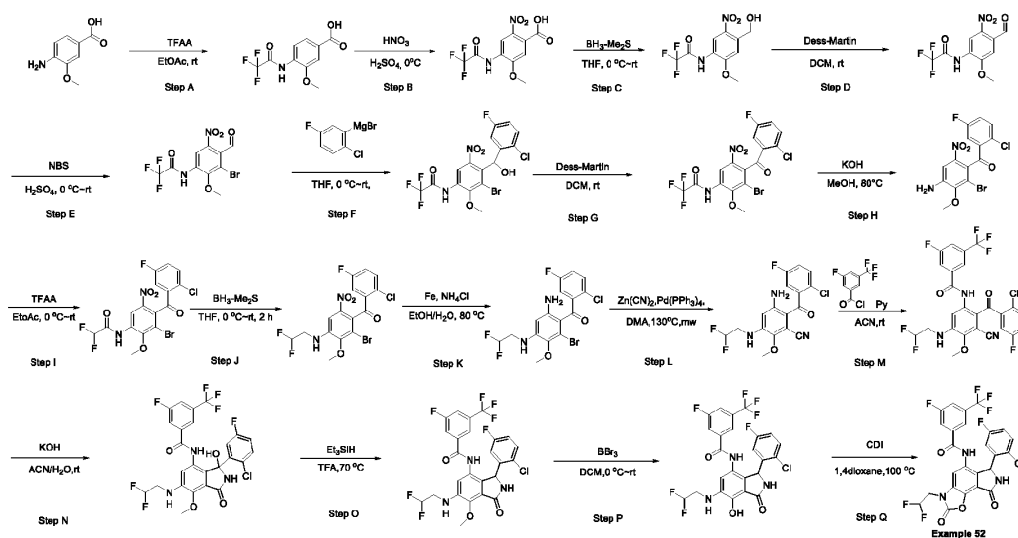
[00383] **Step F:** To a solution of N-[3-(2-chloro-5-fluorophenyl)-3-hydroxy-7-methoxy-1-oxo-6-[(2,2,2-trifluoroethyl)amino]-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide (140 mg, 0.230 mmol) in TFA (5 mL) was added Et₃SiH (267 mg, 2.30 mmol). The reaction mixture was stirred at 70 °C for 2 hr. The reaction was concentrated. The residue was diluted with water, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with ethyl acetate in DCM (0%~10%) to afford compound N-[3-(2-chloro-5-fluorophenyl)-7-methoxy-1-oxo-6-[(2,2,2-trifluoroethyl)amino]-2,3-dihydro-1H-

isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide (130 mg, 0.219 mmol, 95%) as a yellow oil. LCMS m/z: 594.3 [M+H]⁺.

[00384] **Step G:** To a solution of N-[3-(2-chloro-5-fluorophenyl)-7-methoxy-1-oxo-6-[(2,2,2-trifluoroethyl)amino]-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide (130 mg, 0.219 mmol) in DCM (5 mL) was added tribromoborane (0.042 mL, 0.438 mmol) dropwise at under N₂ at 0 °C. The reaction mixture was stirred at room temperature for 18 hr. The reaction mixture was quenched with MeOH (2 mL) and concentrated to obtain crude the N-[3-(2-chloro-5-fluorophenyl)-7-hydroxy-1-oxo-6-[(2,2,2-trifluoroethyl)amino]-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide (100 mg, 0.172 mmol, 78%) as a light red solid. LCMS: m/z 580.1 [M+H]⁺.

[00385] **Step H:** To a solution of N-[3-(2-chloro-5-fluorophenyl)-7-hydroxy-1-oxo-6-[(2,2,2-trifluoroethyl)amino]-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide (20 mg, 0.034 mmol) in dioxane (2 mL) was added CDI (8.39 mg, 0.052 mmol). The reaction was stirred at 100 °C for 5 hr. The reaction mixture was concentrated. The residue was purified by prep-HPLC (acetonitrile with 0.1% FA in water 30% to 70%) to give N-[6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-[1,3]oxazolo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (10 mg, 0.017 mmol, 48%) as a white solid. LCMS: m/z 606.1 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 10.50 (s, 1H), 9.28 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.68 (s, 1H), 7.57 (s, 1H), 7.35 – 7.24 (m, 1H), 7.16 – 7.01 (m, 1H), 6.68 (brs, 1H), 6.05 (brs, 1H), 5.03 – 4.74 (m, 2H).

Example 52 N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-7,8-dihydro-6H-[1,3]oxazolo[5,4-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide



[00386] **Step A:** To a solution of 4-amino-3-methoxybenzoic acid (25 g, 149 mmol) in EtOAc (800 mL) was added a solution of TFAA (24.9 mL, 179 mmol) in EtOAc (100 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 16 h. The mixture was concentrated to give 3-methoxy-4-(2,2,2-trifluoroacetamido)benzoic acid (40 g, 152 mmol, 100%) as a yellow solid. LCMS: m/z 262.1 [M-H]⁻.

[00387] **Step B:** To a solution of 3-methoxy-4-[(trifluoroacetyl)amino]benzoic acid (40 g, 152 mmol) in con.H₂SO₄ (98%, 1000 mL) was added dropwise a solution of con.HNO₃ (13.6 g) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Then the mixture was slowly poured into ice water (2000 mL) and filtered to give 5-methoxy-2-nitro-4-(2,2,2-trifluoroacetamido)benzoic acid (40 g, 129 mmol, 85%) as a brown solid. LCMS: m/z 307.0 [M-H]⁻.

[00388] **Step C:** To the solution of 5-methoxy-2-nitro-4-[(trifluoroacetyl)amino]benzoic acid (40 g, 129 mmol) in THF (400 mL) was added portion-wise BH₃-Me₂S (10M, 39.0 mL, 390 mmol, 3.0 eq) at 0 °C. The reaction mixture was stirred at room temperature for 20 h. The mixture was added water (100 mL) and extracted with EtOAc (300 mL x 2). The combined organic phase was washed with brine (100 mL), dried over Na₂SO₄ and concentrated to give 2,2,2-trifluoro-N-(4-(hydroxymethyl)-2-methoxy-5-nitrophenyl)acetamide (9.0 g, 30.6 mmol, 24%) as a yellow solid. LCMS: m/z 293.0 [M-H]⁻. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.01 (s, 1H), 8.30 (s, 1H), 7.55 (s, 1H), 5.70 (t, *J* = 5.6 Hz, 1H), 4.90 (d, *J* = 5.6 Hz, 2H), 3.98 (s, 3H).

[00389] **Step D:** To a solution of 2,2,2-trifluoro-N-[4-(hydroxymethyl)-2-methoxy-5-nitrophenyl]acetamide (9.0 g, 30.6 mmol) in DCM (20 mL) was added DMP (19.5 g, 45.9 mmol) at 25 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was added water (30 mL) and extracted with DCM (50 mL x 2). The combined organic phase was washed with brine (30 mL), dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (petroleum ether/EtOAc = 3:1) to give 2,2,2-trifluoro-N-(4-formyl-2-methoxy-5-nitrophenyl)acetamide (8.4 g, 28.8 mmol, 94%) as a yellow solid. LCMS: m/z 291 [M-H]⁻. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.22 (s, 1H), 10.30 (s, 1H), 8.45 (s, 1H), 7.49 (s, 1H), 4.04 (s, 3H).

[00390] **Step E:** To a solution of 2,2,2-trifluoro-N-(4-formyl-2-methoxy-5-nitrophenyl)acetamide (8.4 g, 28.8 mmol) in H₂SO₄ (98%, 100 mL) was added NBS (7.7 g, 43.1 mmol) at 0 °C. The reaction mixture was stirred at rt for 18 h. The mixture was poured into ice-water (200 mL) and filtered to give the residue, which was triturated with petroleum ether / EtOAc (3:1, 300 mL) to give N-(3-bromo-4-formyl-2-methoxy-5-nitrophenyl)-2,2,2-trifluoroacetamide (8.4 g, 22.6 mmol, 79%) as a yellow solid. LCMS: m/z 368.9/370.9 [M-H]⁻.

[00391] **Step F:** To a solution of N-(3-bromo-4-formyl-2-methoxy-5-nitrophenyl)-2,2,2-trifluoroacetamide (4.3 g, 11.6 mmol) in THF (125 mL) were added bromo(2-chloro-5-fluorophenyl)magnesium (0.5M, 130 mL, 13.6 g, 57.9 mmol). The reaction was stirred at rt under N₂ for 2 hr. LCMS showed the reaction was completed and. The reaction mixture was quenched with aqueous NH₄Cl, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 30-40%) to afford N-{3-bromo-4-[(2-chloro-5-fluorophenyl)(hydroxy)methyl]-2-methoxy-5-nitrophenyl}-2,2,2-trifluoroacetamide (5.5 g, 10.9 mmol, 95%) as a red oil. LCMS: ESI m/z 501/503 [M+H]⁺.

[00392] **Step G:** To a solution of N-{3-bromo-4-[(2-chloro-5-fluorophenyl)(hydroxy)methyl]-2-methoxy-5-nitrophenyl}-2,2,2-trifluoroacetamide (6 g, 11.9 mmol) in CH₂Cl₂ (200 mL) were added Dess-Martin periodinane (10.1 g, 23.9 mmol). The mixture was stirred at rt for 2 hr. LCMS showed the reaction was completed and. The reaction was diluted with DCM and H₂O. The organic layer was separated and concentrated in vacuo. The residue was purified using silica gel column chromatography eluting with ethyl acetate in petroleum ether (gradient: 15-25%) to

afford N-{3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl}-2,2,2-trifluoroacetamide (5.9 g, 11.8 mmol, 98%) as a red solid. LCMS: ESI m/z 499/501 [M + H]⁺.

[00393] **Step H:** To a solution of N-{3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl}-2,2,2-trifluoroacetamide (5 g, 10.0 mmol) in MeOH (50 mL) were added KOH (3.37 g, 60.0 mmol). The reaction was stirred at 80 °C under N₂ for 1 hr. LCMS showed the reaction was completed and. The reaction mixture was diluted brine, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with ethyl acetate in petroleum ether (gradient: 20-30%) to afford (4-amino-2-bromo-3-methoxy-6-nitrophenyl)(2-chloro-5-fluorophenyl)methanone (2.5 g, 6.19 mmol, 62%) as a yellow solid. LCMS: ESI m/z 403/405 [M + H]⁺.

[00394] **Step I:** To a solution of (4-amino-2-bromo-3-methoxy-6-nitrophenyl)(2-chloro-5-fluorophenyl)methanone (500 mg, 1.24 mmol) in EtOAc (40 mL) were added 2,2-difluoroacetic anhydride (0.172 mL, 1.49 mmol). The reaction was stirred at room temperature under N₂ for 18 hr. LCMS showed the reaction was completed and. The reaction mixture was diluted brine, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The organic layer was separated and concentrated to afford N-{3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl}-2,2-difluoroacetamide (595 mg, 1.23 mmol, 100%) as an orange solid. LCMS: ESI m/z 429/431 [M + H]⁺.

[00395] **Step J:** To a solution of N-{3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl}-2,2-difluoroacetamide (400 mg, 0.831 mmol) in THF (15 mL) were added borane dimethylsulfane (10M, 0.125 mL, 1.24 mmol). The reaction was stirred at 70 °C under N₂ for 2 hr. LCMS showed the reaction was completed and. The cooled reaction mixture was quenched MeOH, diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 30-40%) to afford {2-bromo-4-[(2,2-difluoroethyl)amino]-3-methoxy-6-nitrophenyl}(2-chloro-5-fluorophenyl)methanone (250 mg, 0.535 mmol, 64%) as a yellow solid. LCMS: ESI m/z 467/469 [M + H]⁺.

[00396] **Step K:** To a solution of {2-bromo-4-[(2,2-difluoroethyl)amino]-3-methoxy-6-nitrophenyl}(2-chloro-5-fluorophenyl)methanone (200 mg, 0.428 mmol) in EtOH (15

mL) and H₂O (3 mL) were added Fe (119 mg, 2.13 mmol) and NH₄Cl (114 mg, 2.14 mmol). The reaction was stirred at 80 °C under N₂ for 2 hr. LCMS showed the reaction was completed and. The cooled reaction mixture was filtered, concentrated, diluted water, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with ethyl acetate in petroleum ether (gradient: 30-40%) to afford {6-amino-2-bromo-4-[(2,2-difluoroethyl)amino]-3-methoxyphenyl}(2-chloro-5-fluorophenyl)methanone (165 mg, 0.377 mmol, 88%) as a yellow solid. LCMS: ESI m/z 437/439 [M + H]⁺.

[00397] **Step L:** To a solution of {6-amino-2-bromo-4-[(2,2-difluoroethyl)amino]-3-methoxyphenyl}(2-chloro-5-fluorophenyl)methanone (140 mg, 0.320 mmol) in DMA (10 mL) were added Zn(CN)₂ (56.3 mg, 0.480 mmol), and Pd(PPh₃)₄ (36.9 mg, 0.032 mmol). The reaction was stirred at 130 °C under N₂ for 1.5 hr using M.W. LCMS showed the reaction was completed and. The cooled reaction mixture was diluted water, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in dichloroform (gradient: 10-20%) to afford 3-amino-2-[(2-chloro-5-fluorophenyl)carbonyl]-5-[(2,2-difluoroethyl)amino]-6-methoxybenzene-1-carbonitrile (90 mg, 0.235 mmol, 73%) as a yellow oil. LCMS: ESI m/z 384/386 [M + H]⁺.

[00398] **Step M:** To a solution of 3-amino-2-[(2-chloro-5-fluorophenyl)carbonyl]-5-[(2,2-difluoroethyl)amino]-6-methoxybenzene-1-carbonitrile (100 mg, 0.261 mmol) in ACN (10 mL) were added 3-fluoro-5-(trifluoromethyl)benzoyl chloride (0.060 mL, 0.391 mmol) and Py (0.063 mL, 0.782 mmol). The reaction was stirred at room temperature under N₂ for 2 hr. LCMS showed the reaction was completed and. The reaction mixture was diluted water, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 30-40%) to afford N-{2-[(2-chloro-5-fluorophenyl)carbonyl]-3-cyano-5-[(2,2-difluoroethyl)amino]-4-methoxyphenyl}-3-fluoro-5-(trifluoromethyl)benzamide (110 mg, 0.192 mmol, 74%) as a yellow oil. LCMS: ESI m/z 574 [M + H]⁺.

[00399] **Step N:** To a solution of N-{2-[(2-chloro-5-fluorophenyl)carbonyl]-3-cyano-5-[(2,2-difluoroethyl)amino]-4-methoxyphenyl}-3-fluoro-5-(trifluoromethyl)benzamide (110 mg, 0.192 mmol) in ACN (6 mL) and H₂O (2 mL) were added KOH (32.2 mg, 0.575 mmol). The reaction

was stirred at room temperature under N₂ for 1 hr. LCMS showed the reaction was completed and. The reaction mixture was diluted brine, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The organic layer was separated and concentrated to afford N-[3-(2-chloro-5-fluorophenyl)-6-[(2,2-difluoroethyl)amino]-3-hydroxy-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (110 mg, 0.186 mmol, 97%) as a yellow solid. LCMS: ESI m/z 590 [M - H]⁻.

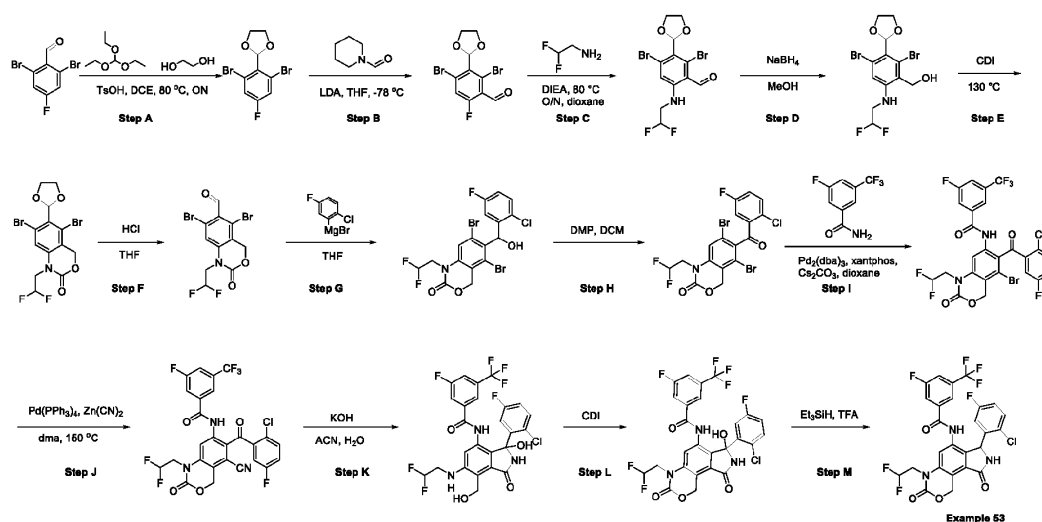
[00400] **Step O:** To a solution of N-[3-(2-chloro-5-fluorophenyl)-6-[(2,2-difluoroethyl)amino]-3-hydroxy-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (110 mg, 0.186 mmol) in TFA (5 mL) were added Et₃SiH (21.6 mg, 0.186 mmol). The reaction was stirred at 70 °C for 1 hr. LCMS showed the reaction was completed and. The cooled reaction mixture was concentrated, diluted aqueous NaHCO₃ and extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 30-40%) to afford N-[3-(2-chloro-5-fluorophenyl)-6-[(2,2-difluoroethyl)amino]-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (80 mg, 0.139 mmol, 75%) as a yellow solid. LCMS: ESI m/z 576 [M + H]⁺.

[00401] **Step P:** To a solution of N-[3-(2-chloro-5-fluorophenyl)-6-[(2,2-difluoroethyl)amino]-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (80 mg, 0.139 mmol) in DCM (4 mL) and tribromoborane (69.6 mg, 0.278 mmol). The reaction was stirred at rt for 18 hr. LCMS showed the reaction was completed and. The reaction was diluted with EA and NaHCO₃. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by prep-TLC ethyl acetate in petroleum ether (gradient: 40-50%) to afford compound N-[3-(2-chloro-5-fluorophenyl)-6-[(2,2-difluoroethyl)amino]-7-hydroxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (71 mg, 0.126 mmol, 91%) as a yellow solid. LCMS: ESI m/z 562 [M + H]⁺.

[00402] **Step Q:** To a solution of N-[3-(2-chloro-5-fluorophenyl)-6-[(2,2-difluoroethyl)amino]-7-hydroxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (40 mg, 0.071 mmol) in dioxane (3 mL) were added CDI (23 mg, 0.142 mmol). The reaction was stirred at 100 °C for 1 hr. LCMS showed the reaction was

completed and. The cooled reaction mixture was diluted water, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to afford N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-7,8-dihydro-6H-[1,3]oxazolo[5,4-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (3.2 mg, 0.005 mmol, 8%) as a white solid. LCMS: ESI m/z 588 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.48 (s, 1H), 9.26 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.68 (s, 1H), 7.47 (s, 1H), 7.34 – 7.25 (m, 1H), 7.15 – 7.05 (m, 1H), 6.60 – 6.30 (m, 1H), 6.02 (brs, 1H), 4.54 – 4.27 (m, 2H).

Example 53 N-[7-(2-chloro-5-fluorophenyl)-4-(2,2-difluoroethyl)-3,9-dioxo-1,3,4,7,8,9-hexahydro[1,3]oxazino[5,4-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide



[00403] **Step A:** To a solution of 2,6-dibromo-4-fluorobenzene-1-carbaldehyde (10 g, 35.5 mmol) in 1,2-dichloroethane (80 mL) was added ethylene glycol (9.9 mL, 177.4 mmol), triethoxymethane (5.0 mL, 30.5 mmol), 4-methylbenzenesulfonic acid (0.06 g, 0.36 mmol) at 25 °C. The reaction mixture was stirred at 80 °C O/N. The reaction mixture was cooled to 20 °C, washed successively with saturated NaHCO₃ (100 mL), and brine (2 * 100 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give residue. The residue was purified using silica gel column chromatography eluting with ethyl acetate in petroleum ether (0%~5%) to afford 2-(2,6-dibromo-4-fluorophenyl)-1,3-dioxolane (7.8 g, 23.9 mmol, 67%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.75 (d, *J* = 8.0 Hz, 2H), 6.22 (s, 1H), 4.22 (m, 2H), 4.01 (m, 2H).

[00404] **Step B:** To a solution of 2-(2,6-dibromo-4-fluorophenyl)-1,3-dioxolane (11.3 g, 34.7 mmol) in THF (110 mL) was added 2N LDA (22.5 mL, 45.1 mmol) dropwise at -78 °C and was stirred at -78 °C for 30min. Hexahydropyridine-1-carbaldehyde (5.9 g, 52.0 mmol) was then slowly added. The reaction mixture was stirred for an additional 30min at -78 °C. Then the mixture was added to sat. NH₄Cl (100 mL), extracted with ethyl acetate (80 mL * 3). The combined organic phases were washed with brine (100 mL), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel (EtOAc in PE = 10%) to give 2,4-dibromo-3-(1,3-dioxolan-2-yl)-6-fluorobenzene-1-carbaldehyde (8 g, 22.6 mmol, 65%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.19 (s, 1H), 7.93 (d, J = 9.2 Hz, 1H), 6.35 (s, 1H), 4.27 – 4.21 (m, 2H), 4.07 – 4.01 (m, 2H).

[00405] **Step C:** To a solution of 2,4-dibromo-3-(1,3-dioxolan-2-yl)-6-fluorobenzene-1-carbaldehyde (3.9 g, 11.0 mmol) in dioxane (40 mL) was added DIEA (1.9 mL, 11.0 mmol) and 2,2-difluoroethan-1-amine (3.11 mL, 44.1 mmol) and was sealed and stirred at 80 °C O/N. The reaction mixture was quenched with 1N HCl (50mL) and was extracted with EtOAc (70 mL*3). The organic layer was separated, 4-methyl-benzenesulfonic acid (2.28 g, 13.2 mmol) was added. The reaction mixture was stirred at rt for 30 min (monitored by LCMS). Brine was added, the organic layer was separated and dried over Na₂SO₄ and concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 5-10%) to afford 2,4-dibromo-6-[(2,2-difluoroethyl) amino]-3-(1,3-dioxolan-2-yl) benzene-1-carbaldehyde (2.7 g, 6.5 mmol, 59%) as a yellow solid. LCMS: m/z 416 [M+H]⁺.

[00406] **Step D:** To a solution of 2,4-dibromo-6-[(2,2-difluoroethyl) amino]-3-(1,3-dioxolan-2-yl) benzene-1-carbaldehyde (760 mg, 1.83 mmol) in MeOH (7 mL) was added NaBH₄ (83.1 mg, 2.2 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and was stirred for 1h. The reaction mixture was quenched with water (10 mL) and was extracted with EtOAc (15 mL*3). The organic layer was separated, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 10-15%) to afford {2,4-dibromo-6-[(2,2-difluoroethyl) amino]-3-(1,3-dioxolan-2-yl) phenyl} methanol (0.3 g, 0.72 mmol, 39 %) as a white solid. LCMS: m/z 418 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.04 (s, 1H), 6.34 – 5.97 (m, 3H), 5.38 (t, J = 5.2 Hz, 1H), 4.73 (d, J = 5.2 Hz, 2H), 4.16 (t, J = 6.8 Hz, 2H), 3.94 (t, J = 6.8 Hz, 2H), 3.76 – 3.58 (m, 2H).

[00407] **Step E:** To a solution of {2,4-dibromo-6-[(2,2-difluoroethyl) amino]-3-(1,3-dioxolan-2-yl) phenyl} methanol (3 g, 7.2 mmol) in dioxane (10 mL) was added CDI (4.67 g, 28.8 mmol) at rt. The reaction mixture was stirred at 130°C until neat. The reaction mixture was quenched with water (10 mL) and was extracted with EtOAc (15 mL*3). The organic layer was separated, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 0-15%) to afford 5,7-dibromo-1-(2,2-difluoroethyl)-6-(1,3-dioxolan-2-yl)-2,4-dihydro-1H-benzo[d] [1,3] oxazin-2-one (1.2 g, 2.71 mmol, 38%) as a white solid. LCMS: m/z 444 [M+H]⁺.

[00408] **Step F:** To a solution of 5,7-dibromo-1-(2,2-difluoroethyl)-6-(1,3-dioxolan-2-yl)-2,4-dihydro-1H-benzo[d] [1,3] oxazin-2-one (700 mg, 1.58 mmol) in THF (7 mL) was added conc.HCl (0.3 mL, 3.20 mmol) at rt. The reaction mixture was stirred for 2h. The reaction mixture was quenched with water (10 mL) and was extracted with EtOAc (15 mL*3). The organic layer was separated, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 20%) to afford 5,7-dibromo-1-(2,2-difluoroethyl)-2-oxo-2,4-dihydro-1H-benzo[d] [1,3] oxazine-6-carbaldehyde (0.6 g, 1.5 mmol, 95%) as a yellow solid. LCMS: m/z 400 [M+H]⁺.

[00409] **Step G:** To a solution of 5,7-dibromo-1-(2,2-difluoroethyl)-2-oxo-2,4-dihydro-1H-benzo[d] [1,3] oxazine-6-carbaldehyde (600 mg, 1.51 mmol) in THF (2 mL) was added bromo(2-chloro-5-fluorophenyl) magnesium (15.0 mL, 7.52 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 30 min. Then the mixture was added to sat. NH₄Cl (15 mL), extracted with ethyl acetate (20 mL * 2). The combined organic phases were washed with brine (20 mL * 2), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel (eluted with EtOAc in petroleum ether = 0 ~15 %) to give 5,7-dibromo-6-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2,2-difluoroethyl)-2,4-dihydro-1H-benzo[d] [1,3] oxazin-2-one (630 mg, 1.2 mmol, 80%) as a yellow solid. LCMS: m/z 528, 530, 532 [M+H]⁺.

[00410] **Step H:** A solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl) (hydroxy) methyl]-1-(2,2-difluoroethyl)-2,4-dihydro-1H-benzo[d] [1,3] oxazin-2-one (650 mg, 1.23 mmol) in DCM (7 mL) was added Dess-Martin periodinane (624.8 mg, 1.47 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h. The mixture was added to ice water (10 mL) and extracted with DCM

(20 mL x 2). The combined organic phase was washed with brine (10 mL x 2), dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by silica gel (PE/ EtOAc = 15%) to give 5,7-dibromo-6-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2,2-difluoroethyl)-2,4-dihydro-1H-benzo[d] [1,3] oxazin-2-one (540 mg, 1.0 mmol, 83%) as a white solid. LCMS(ESI): m/z 528 [M+H]⁺.

[00411] ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.75 (m, 2H), 7.65 – 7.59 (m, 1H), 7.55 (m, 1H), 6.33 (m, 1H), 5.38 (d, J = 7.2 Hz, 2H), 4.49 (m, 2H).

[00412] **Step I:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2,2-difluoroethyl)-2,4-dihydro-1H-benzo[d] [1,3] oxazin-2-one (50 mg, 0.1 mmol), Cs₂CO₃ (61.8 mg, 0.19 mmol), Xant-phos (5.48 mg, 0.01 mmol) and 3-fluoro-5-(trifluoromethyl) benzene-1-carboxamide (21.60 mg, 0.10 mmol) in anhydrous dioxane (2 mL) was added Pd₂(dba)₃ (8.7 mg, 0.01 mmol). The mixture was stirred at 100 °C under N₂ for 2h. The cooled mixture was diluted with water, extracted with EA (10 mL x 3). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel (PE/ EtOAc = 10 %) to give N-{5-bromo-6-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2,2-difluoroethyl)-2-oxo-2,4-dihydro-1H-benzo[d] [1,3] oxazin-7-yl}-5-fluoro-3-(trifluoromethyl) benzamide (10 mg, 0.015 mmol, 16%) as a brown oil. LCMS(ESI): m/z 651, 653[M-H].

[00413] **Step J:** To a solution of N-{5-bromo-6-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2,2-difluoroethyl)-2-oxo-2,4-dihydro-1H-benzo[d] [1,3] oxazin-7-yl}-5-fluoro-3-(trifluoromethyl) benzamide (100 mg, 0.15 mmol), Zn(CN)₂ (26.9 mg, 0.23 mmol) in anhydrous DMA (2 mL) was added Pd(PPh₃)₄ (17.7 mg, 0.02 mmol). The mixture was stirred at 150 °C under N₂ for 2h. The cooled mixture was diluted with water, extracted with EtOAc (10 mL x 3). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by prep-TLC (PE/ EtOAc = 2:1) to give N-{6-[(2-chloro-5-fluorophenyl) carbonyl]-5-cyano-1-(2,2-difluoroethyl)-2-oxo-2,4-dihydro-1H-benzo[d] [1,3] oxazin-7-yl}-5-fluoro-3-(trifluoromethyl) benzamide (20 mg, 0.033 mmol, 22 %) as a yellow solid. LCMS (ESI): m/z 600 [M+H]⁺

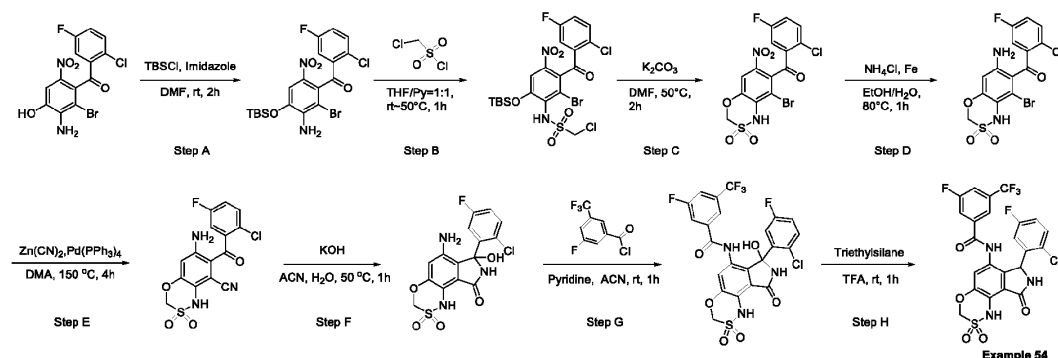
[00414] **Step K:** To a stirred solution of N-{6-[(2-chloro-5-fluorophenyl) carbonyl]-5-cyano-1-(2,2-difluoroethyl)-2-oxo-2,4-dihydro-1H-benzo[d] [1,3] oxazin-7-yl}-5-fluoro-3-(trifluoromethyl) benzamide (20 mg, 0.03 mmol) in CH₃CN (1 mL) was added KOH (2.86 mg, 0.05 mmol) and H₂O (1 mL). The reaction mixture was stirred at rt for 1 h. The reaction was

monitored by TLC. The mixture was treated with H₂O (10 mL) and extracted with EA (3 * 10 mL). The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated to afford N-[3-(2-chloro-5-fluorophenyl)-6-[(2,2-difluoroethyl) amino]-3-hydroxy-7-(hydroxymethyl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl) benzamide (5 mg, 0.01 mmol, 25%) as a yellow oil, and was used without further purification. LCMS (ESI): m/z 590 [M-H]⁻

[00415] **Step L:** To a stirred solution of N-[3-(2-chloro-5-fluorophenyl)-6-[(2,2-difluoroethyl) amino]-3-hydroxy-7-(hydroxymethyl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl) benzamide (5 mg, 0.01 mmol) in dioxane (1 mL) was added CDI (4 mg, 0.03 mmol) at rt. The mixture was stirred O/N at 80 °C. The mixture was treated with H₂O (5 mL) and extracted with EA (3 * 8 mL). The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated to afford N-[7-(2-chloro-5-fluorophenyl)-4-(2,2-difluoroethyl)-7-hydroxy-3,9-dioxo-1,3,4,7,8,9-hexahydro [1,3] oxazino[5,4-e] isoindol-6-yl]-5-fluoro-3-(trifluoromethyl) benzamide (5 mg, 0.002 mmol, 28%) as yellow oil, and was used without further purification. LCMS(ESI): m/z 616 [M-H]⁻

[00416] **Step M:** To a stirred solution of N-[7-(2-chloro-5-fluorophenyl)-4-(2,2-difluoroethyl)-7-hydroxy-3,9-dioxo-1,3,4,7,8,9-hexa-hydro [1,3] oxazino[5,4-e] isoindol-6-yl]-5-fluoro-3-(trifluoromethyl) benzamide (10 mg, 0.02 mmol) in TFA (1 mL) was added triethylsilane (6 mg, 0.05 mmol) at rt. The mixture was stirred for 1h at 60 °C. The mixture was concentrated to give a residue. The residue was purified by prep-TLC (DCM/ MeOH = 10:1) and prep-HPLC to give N-[7-(2-chloro-5-fluorophenyl)-4-(2,2-difluoroethyl)-3,9-dioxo-1,3,4,7,8,9-hexa-hydro [1,3] oxazino[5,4-e] isoindol-6-yl]-5-fluoro-3-(trifluoromethyl) benzamide (1 mg, 0.002 mmol, 10%) as a white solid. LCMS(ESI): m/z 602 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.76 – 7.53 (m, 3H), 7.37 (s, 1H), 7.27 (dd, J = 8.8, 5.2 Hz, 1H), 7.04 – 6.95 (m, 1H), 6.41 – 6.07 (m, 2H), 5.92 (d, J = 2.4 Hz, 2H), 4.45 – 4.32 (m, 2H).

Example 54 N-(7-(2-chloro-5-fluorophenyl)-2,2-dioxido-9-oxo-1,7,8,9-tetrahydro-3H-[1,3,4]oxathiazino[5,6-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00417] **Step A:** To a solution of (3-amino-2-bromo-4-hydroxy-6-nitrophenyl)(2-chloro-5-fluorophenyl)methanone (3.5 g, 8.98 mmol) and imidazole (1.22 g, 18 mmol) in DMF (25 mL), TBSCl (2.71 g, 18 mmol) was added. The resulting mixture was stirred at 23 °C for 2h. The mixture was treated with H₂O (100 mL) and extracted with EA (3x300 mL). The organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with 0-50% ethyl acetate in petroleum ether and dried to afford compound (3-amino-2-bromo-4-{[dimethyl(2-methylprop-2-yl)silyl]oxy}-6-nitrophenyl)(2-chloro-5-fluorophenyl)methanone (2 g, 3.97 mmol, 44%) as a yellow oil. LCMS: m/z 501 [M-H]⁻.

[00418] **Step B:** To a solution of (3-amino-2-bromo-4-{[dimethyl(2-methylprop-2-yl)silyl]oxy}-6-nitrophenyl)(2-chloro-5-fluorophenyl)methanone (2 g, 3.97 mmol) in Py (13 mL) and THF (13 mL) was added chloromethanesulfonyl chloride (0.9 mL, 9.92 mmol). The reaction mixture was refluxed for 1h. The reaction mixture was cooled to 25 °C. quenched with aqueous solution H₂O (30 mL) and extracted with EA (20 mL x 3). The combined organic phases were washed with brine (30 mL), dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with 0-50% ethyl acetate in petroleum ether and dried to afford compound give N-{2-bromo-3-[(2-chloro-5-fluorophenyl)carbonyl]-6-{[dimethyl(2-methylprop-2-yl)silyl]oxy}-4-nitrophenyl}-1-chloromethanesulfonamide (1.6 g, 2.6 mmol, 65%) as a yellow oil. LCMS: m/z 613 [M-H]⁻.

[00419] **Step C:** A solution of N-{2-bromo-3-[(2-chloro-5-fluorophenyl)carbonyl]-6-{[dimethyl(2-methylprop-2-yl)silyl]oxy}-4-nitrophenyl}-1-chloromethanesulfonamide (1.6 g, 2.6 mmol) in DMF (6 mL) were stirred at 50 °C for 2 h. The cooled mixture was treated with H₂O (100 mL) and extracted with EtOAc (3 x 300 mL). The combined organic phase was dried

over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (PE: EA=2: 1) followed to give 8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-6-nitro-1H-2λ⁶-benzo[2,1-e][1,3,4]oxathiazine-2,2-dione (700 mg, 1.5 mmol, 57.9%) as a yellow oil. LCMS: ESI m/z 465 [M + H]⁺.

[00420] **Step D:** To a solution of 8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-6-nitro-1H-2λ⁶-benzo[2,1-e][1,3,4]oxathiazine-2,2-dione (700 mg, 1.5 mmol) in EtOH (28 mL) and H₂O (7 mL) was added Fe (420 mg, 7.52 mmol) and NH₄Cl (402 mg, 7.52 mmol). The reaction mixture was stirred at 80 °C for 3 hrs. The cooled reaction mixture was filtered through Buchner funnel and washed with EA (200mL). The filtrate was concentrated under vacuum. The residue was purified using silica gel column chromatography eluting with 0-10% methanol in dichloroform to afford compound 6-amino-8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-1H-2λ⁶-benzo[2,1-e][1,3,4]oxathiazine-2,2-dione (500 mg, 1.15 mmol, 76%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.36 (s, 1H), 7.62 (dd, *J* = 8.0 Hz, 4.0 Hz, 1H), 7.46 (td, *J* = 8.0 Hz, 4.0 Hz, 1H), 7.23 (dd, *J* = 8.4, 3.2 Hz, 1H), 6.54 (s, 1H), 6.02 (s, 2H), 5.18 (s, 2H).

[00421] **Step E:** To a solution of 6-amino-8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-1H-2λ⁶-benzo[2,1-e][1,3,4]oxathiazine-2,2-dione (100 mg, 0.23 mmol) in DMA (1 mL) was added Zn(CN)₂ (80.9 mg, 0.689 mmol) and Pd(PPh₃)₄ (53.0 mg, 0.046 mmol). The mixture was stirred at 150 °C under N₂ for 4 hours. The cooled mixture was diluted water, extracted with EA. The organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with 0-50% ethyl acetate in petroleum ether to afford compound 6-amino-7-[(2-chloro-5-fluorophenyl)carbonyl]-2,2-dioxo-1H-2λ⁶-benzo[2,1-e][1,3,4]oxathiazine-8-carbonitrile (80 mg, 0.21 mmol, 91%) as a yellow solid. LCMS: ESI m/z 382 [M + H]⁺.

[00422] **Step F:** To a solution of 6-amino-7-[(2-chloro-5-fluorophenyl)carbonyl]-2,2-dioxo-1H-2λ⁶-benzo[2,1-e][1,3,4]oxathiazine-8-carbonitrile (70 mg, 0.183 mmol) in CH₃CN (3 mL) and H₂O (0.3 mL) was added KOH (30.9 mg, 0.55 mmol). The mixture was stirred at 50 °C for 1 h. The cooled mixture was diluted water, extracted with EA. The organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with 0-10% methanol in dichloroform to afford compound 6-amino-7-(2-chloro-5-fluorophenyl)-7-hydroxy-1,7,8,9-tetrahydro-2λ⁶-[1,3,4]oxathiazino[5,6-e]isoindole-2,2,9-trione (40 mg, 0.1 mmol, 55%) as a yellow solid.

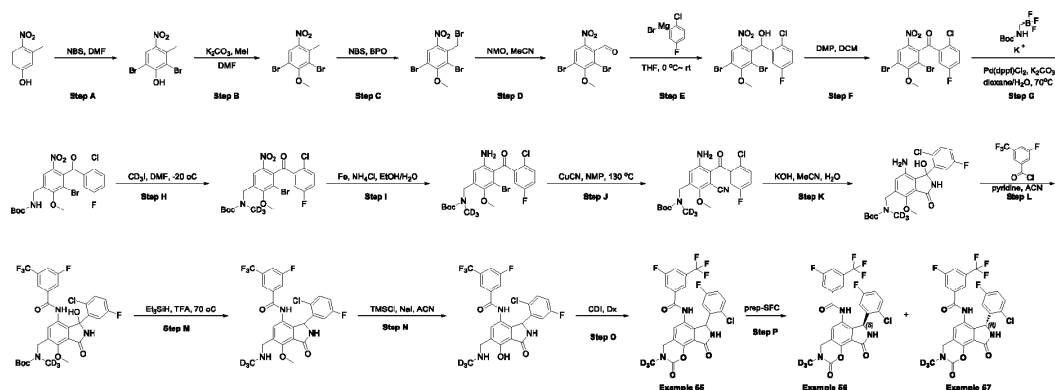
[00423] **Step G:** To a solution of 6-amino-7-(2-chloro-5-fluorophenyl)-7-hydroxy-1,7,8,9-tetrahydro-2 λ^6 -[1,3,4]oxathiazino[5,6-e]isoindole-2,2,9-trione (40 mg, 0.1 mmol) in MeCN (1 mL) was added pyridine (0.04 mL, 0.5 mmol) and 3-fluoro-5-(trifluoromethyl)benzoyl chloride (68 mg, 0.3 mmol). The reaction mixture was stirred at rt for 1 hr. Then the mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic phases were washed with brine (20 mL) dried over Na₂SO₄ and concentrated to give N-[7-(2-chloro-5-fluorophenyl)-7-hydroxy-2,2,9-trioxo-1,7,8,9-tetrahydro-2 λ^6 -[1,3,4]oxathiazino[5,6-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (20 mg, 0.034 mmol, 34%) as a yellow solid. LCMS: ESI m/z 588 [M - H]⁻.

[00424] **Step H:** To a solution of N-[7-(2-chloro-5-fluorophenyl)-7-hydroxy-2,2,9-trioxo-1,7,8,9-tetrahydro-2 λ^6 -[1,3,4]oxathiazino[5,6-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (20 mg, 0.034 mmol) in TFA (1.5 mL) was added triethylsilane (0.3 mL). The mixture was stirred at 70 °C for 1 hour. The cooled mixture was concentrated under vacuum. The residue was purified by prep-HPLC to afford N-[7-(2-chloro-5-fluorophenyl)-2,2,9-trioxo-1,7,8,9-tetrahydro-2 λ^6 -[1,3,4]oxathiazino[5,6-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (1.1 mg, 0.002 mmol, 6%) as a white solid. LCMS: ESI m/z 574 [M + H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.68 – 7.60 (m, 3H), 7.38 – 7.16 (m, 2H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.67 (brs, 1H), 6.10 (brs, 1H), 5.22 (s, 2H).

Example 55 N-[7-(2-chloro-5-fluorophenyl)-2,9-dioxo-3-(trideuteriomethyl)-2,3,4,7,8,9-hexahydro[1,3]oxazino[6,5-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide

Example 56 (S)-N-(7-(2-chloro-5-fluorophenyl)-3-(methyl-d₃)-2,9-dioxo-2,3,4,7,8,9-hexahydro-[1,3]oxazino[6,5-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 57 (R)-N-(7-(2-chloro-5-fluorophenyl)-3-(methyl-d₃)-2,9-dioxo-2,3,4,7,8,9-hexahydro-[1,3]oxazino[6,5-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00425] **Step A.** To a stirred solution of 3-methyl-4-nitrophenol (31.2 g, 203 mmol) in DMF (300 mL) was added NBS (43.5 g, 244 mmol) at 0 °C. After stirred at 65 °C for 3h, the mixture was poured into ice-water (20 mL) and extracted with EtOAc (20 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-20%, EtOAc in PE) to give 2,6-dibromo-3-methyl-4-nitrophenol (45.1 g, 145 mmol, 71 %) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 2.51 (s, 3H).

[00426] **Step B.** To a solution of 2,6-dibromo-3-methyl-4-nitrophenol (44.2 g, 142 mmol) in CH₃CN (450 mL) were added K₂CO₃ (29.5 g, 213 mmol) and CH₃I (13.8 mL, 171 mmol). The reaction mixture was stirred at rt overnight. The reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient : 0-10%] to afford compound 3,5-dibromo-4-methoxy-2-methyl-1-nitrobenzene (41 g, 126 mmol, 89 %) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.30 (s, 1H), 3.87 (s, 3H), 2.47 (s, 3H).

[00427] **Step C.** To a solution of 3,5-dibromo-4-methoxy-2-methyl-1-nitrobenzene (41 g, 126 mmol) in CCl₄ (300 mL) were added NBS (20.4 g, 114 mmol) and BPO (2.3 g, 9.54 mmol). The reaction mixture was stirred at 85 °C overnight. The reaction mixture was diluted with H₂O, extracted with DCM. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA

in PE [Gradient : 0-15 %] to afford compound 3,5-dibromo-2-(bromomethyl)-4-methoxy-1-nitrobenzene (46.1 g, 89 mmol, 94 %) as a white solid.

[00428] **Step D.** To a solution of 3,5-dibromo-2-(bromomethyl)-4-methoxy-1-nitrobenzene (46.1 g, 89 mmol) in CH₃CN (400 mL) was added NMO (20.9 g, 178 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient : 0-30%] to afford compound 2,4-dibromo-3-methoxy-6-nitrobenzene-1-carbaldehyde (35.1 g, 74 mmol, 83 %) as a yellow solid.

[00429] **Step E.** To a solution of 2,4-dibromo-3-methoxy-6-nitrobenzene-1-carbaldehyde (30.5 g, 89 mmol) in THF (400 mL) was added bromo(2-chloro-5-fluorophenyl)magnesium (89 mL, 135 mmol) at 0 °C. The reaction mixture was stirred at RT for 2 h. The reaction mixture was quenched with NH₄Cl, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient : 0-40%] to afford compound (2-chloro-5-fluorophenyl)(2,4-dibromo-3-methoxy-6-nitrophenyl)methanol (40.2 g, 85.6 mmol, 95 %) as a white solid.

[00430] **Step F.** To a stirred solution of (2-chloro-5-fluorophenyl)(2,4-dibromo-3-methoxy-6-nitrophenyl)methanol (40.2 g, 85.6 mmol) in DCM (420 mL) was added DESS-MARTIN (40 g, 94.2 mmol) slowly at 0 °C. After stirred at rt for 3h, the mixture was poured into ice-water (500 mL) and extracted with DCM (200 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-30%, EtOAc in PE) to give (2-chloro-5-fluorophenyl)(2,4-dibromo-3-methoxy-6-nitrophenyl)methanone (35.5 g, 75.9 mmol, 89 %) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.68 (s, 1H), 7.82 – 7.60 (m, 3H), 3.95 (s, 3H).

[00431] **Step G.** To a stirred solution of (2-chloro-5-fluorophenyl)(2,4-dibromo-3-methoxy-6-nitrophenyl)methanone (10 g, 21.4 mmol) in dioxane (80 mL)/ H₂O (20 mL) was added (2,2-dimethyl-4-oxo-5-aza-3-oxahex-6-yl)trifluoro-λ⁵-boranuide (5 g, 25.7 mmol), Pd(dppf)Cl₂ (1.25 g, 1.71 mmol) and K₂CO₃ (5.91 g, 42.8 mmol) at rt. After stirred at 70 °C under N₂ overnight, the cooled mixture was poured into ice-water (100 mL) and extracted with DCM (80 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and

concentrated. The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-50%, EtOAc in PE) to give 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl]amino]methanoate (2.5 g, 4.83 mmol, 22 %) as a brown solid. LCMS: m/z 517 [M+H]⁺.

[00432] **Step H.** To a stirred solution of 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl]amino]methanoate (1.6 g, 3.09 mmol) in DMF (20 mL) was added NaH (370 mg, 9.27 mmol, 60% in mineral oil) slowly at -20 °C. After stirred at -20 °C for 1h, CD₃I (2.24 g, 15.452 mmol) was added to the mixture. After stirred at rt for 2h, the mixture was poured into ice-water (20 mL) and extracted with EtOAc (10 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-30%, EtOAc in PE) to give 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl](trideuteriomethyl)amino]methanoate (1 g, 1.87 mmol, 61 %) as a yellow solid. LCMS: m/z 535 [M+H]⁺.

[00433] **Step I.** To a stirred solution of 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl](trideuteriomethyl)amino]methanoate (1 g, 1.87 mmol) in EtOH (16 mL)/ H₂O (4 mL) was added NH₄Cl (300 mg, 5.61 mmol) and Fe (835 mg, 14.9 mmol) at rt. After stirred at 80 °C for 2h, the mixture was filtered and concentrated. The residue was purified by chromatography (silica gel, 0-50 %, EtOAc in PE) to give crude 2-methylpropan-2-yl [(5-amino-3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxyphenyl)methyl](trideuteriomethyl)amino]methanoate (820 mg, 1.62 mmol, 87 %) as a yellow solid. LCMS: m/z 505 [M+H]⁺.

[00434] **Step J.** To a stirred solution of 2-methylpropan-2-yl [(5-amino-3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxyphenyl)methyl](trideuteriomethyl)amino]methanoate (820 mg, 1.62 mmol) in NMP (10 mL) was added CuCN (291 mg, 3.25 mmol) at rt. After stirred at 130 °C for 5h, the cooled mixture was poured into brine (50 mL) and extracted with EtOAc (30 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-50 %, EtOAc in PE) to give 2-methylpropan-2-yl

[({5-amino-4-[(2-chloro-5-fluorophenyl)carbonyl]-3-cyano-2-methoxyphenyl}methyl)(trideuteriomethyl)amino]methanoate (550 mg, 1.22 mmol, 75 %) as a yellow solid. LCMS: m/z 451 $[M+H]^+$.

[00435] **Step K.** To a stirred solution of 2-methylpropan-2-yl [({5-amino-4-[(2-chloro-5-fluorophenyl)carbonyl]-3-cyano-2-methoxyphenyl}methyl)(trideuteriomethyl)amino]methanoate (500 mg, 1.1 mmol) in ACN (3 mL)/ H₂O (1 mL) was added KOH (622 mg, 11.1 mmol) slowly at rt. After stirred at rt for 1h, the mixture was poured into water (10 mL) and extracted with EtOAc (10 mL*2). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-10%, MeOH in DCM) to give 2-methylpropan-2-yl ({[7-amino-1-(2-chloro-5-fluorophenyl)-1-hydroxy-4-methoxy-3-oxo-2,3-dihydro-1H-isoindol-5-yl]methyl}(trideuteriomethyl)amino)methanoate (480 mg, 1.02 mmol, 92 %) as a white solid. LCMS: m/z 469 $[M+H]^+$.

[00436] **Step L.** To a stirred solution of 2-methylpropan-2-yl ({[7-amino-1-(2-chloro-5-fluorophenyl)-1-hydroxy-4-methoxy-3-oxo-2,3-dihydro-1H-isoindol-5-yl]methyl}(trideuteriomethyl)amino)methanoate (480 mg, 1.02 mmol) in ACN (10 mL) was added pyridine (0.3 mL, 3.1 mmol) and 5-fluoro-3-(trifluoromethyl)benzoyl chloride (348 mg, 1.54 mmol) slowly at rt. After stirred at rt for 1h, the mixture was poured into water (10 mL) and extracted with EtOAc (10 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-10%, MeOH in DCM) to give 2-methylpropan-2-yl ({[1-(2-chloro-5-fluorophenyl)-7-({[5-fluoro-3-(trifluoromethyl)phenyl]carbonyl}amino)-1-hydroxy-4-methoxy-3-oxo-2,3-dihydro-1H-isoindol-5-yl]methyl}(trideuteriomethyl)amino)methanoate (420 mg, 0.637 mmol, 62 %) as a brown solid. LCMS: m/z 659 $[M+H]^+$.

[00437] **Step M.** To a stirred solution of 2-methylpropan-2-yl ({[1-(2-chloro-5-fluorophenyl)-7-({[5-fluoro-3-(trifluoromethyl)phenyl]carbonyl}amino)-1-hydroxy-4-methoxy-3-oxo-2,3-dihydro-1H-isoindol-5-yl]methyl}(trideuteriomethyl)amino)methanoate (420 mg, 0.637 mmol) in TFA (5 mL) was added Et₃SiH (2 mL) at rt. After stirred at 70 °C for 2h, the cooled mixture was concentrated. The residue was purified by chromatography (silica gel, 0-10%, MeOH in DCM) to give N-[3-(2-chloro-5-fluorophenyl)-7-methoxy-1-oxo-6-{{[(trideuteriomethyl)amino]methyl}-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-

(trifluoromethyl)benzamide (320 mg, 0.589 mmol, 92 %) as a white solid. LCMS: m/z 543 $[M+H]^+$.

[00438] **Step N.** To a stirred solution of N-[3-(2-chloro-5-fluorophenyl)-7-methoxy-1-oxo-6-[[trideuteriomethyl]amino]methyl]-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (150 mg, 0.276 mmol) in ACN (6 mL) was added TMSCl (150 mg, 1.38 mmol) and NaI (207 mg, 1.38 mmol) at rt. After stirred at 90 °C for 5h, the cooled mixture was poured into water (10 mL) and extracted with EtOAc (10 mL*2). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-12%, MeOH in DCM) to give crude N-[3-(2-chloro-5-fluorophenyl)-7-hydroxy-1-oxo-6-[[trideuteriomethyl]amino]methyl]-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (110 mg, 0.21 mmol, 75 %) as a white solid. LCMS: m/z 529 $[M+H]^+$.

[00439] **Step O.** To a stirred solution of N-[3-(2-chloro-5-fluorophenyl)-7-hydroxy-1-oxo-6-[[trideuteriomethyl]amino]methyl]-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (100 mg, 0.189 mmol) in dioxane (5 mL) was added CDI (33 mg, 0.21 mmol) at rt. After stirred at 50 °C for 1h, the mixture was poured into water (10 mL) and extracted with EtOAc (10 mL*2). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC (C18, 40 ~ 90 % MeCN in H₂O with 0.1 % TFA) to give N-[7-(2-chloro-5-fluorophenyl)-2,9-dioxo-3-(trideuteriomethyl)-2,3,4,7,8,9-hexahydro[1,3]oxazino[6,5-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (55 mg, 0.09 mmol, 47 %) as a white solid. LCMS: m/z 555 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.40 (s, 1H), 9.20 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.64 (s, 1H), 7.36 (s, 1H), 7.32 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.12 – 7.06 (m, 1H), 5.92 (brs, 1H), 4.62 (t, 2H).

[00440] **Step P.** N-[7-(2-chloro-5-fluorophenyl)-2,9-dioxo-3-(trideuteriomethyl)-2,3,4,7,8,9-hexahydro[1,3]oxazino[6,5-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (50 mg, 0.090 mmol) was purified by SFC to give P1 Example 56: (R)-N-(7-(2-chloro-5-fluorophenyl)-3-(methyl-*d*₃)-2,9-dioxo-2,3,4,7,8,9-hexahydro-[1,3]oxazino[6,5-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (10.9 mg, 22%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.36 (s, 1H), 9.04 (s, 1H), 7.96 (d, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.64 (s, 1H), 7.36 (s, 1H), 7.32 (s, 1H), 7.08 (s, 1H), 6.64 (brm, 1H), 5.96 (s, 1H), 4.60 (s, 2H).

[00441] P2 Example 57: (S)-N-(7-(2-chloro-5-fluorophenyl)-3-(methyl-d3)-2,9-dioxo-2,3,4,7,8,9-hexahydro-[1,3]oxazino[6,5-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (19.5 mg, 39%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.36 (s, 1H), 9.04 (s, 1H), 7.96 (d, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.64 (s, 1H), 7.36 (s, 1H), 7.32 (s, 1H), 7.08 (s, 1H), 6.64 (brn, 1H), 5.96 (s, 1H), 4.60 (s, 2H).

[00442] Preparative separation method:

Instrument: SHIMADZU PREP SOLUTION SFC

Column: ChiralPak IA, 250×30mm I.D., 5μm

Mobile phase: A for CO₂ and B for MeOH

Gradient: B 45%

Flow rate: 60mL/min

Back pressure: 100 bar

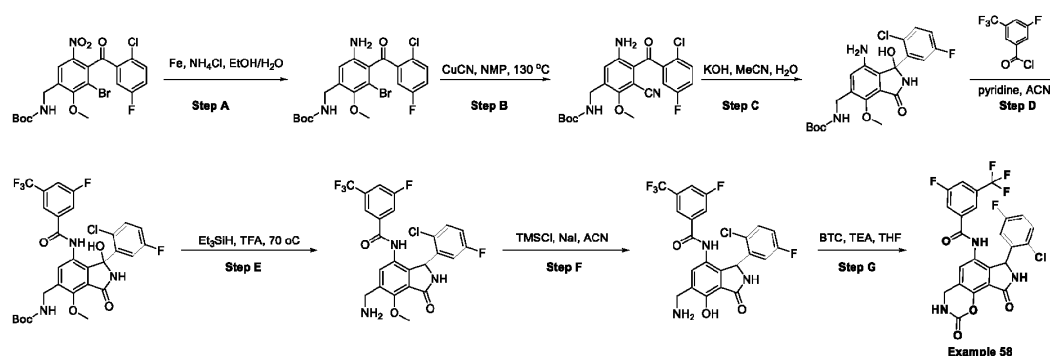
Column temperature: 35°C

Wavelength: 220nm

Cycle-time: 12min

Eluted time: 2H

Example 58 N-(7-(2-chloro-5-fluorophenyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-[1,3]oxazino[6,5-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00443] **Step A.** To a stirred solution of 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl]amino]methanoate (800 mg, 1.54 mmol) in EtOH (12 mL)/ H₂O (3 mL) was added NH₄Cl (248 mg, 4.64 mmol) and Fe (690 mg, 12.3 mmol) at rt. After stirred at 80 °C for 2h, the cooled mixture was filtered and concentrated. The residue was purified by chromatography (silica gel, 0-50 %, EtOAc in PE) to

give crude 2-methylpropan-2-yl [(5-amino-3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxyphenyl)methyl]amino]methanoate (660 mg, 1.35 mmol, 87%) as a yellow solid. LCMS: m/z 488 $[M+H]^+$.

[00444] **Step B.** To a stirred solution of 2-methylpropan-2-yl [(5-amino-3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxyphenyl)methyl]amino]methanoate (650 mg, 1.33 mmol) in NMP (10 mL) was added CuCN (358 mg, 3.99 mmol) at rt. After stirred at 130 °C for 3h, the cooled mixture was poured into brine (50 mL) and extracted with EtOAc (30 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated until there was no more drops. The residue was purified by chromatography (silica gel, 0-60 %, EtOAc in PE) to give crude 2-methylpropan-2-yl [(5-amino-4-[(2-chloro-5-fluorophenyl)carbonyl]-3-cyano-2-methoxyphenyl)methyl]amino]methanoate (300 mg, 0.69 mmol, 52%) as a yellow solid. LCMS: m/z 434 $[M+H]^+$.

[00445] **Step C.** To a stirred solution of 2-methylpropan-2-yl [(5-amino-4-[(2-chloro-5-fluorophenyl)carbonyl]-3-cyano-2-methoxyphenyl)methyl]amino]methanoate (300 mg, 0.69 mmol) in ACN (3 mL)/ H₂O (1 mL) was added KOH (194 mg, 3.45 mmol) slowly at rt. After stirred at rt for 1h, the mixture was poured into water (10 mL) and extracted with EtOAc (10 mL*2). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-10%, MeOH in DCM) to give crude 2-methylpropan-2-yl ([7-amino-1-(2-chloro-5-fluorophenyl)-1-hydroxy-4-methoxy-3-oxo-2,3-dihydro-1H-isoindol-5-yl)methyl]amino]methanoate (300 mg, 0.66 mmol, 96%) as a yellow solid. LCMS: m/z 452 $[M+H]^+$.

[00446] **Step D.** To a stirred solution of 2-methylpropan-2-yl ([7-amino-1-(2-chloro-5-fluorophenyl)-1-hydroxy-4-methoxy-3-oxo-2,3-dihydro-1H-isoindol-5-yl)methyl]amino]methanoate (250 mg, 0.55 mmol) in ACN (5 mL) was added pyridine (0.2 mL, 1.67 mmol) and 5-fluoro-3-(trifluoromethyl)benzoyl chloride (188 mg, 0.83 mmol) slowly at rt. After stirred at rt for 2h, the mixture was poured into water (10 mL) and extracted with EtOAc (10 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-10%, MeOH in DCM) to give 2-methylpropan-2-yl ([1-(2-chloro-5-fluorophenyl)-7-([5-fluoro-3-(trifluoromethyl)phenyl]carbonyl)amino]-1-hydroxy-4-methoxy-3-oxo-2,3-dihydro-1H-isoindol-

5-yl)methyl}amino)methanoate (160 mg, 0.25 mmol, 45%) as a white solid. LCMS: m/z 642 $[M+H]^+$.

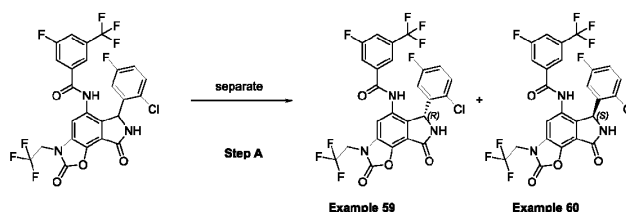
[00447] **Step E.** To a stirred solution of 2-methylpropan-2-yl ({[1-(2-chloro-5-fluorophenyl)-7-({[5-fluoro-3-(trifluoromethyl)phenyl]carbonyl}amino)-1-hydroxy-4-methoxy-3-oxo-2,3-dihydro-1H-isoindol-5-yl]methyl}amino)methanoate (160 mg, 0.25 mmol) in TFA (4 mL) was added Et_3SiH (1 mL) at rt. After stirred at 70 °C for 2h, the cooled mixture was concentrated. The residue was purified by chromatography (silica gel, 0-10%, MeOH in DCM) to give N-[6-(aminomethyl)-3-(2-chloro-5-fluorophenyl)-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (120 mg, 0.23 mmol, 91%) as a white solid. LCMS: m/z 526 $[M+H]^+$.

[00448] **Step F.** To a stirred solution of N-[6-(aminomethyl)-3-(2-chloro-5-fluorophenyl)-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (80 mg, 0.152 mmol) in ACN (3 mL) was added TMSCl (83 mg, 0.76 mmol) and NaI (114 mg, 0.76 mmol) at rt. After stirred at 100 °C for 5h, the mixture was poured into water (10 mL) and extracted with EtOAc (10 mL*2). The combined organic phase was washed with brine, dried with Na_2SO_4 , filtered and concentrated. The residue was purified by chromatography (silica gel, 0-12%, MeOH in DCM) to give crude N-[6-(aminomethyl)-3-(2-chloro-5-fluorophenyl)-7-hydroxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (50 mg, 0.063 mmol, 42%) as a yellow oil. LCMS: m/z 512 $[M+H]^+$.

[00449] **Step G.** To a stirred solution of N-[6-(aminomethyl)-3-(2-chloro-5-fluorophenyl)-7-hydroxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (40 mg, 0.06 mmol) in THF (2 mL) was added TEA (24 mg, 0.23 mmol) and triphosgene (46 mg, 0.16 mmol) at rt. After stirred at rt for 1h, the mixture was poured into water (10 mL) and extracted with EtOAc (10 mL*2). The combined organic phase was washed with brine, dried with Na_2SO_4 , filtered and concentrated. The residue was purified by prep-HPLC (C18, 40 ~ 90 % MeCN in H_2O with 0.1 % TFA) to give N-[7-(2-chloro-5-fluorophenyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro[1,3]oxazino[6,5-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (2 mg, 0.004 mmol, 5%) as a white solid. LCMS: m/z 538 $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.32 (s, 1H), 9.04 (s, 1H), 8.12 (s, 1H), 7.96 (d, $J = 8.8$ Hz, 1H), 7.72 (d, $J = 9.2$ Hz, 1H), 7.64 (s, 1H), 7.36 (s, 1H), 7.32 (dd, $J = 8.8, 5.2$ Hz, 1H), 7.13 – 7.05 (m, 1H), 5.92 (brs, 1H), 4.52 (t, 2H).

Example 59 (R)-N-(6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-3,6,7,8-tetrahydro-2H-oxazolo[5,4-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 60 (S)-N-(6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-3,6,7,8-tetrahydro-2H-oxazolo[5,4-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00450] **Step A:** The N-[6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-[1,3]oxazolo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (30 mg, 0.050 mmol) was separated by SFC to afford P1: Example 59 (12.2 mg, 0.020 mmol, 41 %) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.50 (s, 1H), 9.28 (s, 1H), 7.95 (d, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 9.6$ Hz, 1H), 7.68 (s, 1H), 7.57 (s, 1H), 7.35 – 7.25 (m, 1H), 7.14 – 7.05 (m, 1H), 6.69 (brs, 1H), 6.03 (brs, 1H), 5.08 – 4.77 (m, 2H). And P2: Example 60 N-[(6R)-6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-[1,3]oxazolo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (13.1 mg, 0.022 mmol, 44%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.50 (s, 1H), 9.28 (s, 1H), 7.95 (d, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 9.6$ Hz, 1H), 7.68 (s, 1H), 7.57 (s, 1H), 7.35 – 7.25 (m, 1H), 7.14 – 7.05 (m, 1H), 6.69 (brs, 1H), 6.03 (brs, 1H), 5.08 – 4.77 (m, 2H).

[00451] Preparative prep-SFC separation method:

Instrument: Waters Thar 80 preparative SFC

Column: (R,R)-WHELK, 250×30 mm I.D., 5 μm

Mobile phase: A for CO_2 and B for MeOH

Gradient: B 50%

Flow rate: 60 mL/min

Back pressure: 100 bar

Column temperature: 35 $^\circ\text{C}$

Wavelength: 220 nm

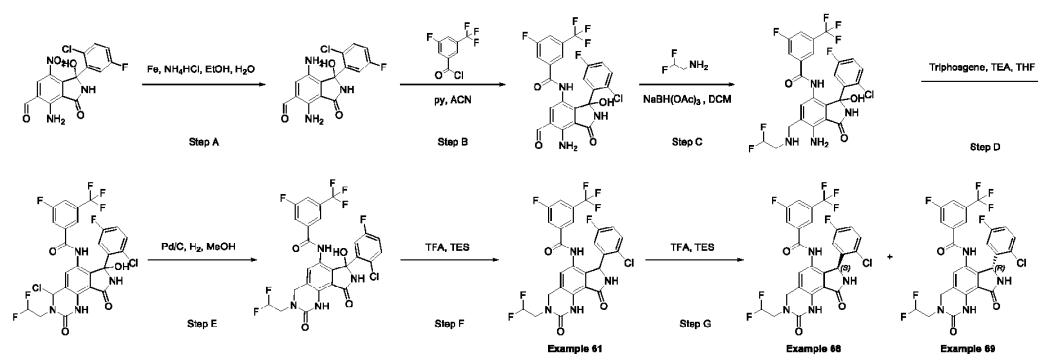
Cycle-time: 20 min

Eluted time: 3 H

Example 61 N-(7-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 68 (S)-N-(7-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 69 (R)-N-(7-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00452] **Step A:** To a solution of 4-amino-1-(2-chloro-4-fluorophenyl)-1-hydroxy-7-nitro-3-oxo-2,3-dihydro-1H-isoindole-5-carbaldehyde (180 mg, 0.492 mmol) and Fe (138 mg, 2.46 mmol) in EtOH (5 mL) was added NH₄Cl (133 mg, 2.46 mmol) in H₂O (1 mL). The reaction mixture was heated to 85 °C for 2 h. The mixture cooled mixture was filtered, concentrated, and purified by column to give 4,7-diamino-1-(2-chloro-4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1H-isoindole-5-carbaldehyde (50 mg, 0.149 mmol, 30%) as a brown solid. LCMS: m/z 336 [M+H]⁺

[00453] **Step B:** To a solution of 4,7-diamino-1-(2-chloro-4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1H-isoindole-5-carbaldehyde (48 mg, 0.143 mmol) in ACN (3 mL) was added Py (56.6 mg, 0.715 mmol) and 3-fluoro-5-(trifluoromethyl)benzoyl chloride (38.9 mg, 0.172 mmol). The reaction mixture was stirred at rt for 30 min. The mixture was diluted with water (~10 mL) and extracted with ethyl acetate (~10 mL x 2). The combined organic phases were washed with brine (20 mL), dried over Na₂SO₄ and concentrated to give N-[7-amino-3-(2-chloro-4-fluorophenyl)-6-formyl-3-hydroxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (45 mg, 86 μmol, 60%) as a brown solid. LCMS: m/z 526 [M+H]⁺

[00454] **Step C:** To a solution of N-[7-amino-3-(2-chloro-4-fluorophenyl)-6-formyl-3-hydroxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (45 mg, 86

μmol) and 2,2-difluoroethan-1-amine (14 mg, 0.171 mmol) in 1,2-dichloroethane (5 mL) was added HOAc (7 mg, 0.038 mmol). The mixture was stirred at rt for 1h, then NaBH(OAc)₃ (90.7 mg, 0.428 mmol) was added. The mixture was stirred for another 1h, then diluted with DCM and H₂O. The organic phase was concentrated. The residue was purified by column (eluted with MeOH: DCM=10%) to give N-[7-amino-3-(2-chloro-4-fluorophenyl)-6-[(2,2-difluoroethyl)amino]methyl]-3-hydroxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (30 mg, 51 μmol, 59%) as a brown solid. LCMS: m/z 591 [M+H]⁺.

[00455] **Step D:** To a solution of N-[7-amino-3-(2-chloro-4-fluorophenyl)-6-[(2,2-difluoroethyl)amino]methyl]-3-hydroxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (20 mg, 34 μmol) in THF (2 mL) was added triphosgene (3 mg, 10 μmol) in THF (0.5 mL) at 0 °C. The mixture was stirred for another 10min. The mixture was quenched with H₂O, extracted with EtOAc (10 mL*2). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo to give N-[4-chloro-7-(2-chloro-4-fluorophenyl)-3-(2,2-difluoroethyl)-7-hydroxy-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (15 mg, 23 μmol, 68%) as a brown solid. LCMS: m/z 651 [M+H]⁺.

[00456] **Step E:** To a solution of N-[4-chloro-7-(2-chloro-4-fluorophenyl)-3-(2,2-difluoroethyl)-7-hydroxy-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (15 mg, 23 μmol) in MeOH (2 mL) was added Pd/C (3 mg). The mixture was stirred at 50 °C under H₂ for 1 h. Then the mixture was filtered, and the filtrate was concentrated to give N-[7-(2-chloro-4-fluorophenyl)-3-(2,2-difluoroethyl)-7-hydroxy-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (14 mg, 23 μmol, 99%) as a brown solid (crude). LCMS: m/z 617 [M+H]⁺.

[00457] **Step F:** To a solution of N-[7-(2-chloro-4-fluorophenyl)-3-(2,2-difluoroethyl)-7-hydroxy-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (14 mg, 23 μmol) in TFA (2 mL) was added Et₃SiH (0.2 mL). The reaction mixture was stirred at 60 °C for 30min. The reaction mixture was concentrated to give a residue. The residue was purified by pre-HPLC to give N-[7-(2-chloro-4-fluorophenyl)-3-(2,2-difluoroethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (5 mg, 8 μmol, 37%) as a white solid. LCMS: m/z 601 [M+H]⁺.

¹H NMR (400 MHz, CD₃OD) δ 7.78 – 7.54 (m, 3H), 7.26 (m, 2H), 7.08 – 6.92 (m, 1H), 6.68 (s, 1H), 6.27 – 5.98 (m, 2H), 4.78 (s, 2H), 3.93 – 3.72 (m, 2H)

[00458] **Step G:** N-(7-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (P-329) was separated by prep-SFC to afford

[00459] P1 Example 68: (S)-N-(7-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (38.9 mg, 99% ee) as a white solid. LCMS: ESI m/z 601[M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.78 – 7.54 (m, 3H), 7.26 (m, 2H), 7.08 – 6.92 (m, 1H), 6.68 (s, 1H), 6.27 – 5.98 (m, 2H), 4.78 (s, 2H), 3.93 – 3.72 (m, 2H).

[00460] P2 Example 89: (R)-N-(7-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (35.1 mg, 99% ee) as a white solid. LCMS: ESI m/z 601[M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.78 – 7.54 (m, 3H), 7.26 (m, 2H), 7.08 – 6.92 (m, 1H), 6.68 (s, 1H), 6.27 – 5.98 (m, 2H), 4.78 (s, 2H), 3.93 – 3.72 (m, 2H).

[00461] Preparative separation method

Instrument: SHIMADZU PREP SOLUTION SFC

Column: ChiralPak IH, 250×20mm I.D., 5μm

Mobile phase: A for CO₂ and B for MeOH

Gradient: B 20%

Flow rate: 40mL /min

Back pressure: 100 bar

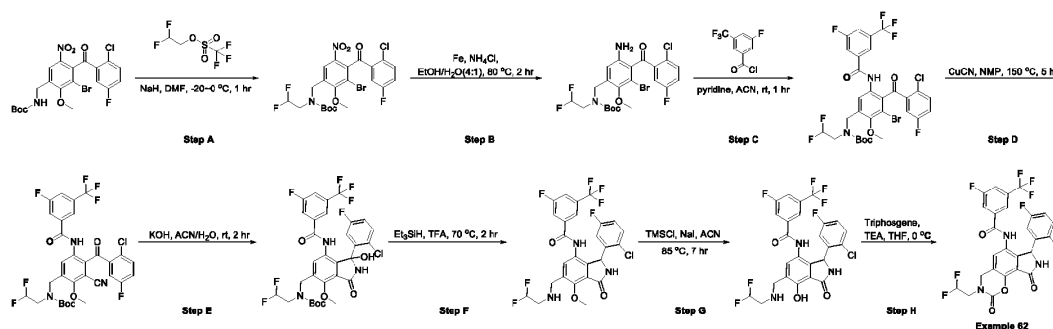
Column temperature: 35°C

Wavelength: 220nm

Cycle-time: 6min

Eluted time: 2H

Example 62 N-[7-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro[1,3]oxazino[6,5-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide



[00462] **Step A:** To a solution of 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl]amino]methanoate (750 mg, 1.449 mmol) in DMF (5 mL) at -20 °C was added NaH (289 mg, 7.24 mmol, 60% in mineral oil). The reaction was stirred at -20 °C for 10 min then 2,2-difluoroethyl trifluoromethanesulfonate (1550 mg, 7.243 mmol) was added dropwise. The reaction was stirred at 0 °C for 1 hr. The reaction mixture was quenched with water, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by chromatography eluted with PE/EA (100/1~15/1) to afford 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl](2,2-difluoroethyl)amino]methanoate (530 mg, 0.911 mmol, 63%) as a yellow oil. LCMS: m/z 483.0 [M+H-100]⁺

[00463] **Step B:** To a solution of 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl](2,2-difluoroethyl)amino]methanoate (530 mg, 0.911 mmol) in EtOH (6 mL) and H₂O (1.50 mL) were added Fe (254 mg, 4.55 mmol) and NH₄Cl (243 mg, 4.55 mmol). The reaction was stirred at 80 °C for 2 hr. The cooled reaction mixture was filtered, concentrated. The residue was diluted with water, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated to afford crude compound 2-methylpropan-2-yl [(5-amino-3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxyphenyl)methyl](2,2-difluoroethyl)amino]methanoate (500 mg, 0.725 mmol, 80%) as a yellow oil. LCMS: m/z 495.1 [M-56+H]⁺

[00464] **Step C:** To a solution of 2-methylpropan-2-yl [(5-amino-3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxyphenyl)methyl](2,2-difluoroethyl)amino]methanoate (330 mg, 0.598 mmol) in ACN (5 mL) were added pyridine (0.145 mL, 1.794 mmol) and 3-fluoro-5-(trifluoromethyl)benzoyl chloride (0.110 mL, 0.718 mmol). The reaction was stirred at rt for 1 hr. The reaction mixture was diluted water, extracted with EA. The organic layer was washed

with brine, dried over Na₂SO₄ and concentrated to afford crude compound 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-5-({[3-fluoro-5-(trifluoromethyl)phenyl]carbonyl}amino)-2-methoxyphenyl)methyl](2,2-difluoroethyl)amino]methanoate (400 mg, 0.539 mmol, 90%) as a yellow oil. LCMS: m/z 741.0 [M-H]⁻.

[00465] **Step D:** To a solution of 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-5-({[3-fluoro-5-(trifluoromethyl)phenyl]carbonyl}amino)-2-methoxyphenyl)methyl](2,2-difluoroethyl)amino]methanoate (350 mg, 0.472 mmol) in NMP (5 mL) was added CuCN (126 mg, 1.41 mmol). The reaction mixture was degassed with N₂ and it was stirred under N₂ atmosphere at 150 °C for 5 hr. The cooled reaction mixture was diluted with water, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with EA/PE (1/100~2/1) to afford compound 2-methylpropan-2-yl [(4-[(2-chloro-5-fluorophenyl)carbonyl]-3-cyano-5-({[3-fluoro-5-(trifluoromethyl)phenyl]carbonyl}amino)-2-methoxyphenyl)methyl](2,2-difluoroethyl)amino]methanoate (200 mg, 0.291 mmol, 62%) as a yellow oil. LCMS: m/z 588.3 [M+H-100]⁺.

[00466] **Step E:** To a solution of 2-methylpropan-2-yl [(4-[(2-chloro-5-fluorophenyl)carbonyl]-3-cyano-5-({[3-fluoro-5-(trifluoromethyl)phenyl]carbonyl}amino)-2-methoxyphenyl)methyl](2,2-difluoroethyl)amino]methanoate (500 mg, 0.727 mmol) in ACN (5 mL) and H₂O (1.00 mL) was added KOH (203.89 mg, 3.634 mmol). The reaction was stirred at rt for 2 hr. The reaction mixture was diluted with water, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (1%~60%) to afford compound 2-methylpropan-2-yl ([1-(2-chloro-5-fluorophenyl)-7-({[3-fluoro-5-(trifluoromethyl)phenyl]carbonyl}amino)-1-hydroxy-4-methoxy-3-oxo-2,3-dihydro-1H-isoindol-5-yl]methyl)(2,2-difluoroethyl)amino]methanoate (300 mg, 0.425 mmol, 58%) as a white solid. LCMS: m/z 704.0 [M-H]⁻.

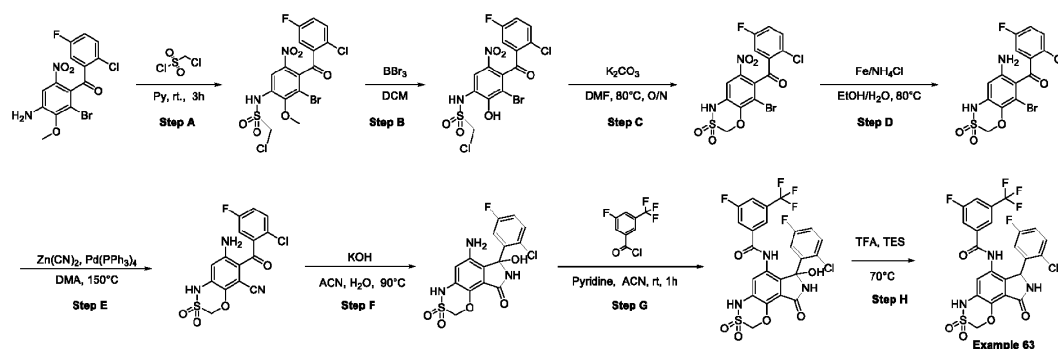
[00467] **Step F:** To a solution of 2-methylpropan-2-yl ([1-(2-chloro-5-fluorophenyl)-7-({[3-fluoro-5-(trifluoromethyl)phenyl]carbonyl}amino)-1-hydroxy-4-methoxy-3-oxo-2,3-dihydro-1H-isoindol-5-yl]methyl)(2,2-difluoroethyl)amino]methanoate (150 mg, 0.212 mmol) in TFA (5 mL) was added Et₃SiH (246.51 mg, 2.120 mmol). The reaction mixture was stirred at 70 °C for 2

hr. The cooled reaction mixture was concentrated. The residue was diluted with aqueous NaHCO₃, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with ethyl acetate in DCM (0%~10%) to afford compound N-[3-(2-chloro-5-fluorophenyl)-6-{{(2,2-difluoroethyl)amino}methyl}-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide (100 mg, 0.170 mmol, 80%) as a yellow oil. LCMS: m/z 590.1 [M+H]⁺.

[00468] **Step G:** To a solution of N-[3-(2-chloro-5-fluorophenyl)-6-{{(2,2-difluoroethyl)amino}methyl}-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide (10 mg, 0.017 mmol) in ACN (5 mL) was added TMSCl (9.21 mg, 0.085 mmol) and NaI (12.7 mg, 0.085 mmol, 60% in mineral oil). The reaction mixture was stirred at 85 °C for 7 hr. The cooled reaction mixture was diluted water, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated in vacuo to afford compound N-[3-(2-chloro-5-fluorophenyl)-6-{{(2,2-difluoroethyl)amino}methyl}-7-hydroxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide (100 mg, 0.174 mmol, 68 %) as a yellow oil. LCMS: m/z 576.3 [M+H]⁺

[00469] **Step H:** To a solution of N-[3-(2-chloro-5-fluorophenyl)-6-{{(2,2-difluoroethyl)amino}methyl}-7-hydroxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide (10 mg, 0.017 mmol) in THF (3 mL) was added TEA (0.002 mL, 0.017 mmol). Trichloromethyl [(trichloromethyl)oxy]methanoate (1.55 mg, 0.005 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Then the reaction mixture was concentrated to give a residue, which was purified by prep-HPLC (acetonitrile with 0.1% FA in water 30% to 70%) to give N-[7-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro[1,3]oxazino[6,5-e]isoindol-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (3 mg, 0.005 mmol, 28%) as a white solid. LCMS: m/z 602.1 [M+H]⁺. ¹HNMR(400 MHz, CD₃OD) δ 7.74 – 7.57 (m, 3H), 7.38 (s, 1H), 7.26 (dd, J = 8.8, 5.0 Hz, 1H), 7.04 – 6.94 (m, 1H), 6.65 (brs, 1H), 6.39 – 5.99 (m, 2H), 4.78 (s, 2H), 3.97 – 3.79 (m, 2H).

Example 63 N-(7-(2-chloro-5-fluorophenyl)-3,3-dioxido-9-oxo-4,7,8,9-tetrahydro-2H-[1,3,4]oxathiazino[6,5-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00470] **Step A:** To a solution of (4-amino-2-bromo-3-methoxy-6-nitrophenyl)(2-chloro-5-fluorophenyl)methanone (800 mg, 1.98 mmol) in pyridine (10 mL) was added chloromethanesulfonyl chloride (369 mg, 2.48 mmol). The reaction mixture was stirred at 25 °C for 3 hours. The mixture was diluted with H₂O, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with 0-30% ethyl acetate in petroleum ether to afford N-(3-bromo-4-(2-chloro-5-fluorobenzoyl)-2-methoxy-5-nitrophenyl)-1-chloromethanesulfonamide (560 mg, 0.98 mmol, 49%) as a yellow solid. LCMS: ESI m/z 515 [M + H]⁺.

[00471] **Step B:** To a solution of N-(3-bromo-4-(2-chloro-5-fluorobenzoyl)-2-methoxy-5-nitrophenyl)-1-chloromethanesulfonamide (560 mg, 1.09 mmol) in DCM (10 mL) was added tribromoborane (815 mg, 3.26 mmol). The reaction mixture was stirred at 25 °C overnight. The mixture was diluted with aqueous NaHCO₃, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with 0-50% ethyl acetate in petroleum ether to afford N-(3-bromo-4-(2-chloro-5-fluorobenzoyl)-2-hydroxy-5-nitrophenyl)-1-chloromethanesulfonamide (320 mg, 0.57 mmol, 53%) as a yellow solid. LCMS: ESI m/z 501 [M + H]⁺.

[00472] **Step C:** To a solution of N-(3-bromo-4-(2-chloro-5-fluorobenzoyl)-2-hydroxy-5-nitrophenyl)-1-chloromethanesulfonamide (320 mg, 0.64 mmol) in DMF (5 mL) was added K₂CO₃ (265 mg, 1.9 mmol). The reaction mixture was stirred at 80 °C overnight. The cooled mixture was diluted with H₂O, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with 0-30% ethyl acetate in petroleum ether to afford compound (5-bromo-7-nitro-2,2-dioxido-1H,3H-benzo[e][1,3,4]oxathiazin-6-yl)(2-chloro-5-

fluorophenyl)methanone (200 mg, 0.39 mmol, 61%) as a yellow solid. LCMS: ESI m/z 465 [M + H]⁺.

[00473] **Step D:** To a solution of (5-bromo-7-nitro-2,2-dioxido-1H,3H-benzo[e][1,3,4]oxathiazin-6-yl)(2-chloro-5-fluorophenyl)methanone (200 mg, 0.43 mmol) in EtOH (3 mL) and H₂O (0.5 mL) was added NH₄Cl (115 mg, 2.15 mmol) and Fe (120 mg, 2.15 mmol). The mixture was stirred at 85 °C for 3 hours. The cooled reaction mixture was filtered through Buchner funnel. The filtrate was concentrated under vacuum. The residue was purified using silica gel column chromatography eluting with 0-30% ethyl acetate in petroleum ether to afford compound (7-amino-5-bromo-2,2-dioxido-1H,3H-benzo[e][1,3,4]oxathiazin-6-yl)(2-chloro-5-fluorophenyl)methanone (150 mg, 0.31 mmol, 72%) as a yellow solid. LCMS: ESI m/z 635 [M + H]⁺.

[00474] **Step E:** To a solution of (7-amino-5-bromo-2,2-dioxido-1H,3H-benzo[e][1,3,4]oxathiazin-6-yl)(2-chloro-5-fluorophenyl)methanone (150 mg, 0.34 mmol) in DMA (3 mL) was added Zn(CN)₂ (121 mg, 1.03 mmol) and palladium(0) tetrakis(triphenylphosphane) (80 mg, 0.07 mmol). The mixture was stirred at 150 °C under N₂ for 5 hour. The cooled mixture was diluted with H₂O, extracted with EA. The organic layer was washed with and brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with 0-100% ethyl acetate in petroleum ether to afford compound 7-amino-6-(2-chloro-5-fluorobenzoyl)-1H,3H-benzo[e][1,3,4]oxathiazine-5-carbonitrile 2,2-dioxide (70 mg, 0.18 mmol, 53%) as a yellow solid. LCMS: ESI m/z 382 [M + H]⁺.

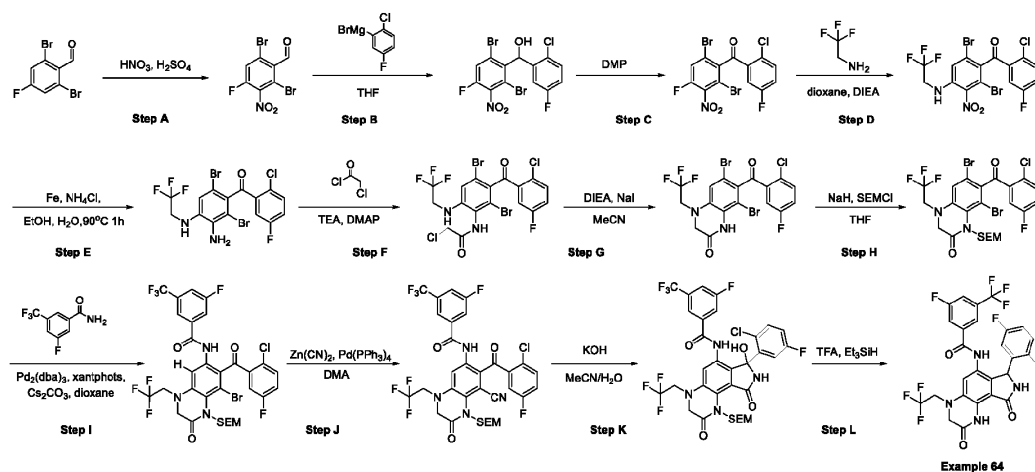
[00475] **Step F:** To a solution of 7-amino-6-(2-chloro-5-fluorobenzoyl)-1H,3H-benzo[e][1,3,4]oxathiazine-5-carbonitrile 2,2-dioxide (60 mg, 0.157 mmol) in CH₃CN (5 mL) and H₂O (0.5 mL) was added potassium hydroxide (26 mg, 0.47 mmol). The mixture was stirred at 90 °C for 1 hour. The cooled mixture was diluted with H₂O, extracted with EA. The organic layer was washed with and brine, dried over Na₂SO₄ and concentrated to afford compound 6-amino-7-(2-chloro-5-fluorophenyl)-7-hydroxy-7,8-dihydro-2H-[1,3,4]oxathiazino[6,5-e]isoindol-9(4H)-one 3,3-dioxide (60 mg, 0.075 mmol, crude) as a yellow solid. LCMS: ESI m/z 400 [M + H]⁺.

[00476] **Step G:** To a solution of 6-amino-7-(2-chloro-5-fluorophenyl)-7-hydroxy-7,8-dihydro-2H-[1,3,4]oxathiazino[6,5-e]isoindol-9(4H)-one 3,3-dioxide (60 mg, 0.15

mmol) in CH₃CN (5 mL) was added pyridine (0.06 mL, 0.75 mmol) and 5-fluoro-3-(trifluoromethyl)benzoyl chloride (102 mg, 0.45 mmol). The mixture was stirred at 25 °C for 1 hour. The mixture was diluted with H₂O, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with 0-10% methanol in dichloroform to afford compound N-(7-(2-chloro-5-fluorophenyl)-7-hydroxy-3,3-dioxido-9-oxo-4,7,8,9-tetrahydro-2H-[1,3,4]oxathiazino[6,5-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (60 mg, 0.05 mmol, 34%) as a yellow solid. LCMS: ESI m/z 590 [M + H]⁺.

[00477] **Step H:** To a solution of N-(7-(2-chloro-5-fluorophenyl)-7-hydroxy-3,3-dioxido-9-oxo-4,7,8,9-tetrahydro-2H-[1,3,4]oxathiazino[6,5-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (60 mg, 0.1 mmol) in TFA (2 mL) was added Et₃SiH (59 mg, 0.5 mmol). The mixture was stirred at 70 °C for 1 hour. The cooled mixture was concentrated under vacuum. The residue was purified using prep-HPLC to afford compound N-(7-(2-chloro-5-fluorophenyl)-3,3-dioxido-9-oxo-4,7,8,9-tetrahydro-2H-[1,3,4]oxathiazino[6,5-e]isoindol-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (3.2 mg, 0.006 mmol, 5%) as a white solid. LCMS: ESI m/z 574 [M + H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.71 – 7.57 (m, 3H), 7.29 – 7.22 (m, 1H), 7.06 – 6.94 (m, 2H), 6.66 (brs, 1H), 6.10 (brs, 1H), 5.22 (d, *J*_{AB} = 11.2 Hz, 1H), 5.18 (d, *J*_{AB} = 11.2 Hz, 1H).

Example 64 N-[7-(2-chloro-5-fluorophenyl)-2,9-dioxo-4-(2,2,2-trifluoroethyl)-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-f]quinoxalin-6-yl]-3-fluoro-5-(trifluoromethyl)benzamide



[00478] **Step A:** To a solution of 2,6-dibromo-4-fluorobenzene-1-carbaldehyde (10 g, 35.4 mmol) in con. H₂SO₄ (100 mL) was added dropwise con. HNO₃ (1.48 mL, 35.4 mmol) at 0 °C. The reaction mixture was stirred at RT for 2 h. The reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to afford compound 2,6-dibromo-4-fluoro-3-nitrobenzene-1-carbaldehyde (10 g, 30.5 mmol, 86%) as a brown solid. LCMS: ESI m/z 327 [M + H]⁺.

[00479] **Step B:** To a solution of 2,6-dibromo-4-fluoro-3-nitrobenzene-1-carbaldehyde (10 g, 30.5 mmol) in THF (100 mL) was added bromo(2-chloro-5-fluorophenyl)magnesium (152 mL, 152 mmol, 1M) at 0 °C. The reaction mixture was stirred at RT for 2h. The reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient : 0-10%] to afford compound (2-chloro-5-fluorophenyl)(2,6-dibromo-4-fluoro-3-nitrophenyl)methanol (6 g, 13.1 mmol, 42%) as a yellow solid. LCMS: ESI m/z 457 [M + H]⁺.

[00480] **Step C:** To a solution of (2-chloro-5-fluorophenyl)(2,6-dibromo-4-fluoro-3-nitrophenyl)methanol (5.5 g, 12.0 mmol) in DCM (70 mL) was added 1,1,1-triacetoxy-1,3-dihydro-1λ5-benzo[d][1,2]iodoxol-3-one (10.2 g, 24.0 mmol). The reaction mixture was stirred at RT for 2 h. The reaction mixture was quenched with Na₂S₂O₃, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient : 0-50%] to afford compound (2-chloro-5-fluorophenyl)(2,6-dibromo-4-fluoro-3-nitrophenyl)methanone (5 g, 10.9 mmol, 91%) as a white solid. LCMS: ESI m/z 455 [M + H]⁺.

[00481] **Step D:** To a solution of (2-chloro-5-fluorophenyl)(2,6-dibromo-4-fluoro-3-nitrophenyl)methanone (5 g, 10.9 mmol) in dioxane (50 mL) were added DIEA (4.26 g, 32.9 mmol) and 2,2,2-trifluoroethan-1-amine (2.1 g, 21.9 mmol). The reaction mixture was stirred at RT overnight. The reaction mixture was concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient : 0-30%] to afford compound (2-chloro-5-fluorophenyl){2,6-dibromo-3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}methanone (3 g, 5.61 mmol, 51%) as a white solid. LCMS: ESI m/z 534 [M + H]⁺.

[00482] **Step E:** To a solution of (2-chloro-5-fluorophenyl){2,6-dibromo-3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}methanone (3 g, 5.61 mmol) in EtOH (30 mL) and H₂O

(5 mL) were added Fe (1.57 g, 28.0 mmol) and NH₄Cl (3.0 g, 56.1 mmol). The reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was cooled to rt, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient : 0-50%] to afford compound {3-amino-2,6-dibromo-4-[(2,2,2-trifluoroethyl)amino]phenyl}(2-chloro-5-fluorophenyl)methanone (2.5 g, 4.9 mmol, 88%) as a white solid. LCMS: ESI m/z 504 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.72 – 7.65 (m, 1H), 7.60 – 7.48 (m, 1H), 7.29 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.98 (s, 1H), 6.06 (t, *J* = 6.4 Hz, 1H), 5.26 (s, 2H), 4.20 – 4.08 (m, 2H).

[00483] **Step F:** To a solution of {3-amino-2,6-dibromo-4-[(2,2,2-trifluoroethyl)amino]phenyl}(2-chloro-5-fluorophenyl)methanone (3.1 g, 6.14 mmol) in DMF (30 mL) were added pyridine (1.5 mL, 18.4 mmol) and chloroacetyl chloride (0.6 mL, 7.37 mmol). The reaction mixture was stirred at RT for 2 h. The reaction mixture was quenched with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient : 0-60%] to afford compound 2-chloro-N-{2,4-dibromo-3-[(2-chloro-5-fluorophenyl)carbonyl]-6-[(2,2,2-trifluoroethyl)amino]phenyl}acetamide (1.5 g, 2.58 mmol, 42.%) as a white solid. LCMS: ESI m/z 581 [M + H]⁺.

[00484] **Step G:** To a solution of 2-chloro-N-{2,4-dibromo-3-[(2-chloro-5-fluorophenyl)carbonyl]-6-[(2,2,2-trifluoroethyl)amino]phenyl}acetamide (1.5 g, 2.58 mmol) in CH₃CN (15 mL) was added DIEA (0.67 g, 5.16 mmol). The reaction mixture was stirred at 130 °C for 1h. The cooled reaction mixture was concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient : 0-50%] to afford compound 6,8-dibromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-4-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroquinoxalin-2-one (500 mg, 0.918 mmol, 35%) as a white solid. LCMS: ESI m/z 544 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.99 (s, 1H), 7.73 – 7.69 (m, 1H), 7.61 – 7.56 (m, 1H), 7.45 – 7.41 (m, 1H), 7.39 (s, 1H), 4.50 – 4.37 (m, 2H), 4.04 (s, 3H).

[00485] **Step H:** To a solution of 6,8-dibromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-4-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroquinoxalin-2-one (1500 mg, 2.755 mmol) in THF (15 mL) were added NaH (220 mg, 5.51 mmol, 60% in mineral oil) and 1-chloro-5,5-dimethyl-2-oxa-5-silahexane (688 mg, 4.13 mmol). The reaction mixture was stirred at RT for 1 h. The reaction mixture was quenched with H₂O, extracted with EA. The organic phase was washed

with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient : 0-40%] to afford compound 6,8-dibromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-4-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroquinoxalin-2-one (500 mg, 0.741 mmol, 27%) as a white solid. LCMS: ESI m/z 675 [M + H]⁺

[00486] **Step I:** To a solution of 6,8-dibromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-4-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroquinoxalin-2-one (500 mg, 0.741 mmol) in dioxane (6 mL) were added 5-fluoro-3-(trifluoromethyl)benzene-1-carboxamide (228 mg, 1.1 mmol), Pd₂(dba)₃ (84.1 mg, 0.092 mmol), Xantphos (106 mg, 0.184 mmol) and Cs₂CO₃ (598 mg, 1.83 mmol). The reaction mixture was stirred at 100 °C for 5 h. The reaction mixture was quenched with H₂O, extracted with EA, washed with brine, filtered and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 0-50%] to afford compound N-{8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-2-oxo-4-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroquinoxalin-6-yl}-3-fluoro-5-(trifluoromethyl)benzamide (300 mg, 0.375 mmol, 50%) as a white solid. LCMS: ESI m/z 801 [M + H]⁺.

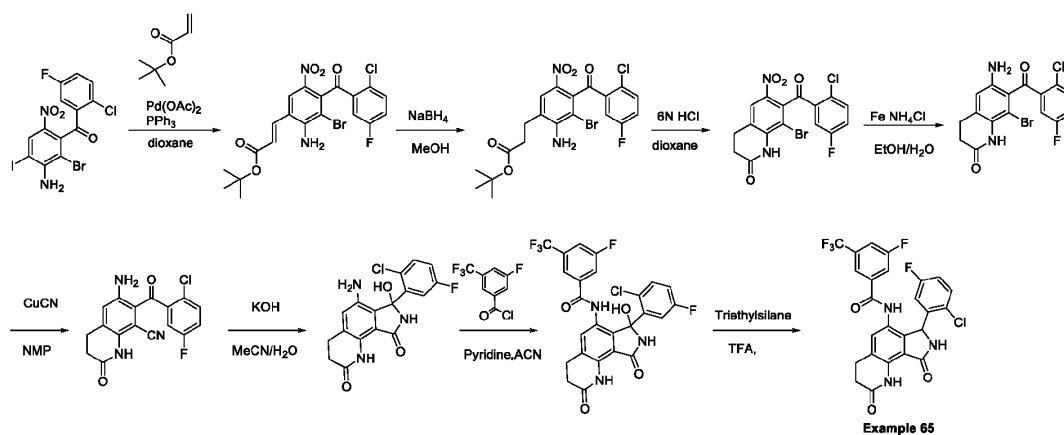
[00487] **Step J:** To a solution of N-{8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-2-oxo-4-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroquinoxalin-6-yl}-3-fluoro-5-(trifluoromethyl)benzamide (130 mg, 0.162 mmol) in DMA (3 mL) were added Pd(PPh₃)₄ (18.7 mg, 0.016 mmol) and Zn(CN)₂ (38.1 mg, 0.325 mmol). The reaction mixture was stirred at 150 °C 1 h at MW. The reaction mixture was diluted with H₂O, extracted with EA, washed with brine, filtered, and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient : 0-80%] to afford compound N-{7-[(2-chloro-5-fluorophenyl)carbonyl]-8-cyano-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-2-oxo-4-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroquinoxalin-6-yl}-3-fluoro-5-(trifluoromethyl)benzamide (30 mg, 0.040 mmol, 24%) as a yellow solid. LCMS: ESI m/z 747 [M + H]⁺.

[00488] **Step K:** To a solution of N-{7-[(2-chloro-5-fluorophenyl)carbonyl]-8-cyano-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-2-oxo-4-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroquinoxalin-6-yl}-3-fluoro-5-(trifluoromethyl)benzamide (30 mg, 0.040 mmol) in CH₃CN (1 mL) and H₂O (0.5 mL) was added KOH (4.5 mg, 0.080 mmol). The reaction mixture was stirred at RT 10 min. The reaction mixture was diluted with H₂O, extracted with EA. The organic phase was

washed with brine, dried over Na_2SO_4 and concentrated to afford compound N-[7-(2-chloro-5-fluorophenyl)-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-7-hydroxy-2,9-dioxo-4-(2,2,2-trifluoroethyl)-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-f]quinoxalin-6-yl]-3-fluoro-5-(trifluoromethyl)benzamide (30 mg, 0.039 mmol, 97%) as a yellow solid. LCMS: ESI m/z 765 $[\text{M} + \text{H}]^+$.

[00489] **Step L:** To a solution of N-[7-(2-chloro-5-fluorophenyl)-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-7-hydroxy-2,9-dioxo-4-(2,2,2-trifluoroethyl)-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-f]quinoxalin-6-yl]-3-fluoro-5-(trifluoromethyl)benzamide (30 mg, 0.039 mmol) in TFA (1 mL) was added Et_3SiH (22.8 mg, 0.196 mmol). The reaction mixture was stirred at 60 °C for 30 min. The cooled reaction mixture was concentrated. The residue was purified by prep-HPLC to afford compound N-[7-(2-chloro-5-fluorophenyl)-2,9-dioxo-4-(2,2,2-trifluoroethyl)-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-f]quinoxalin-6-yl]-3-fluoro-5-(trifluoromethyl)benzamide (2.4 mg, 0.004 mmol, 9%) as a white solid. LCMS: ESI m/z 801 $[\text{M} + \text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.33 (s, 1H), 9.65 (s, 1H), 9.25 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.67 (s, 1H), 7.35 – 7.27 (m, 1H), 7.21 (s, 1H), 7.16 – 7.06 (m, 1H), 7.00 (s, 1H), 5.90 (s, 1H), 4.63 – 4.19 (m, 2H), 4.17 (s, 2H).

Example 65 N-(7-(2-chloro-5-fluorophenyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00490] **Step A:** To a stirred mixture of (3-amino-2-bromo-4-iodo-6-nitrophenyl)(2-chloro-5-fluorophenyl)methanone (100 mg, 0.200 mmol) in dioxane (3 mL) was added dropwise PPh_3 (10.5 mg, 0.04 mmol) 2-methylpropan-2-yl prop-2-enoate (51 mg, 0.400 mmol) and $\text{Pd}(\text{OAc})_2$ (4.5 mg, 0.020 mmol) at rt under N_2 atmosphere. The mixture was stirred 100 °C overnight. The

cooled reaction was quenched with water at rt. The resulting mixture was extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 55%] to afford compound 2-methylpropan-2-yl (2E)-3-{2-amino-3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-5-nitrophenyl}prop-2-enoate (70 mg, 0.14 mmol, 70 %) as a white solid. LCMS: ESI m/z 501 [M+H]⁺

[00491] **Step B:** To a stirred mixture of 2-methylpropan-2-yl (2E)-3-{2-amino-3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-5-nitrophenyl}prop-2-enoate (50 mg, 0.100 mmol) in MeOH (3 mL) was added dropwise NaBH₄ (20 mg, 0.529 mmol) at 0 °C. The mixture was stirred at RT for an additional 1h. The reaction was quenched with water at RT. The resulting mixture was extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified using silica gel column chromatography eluting with EA in RE [Gradient: 47%] to afford compound 2-methylpropan-2-yl 3-{2-amino-3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-5-nitrophenyl}propanoate (25 mg, 0.050 mmol, 50%) as a white solid. LCMS: ESI m/z 503 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.97 (s, 1H), 7.71 – 7.53 (m, 3H), 6.97 (s, 2H), 2.91 (t, *J* = 7.0 Hz, 2H), 2.57 (t, *J* = 7.0 Hz, 2H), 1.38 (s, 9H).

[00492] **Step C:** To a solution of 2-methylpropan-2-yl 3-{2-amino-3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-5-nitrophenyl}propanoate (10 mg, 0.020 mmol) in dioxane (3 mL) were added 6N HCl (0.080 mL, 0.040 mmol) and (bromomethyl)benzene (2 mL, 15.6 mmol). The reaction mixture was stirred at 60 °C for 2h. The reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried by Na₂SO₄, filtered and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 40%] to afford compound 8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-6-nitro-1,2,3,4-tetrahydroquinolin-2-one (5 mg, 0.012 mmol, 59%) as a white solid. LCMS: ESI m/z 429 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.96 (s, 1H), 8.33 (s, 1H), 7.76 – 7.43 (m, 3H), 3.19 – 3.06 (m, 2H), 2.68 – 2.55 (m, 2H).

[00493] **Step D:** To a solution of 8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-6-nitro-1,2,3,4-tetrahydroquinolin-2-one (50 mg, 0.116 mmol) in EtOH/H₂O (8 mL) were added Fe (32 mg, 0.584 mmol) and NH₄Cl (31 mg, 0.584 mmol). The reaction mixture was stirred at 70 °C

for 3h. The cooled reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried by Na₂SO₄, filtered and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 35%] to afford compound 6-amino-8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-1,2,3,4-tetrahydroquinolin-2-one (40 mg, 0.101 mmol, 90%) as a white solid. LCMS: ESI m/z 398 [M+H]⁺

[00494] **Step E:** To a solution of 6-amino-8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-1,2,3,4-tetrahydroquinolin-2-one (40 mg, 0.101 mmol) in NMP (6 mL) were added CuCN (40 mg, 0.201 mmol). The reaction mixture was stirred at 150 °C for 1h. The reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried by Na₂SO₄, filtered and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 30%] to afford compound 6-amino-7-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-1,2,3,4-tetrahydroquinoline-8-carbonitrile (20 mg, 0.058 mmol, 58%) as a white solid. LCMS: ESI m/z 344 [M+H]⁺.

[00495] **Step F:** To a solution of 6-amino-7-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-1,2,3,4-tetrahydroquinoline-8-carbonitrile (20 mg, 0.058 mmol) in MeCN/H₂O (4 mL) were added potassium hydroxide (10 mg, 0.174 mmol). The reaction mixture was stirred at RT for 1h. The reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried by Na₂SO₄, filtered and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 35%] to afford compound 7-bromo-4-chloro-1-(2-chloro-5-fluorophenyl)-1-hydroxy-2-[(4-methoxyphenyl)methyl]-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-3-one (10 mg, 0.014 mmol, 70%) as a white solid. LCMS: ESI m/z 362 [M+H]⁺

[00496] **Step G:** To a solution of 6-amino-7-(2-chloro-5-fluorophenyl)-7-hydroxy-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinoline-2,9-dione (10 mg, 0.028 mmol) in ACN (5 mL) were added pyridine (0.1 mL, 0.840 mmol) and 5-fluoro-3-(trifluoromethyl) benzoyl chloride (6.26 mg, 0.028 mmol). The reaction mixture was stirred at RT for 1h. The reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried by Na₂SO₄, filtered and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 45%] to afford compound N-[7-(2-chloro-5-fluorophenyl)-7-hydroxy-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinolin-6-yl]-5-

fluoro-3-(trifluoromethyl)benzamide (10 mg, 0.018 mmol, 65%) as a white solid. LCMS: ESI m/z 552 $[M+H]^+$

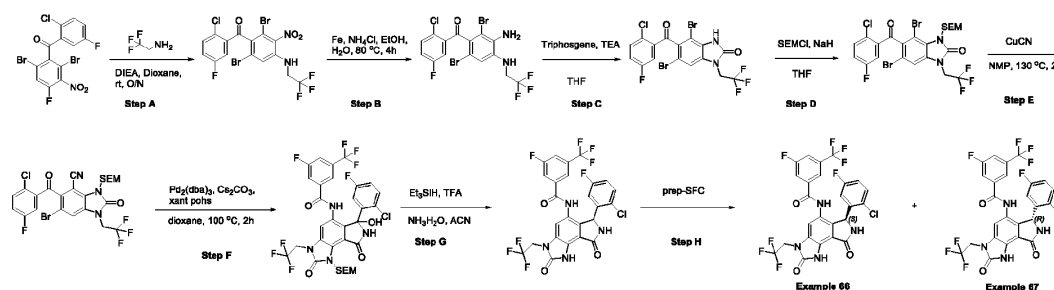
[00497] **Step H:** To a solution of N-[7-(2-chloro-5-fluorophenyl)-7-hydroxy-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (10 mg, 0.018 mmol) in TFA (5 mL) were dropwise added triethylsilane (2.11 mg, 0.018 mmol). The reaction mixture was stirred at 70 °C for 2h. The cooled reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried by Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC to afford compound N-[7-(2-chloro-5-fluorophenyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (0.9 mg, 0.002 mmol, 10%) as a white solid. LCMS: ESI m/z 536 $[M+H]^+$. ¹H NMR (400 MHz, CD₃OD) δ 7.66 – 7.62 (m, 2H), 7.36 – 7.15 (m, 2H), 7.08 – 6.89 (m, 1H), 6.67 (s, 1H), 6.14 (s, 1H), 2.82 – 2.67 (m, 2H), 2.16 (t, J = 8.0 Hz, 2H).

Example 66 (S)-N-(6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-

1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 67 (R)-N-(6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-

1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00498] **Step A:** To a solution of (2-chloro-5-fluorophenyl) (2,6-dibromo-4-fluoro-3-nitrophenyl) methanone (14 g, 30.7 mmol) in dioxane (15 mL) was added DIPEA (10.7 mL, 61.5 mmol) and 2,2,2-trifluoroethan-1-amine (7.24 mL, 92.2 mmol). The reaction was stirred at rt O/N. The reaction mixture was diluted with water, extracted with EA (100 mL*3). The organic layer was separated, washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 5-8%) to afford (2-chloro-5-fluorophenyl) {2,6-dibromo-3-nitro-4-

[(2,2,2-trifluoroethyl) amino] phenyl} methanone (4.9 g, 9.2 mmol, 30%) as a yellow solid.

LCMS: m/z 533, 535[M-H].

[00499] **Step B:** To a solution of (2-chloro-5-fluorophenyl) {2,6-dibromo-3-nitro-4-[(2,2,2-trifluoroethyl) amino] phenyl} methanone (3 g, 5.6 mmol) in EtOH (28 mL) was added Fe (3.13 g, 56.1 mmol) and sat. NH₄Cl (7 mL). The reaction was stirred at 80°C for 3h. The reaction mixture was filtrated and concentrated in vacuo, water was added, and the mixture was extracted with EtOAc (100 mL*3). The organic layer was separated, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 20%) to afford {3-amino-2,6-dibromo-4-[(2,2,2-trifluoroethyl) amino] phenyl} (2-chloro-5-fluorophenyl) methanone (2 g, 4.0 mmol, 71%) as an orange solid. LCMS: m/z 505 [M+H]⁺.

[00500] **Step C:** To a solution of {3-amino-2,6-dibromo-4-[(2,2,2-trifluoroethyl) amino] phenyl} (2-chloro-5-fluorophenyl) methanone (1.7 g, 3.4 mmol), TEA (0.94 mL, 6.74 mmol) in anhydrous THF (20 mL) was added trichloromethyl [(trichloromethyl) oxy] methanoate (1.20 g, 4.1 mmol) at 0°C and the mixture was stirred at rt for 2h. The reaction mixture was quenched by water, and the mixture was extracted with EtOAc (100 mL*3). The organic layer was separated, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 0%~20%) to afford 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (1.7 g, 3.2 mmol, 95%) as an off-white solid. LCMS: m/z 531 [M+H]⁺.

[00501] **Step D:** To the suspension of NaH (0.24 g, 10.2 mmol) in dry THF (20 mL), 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (1.8 g, 3.4 mmol) was added in portions at 0°C. After the completion of addition, the mixture was stirred for additional 1 hour at 0°C. Then 1-chloro-5,5-dimethyl-2-oxa-5-silahexane (0.60 mL, 3.4 mmol) was added slowly, the mixture was stirred for 10 min at 0°C, then warmed up to room temperature and stirred for 2 hrs. The reaction mixture was quenched by water, and the mixture was extracted with EtOAc (100 mL*3). The organic layer was separated, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 0%~20%) to afford 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-3-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (1.5 g, 2.27 mmol,

66.9%) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.93 (s, 1H), 7.80 – 7.68 (m, 1H), 7.64 – 7.55 (m, 1H), 7.45 (d, J = 6.4 Hz, 1H), 5.51 (s, 2H), 4.93 (d, J = 9.2 Hz, 2H), 3.56 (t, J = 8.0 Hz, 2H), 0.82 (t, J = 8.0 Hz, 2H), -0.05 – -0.15 (m, 9H).

[00502] **Step E:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-3-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d] imidazol-2-one (500 mg, 0.76 mmol) in NMP (1 mL) was added CuCN (67.8 mg, 0.76 mmol) and the mixture was stirred at 130 °C for 3h. The cooled reaction mixture was diluted with water, extracted with EtOAc (50 mL*3). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 0%~12%) to afford 6-bromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-3-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-2-oxo-1-(2,2,2-trifluoroethyl) benzo[d] imidazole-4-carbonitrile (100 mg, 0.17 mmol, 22%) as a yellow oil.

[00503] **Step F:** To a solution of 6-bromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-3-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-2-oxo-1-(2,2,2-trifluoroethyl) benzo[d] imidazole-4-carbonitrile (350 mg, 0.58 mmol), Cs₂CO₃ (563.7 mg, 1.7 mmol), Xant-PHOS (33.4 mg, 0.058 mmol) and 3-fluoro-5-(trifluoromethyl) benzene-1-carboxamide (119 mg, 0.58 mmol) in anhydrous dioxane (3 mL) was added Pd₂(dba)₃ (52.8 mg, 0.06 mmol). The reaction mixture was stirred at 100 °C for 2h. The cooled reaction mixture was concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 0%~15%) to afford N-[6-(2-chloro-5-fluorophenyl)-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-6-hydroxy-2,8-dioxo-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl) benzamide (80 mg, 0.11 mmol, 18%) as a yellow oil.

[00504] **Step G:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-6-hydroxy-2,8-dioxo-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl) benzamide (60 mg, 0.08 mmol) in TFA (1 mL) was added triethylsilane (0.1 mL, 0.01 mmol), and the mixture was stirred at 70 °C for 1h. The cooled reaction mixture was concentrated in vacuo, ACN (1 mL) and ammonium hydroxide (0.1 mL, 0.01mmol) was added, and the mixture was stirred at rt for 1h. The reaction mixture was concentrated in vacuo. The residue was purified by prep-TLC (PE: EA=1:2) to afford N-[6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-1,6,7,8-tetrahydroimidazo[4,5-

e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (28 mg, 0.046 mmol, 58%) as a white solid. LCMS (ESI): m/z 605 [M+H]⁺

[00505] **Step H:** N-[6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-1,6,7,8-tetrahydroimidazo[4,5-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl) benzamide (28 mg, 0.046 mmol) was separated by prep-SFC to give

[00506] P1: Example 66 (S)-N-(6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (9.7 mg, 0.016 mmol, 69%) as a white solid. LCMS: ESI m/z 605 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.93 (s, 1H), 10.36 (s, 1H), 9.08 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 9.2 Hz, 1H), 7.69 (s, 1H), 7.38 (s, 1H), 7.32 – 7.25 (m, 1H), 7.09 (t, J = 6.8 Hz, 1H), 5.98 (s, 1H), 4.88 – 4.74 (m, 2H).

[00507] P2: Example 67 (S)-N-(6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (9.3 mg, 0.015 mmol, 66%) as a white solid. LCMS: ESI m/z 605 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.93 (s, 1H), 10.36 (s, 1H), 9.08 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 9.2 Hz, 1H), 7.69 (s, 1H), 7.38 (s, 1H), 7.33 – 7.25 (m, 1H), 7.09 (t, J = 6.8 Hz, 1H), 5.97 (s, 1H), 4.86 – 4.75 (m, 2H).

[00508] Preparative SFC separation method:

Instrument: SHIMADZU PREP SOLUTION SFC

Column: ChiralPak IB, 250×30mm I.D., 5μm

Mobile phase: A for CO₂ and B for MEOH

Gradient: B 10%

Flow rate: 60mL /min

Back pressure: 100 bar

Column temperature: 35°C

Wavelength: 220 nm

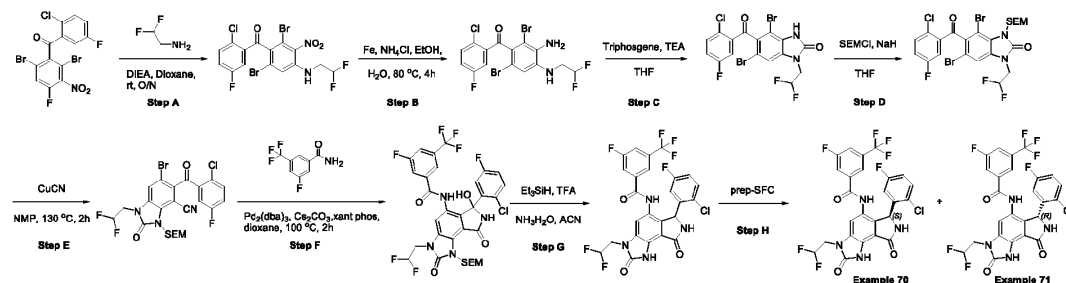
Cycle-time: 30 min

Eluted time: 4H

Example 70 (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 71 (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-1,2,3,6,7,8-

hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00509] **Step A:** To a solution of (2-chloro-5-fluorophenyl) (2,6-dibromo-4-fluoro-3-nitrophenyl) methanone (10 g, 22.0 mmol) in dioxane (10 mL) was added DIPEA (3.8 mL, 22.0 mmol) and 2-amino-1,1-diethoxyethane (3.8 mL, 22.0 mmol). The reaction was stirred at rt O/N. The reaction mixture was diluted with water, extracted with EtOAc (150 mL*3). The organic layer was separated, washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 5-8%) to afford (2-chloro-5-fluorophenyl) {2,6-dibromo-4-[(2,2-difluoroethyl) amino]-3-nitrophenyl} methanone (2.2 g, 4.26 mmol, 19%) as a yellow solid. LCMS(ESI): m/z 515, 517, 519 [M-H]⁻.

[00510] **Step B:** To a solution of (2-chloro-5-fluorophenyl) {2,6-dibromo-4-[(2,2-difluoroethyl) amino]-3-nitrophenyl} methanone (2.2 g, 4.26 mmol) in EtOH (15 mL) was added Fe (2.38 g, 42.6 mmol) and sat. NH₄Cl (5 mL). The reaction was stirred at 80 °C for 2h. The reaction mixture was filtered, concentrated, diluted with water, and extracted with EtOAc (50 mL*3). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 20%) to afford {3-amino-2,6-dibromo-4-[(2,2-difluoroethyl)amino]phenyl} (2-chloro-5-fluorophenyl) methanone (1.7 g, 3.5 mmol, 82%) as an orange solid. LCMS: m/z 487 [M+H]⁺.

[00511] **Step C:** To a solution of {3-amino-2,6-dibromo-4-[(2,2-difluoroethyl) amino] phenyl} (2-chloro-5-fluorophenyl) methanone (1.3 g, 2.67 mmol), TEA (0.74 mL, 5.34 mmol) in THF (15 mL) was added trichloromethyl [(trichloromethyl)oxy] methanoate (0.5 g, 1.69 mmol) at 0 °C. The reaction was stirred at rt for 2h. Water was added, and the mixture was extracted with EtOAc (50 mL*3). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl

acetate in petroleum ether (gradient: 15%~30%) to afford 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2,2-difluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (1.3 g, 2.54 mmol, 95%) as a white solid. LCMS: m/z 513 $[M+H]^+$.

[00512] **Step D:** To the suspension of NaH (35.1 mg, 0.88 mmol, 60% in mineral oil) in dry THF (5 mL) was added in portions 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2,2-difluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (300 mg, 0.59 mmol) at 0 °C. After the completion of addition, the mixture was stirred for an additional 1 hour at 0 °C. Then 1-chloro-5,5-dimethyl-2-oxa-5-silahexane (0.21 mL, 1.17 mmol) was added slowly. The mixture was stirred for 10 min at 0 °C and then allowed to warm to room temperature and stirred for 2h. The reaction mixture was quenched by water, and the mixture was extracted with EtOAc (15 mL*3). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 0%~20%) to afford 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2,2-difluoroethyl)-3-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (340 mg, 0.53 mmol, 90%) as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.93 (s, 1H), 7.85 – 7.77 (m, 1H), 7.76 – 7.65 (m, 1H), 7.53 (d, J = 6.4 Hz, 1H), 6.69 – 6.32 (m, 1H), 5.60 (s, 2H), 4.64 – 4.48 (m, 2H), 3.66 (t, J = 8.0 Hz, 2H), 0.93 (t, J = 8.0 Hz, 2H), 0.06 – -0.08 (m, 9H).

[00513] **Step E:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-3-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo [d]imidazol-2-one (500 mg, 0.76 mmol) in NMP (30 mL) was added CuCN (0.35 g, 3.92 mmol), and the mixture was stirred at 130°C for 3h. The reaction mixture was concentrated in vacuo. The reaction mixture was quenched by water, and the mixture was extracted with EtOAc (100 mL*3). The organic layer was separated, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 0%~12%) to afford 6-bromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2,2-difluoroethyl)-3-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-2-oxobenzo[d]imidazole-4-carbonitrile (500 mg, 0.85 mmol, 20%) as a yellow oil.

[00514] **Step F:** To a solution of 6-bromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2,2-difluoroethyl)-3-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-2-oxobenzo[d]imidazole-4-carbonitrile (500 mg, 0.85 mmol), Cs₂CO₃ (829 mg, 2.55 mmol), Xant-phos (49.1 mg, 0.085 mmol) and 3-fluoro-5-(trifluoromethyl) benzene-1-carboxamide (119 mg, 0.58 mmol) in anhydrous dioxane (2

mL) was added $\text{Pd}_2(\text{dba})_3$ (77.8 mg, 0.085 mmol). The mixture was stirred at 100 °C for 2h. The cooled reaction mixture was concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 0%~15%) to afford N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-6-hydroxy-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl) benzamide (120 mg, 0.16 mmol, 19%) as a yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.68 (s, 1H), 9.26 (s, 1H), 7.97 – 7.90 (m, 1H), 7.74 – 7.66 (m, 3H), 7.47 (s, 1H), 7.36 – 7.28 (m, 2H), 7.25 (s, 1H), 7.06 – 6.98 (m, 1H), 6.35 (s, 1H), 5.99 – 5.87 (m, 2H), 4.46 – 4.35 (m, 2H), 3.67 – 3.59 (m, 2H), 0.85 – 0.81 (m, 2H), -0.06 (s, 9H).

[00515] **Step G:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-(5,5-dimethyl-2-oxa-5-silahex-1-yl)-6-hydroxy-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl) benzamide (100 mg, 0.14 mmol) in TFA (2 mL) was added triethylsilane (0.2 mL, 0.03 mmol), and the mixture was stirred at 70 °C for 1h. The cooled reaction mixture was concentrated in vacuo, ACN (2 mL) and ammonium hydroxide (0.2 mL, 0.03 mmol) was added, and the mixture was stirred at rt for 1h. The reaction mixture was concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 50%~75%) to afford N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-1,6,7,8-tetrahydroimidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl) benzamide (50 mg, 0.085 mmol, 63%) as a light yellow solid.

LCMS(ESI): 587 $[\text{M}+\text{H}]^+$

[00516] **Step H:** N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-1,6,7,8-tetrahydroimidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl) benzamide (50 mg, 0.085 mmol) was separated by SFC to give

[00517] P1: Example 70 (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (11.2 mg, 0.019 mmol, 45%) as a white solid. LCMS: ESI m/z 587 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.81 (s, 1H), 10.35 (s, 1H), 9.05 (s, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 7.74 (d, $J = 8.8$ Hz, 1H), 7.69 (s, 1H), 7.34 – 7.26 (m, 2H), 7.13 – 7.05 (m, 1H), 6.84 – 6.16 (m, 2H), 5.98 (s, 1H), 4.39 – 4.28 (m, 2H).

[00518] P2: Example 71 (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (10.3

mg, 0.018 mmol, 41%) as a white solid. LCMS: ESI m/z 587 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 11.81 (s, 1H), 10.35 (s, 1H), 9.05 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.69 (s, 1H), 7.34 – 7.26 (m, 2H), 7.13 – 7.05 (m, 1H), 6.84 – 6.16 (m, 2H), 5.98 (s, 1H), 4.39 – 4.28 (m, 2H).

[00519] Preparative SFC separation method:

Instrument: SHIMADZU PREP SOLUTION SFC

Column: ChiralPak IB, 250×30mm I.D., 5 μ m

Mobile phase: A for CO₂ and B for ME₂OH

Gradient: B 40%

Flow rate: 60 mL/min

Back pressure: 100 bar

Column temperature: 35°C

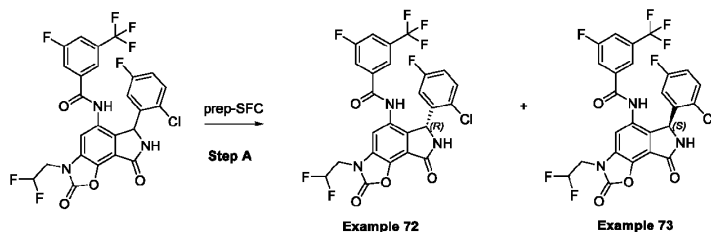
Wavelength: 220 nm

Cycle-time: 10 min

Eluted time: 2H

Example 72 (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-3,6,7,8-tetrahydro-2H-oxazolo[5,4-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 73 (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-3,6,7,8-tetrahydro-2H-oxazolo[5,4-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00520] **Step A:** N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-7,8-dihydro-6H-[1,3]oxazolo[5,4-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (70 mg) was separated by SFC to give

[00521] P1: Example 72 (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-3,6,7,8-tetrahydro-2H-oxazolo[5,4-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (19.1 mg, 54% yield) as a yellow solid. LCMS: ESI m/z 588 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.48 (s, 1H), 9.26 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.68 (s, 1H), 7.47

(s, 1H), 7.38 – 7.22 (m, 1H), 7.16 – 7.05 (m, 1H), 6.60 – 6.30 (m, 1H), 6.02 (brs, 1H), 4.57 – 4.20 (m, 2H).

[00522] P2: Example 73 (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-3,6,7,8-tetrahydro-2H-oxazolo[5,4-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (21.3 mg, 60% yield) as a yellow solid. LCMS: ESI m/z 588 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.48 (s, 1H), 9.26 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.68 (s, 1H), 7.47 (s, 1H), 7.38 – 7.22 (m, 1H), 7.16 – 7.05 (m, 1H), 6.60 – 6.30 (m, 1H), 6.02 (brs, 1H), 4.57 – 4.20 (m, 2H).

[00523] Preparative SFC separation method:

Instrument: Waters Thar 80 preparative SFC

Column: (R,R)-WHELK, 250×30 mm I.D., 5 μm

Mobile phase: A for CO₂ and B for MeOH

Gradient: B 50%

Flow rate: 60 mL/min

Back pressure: 100 bar

Column temperature: 35 °C

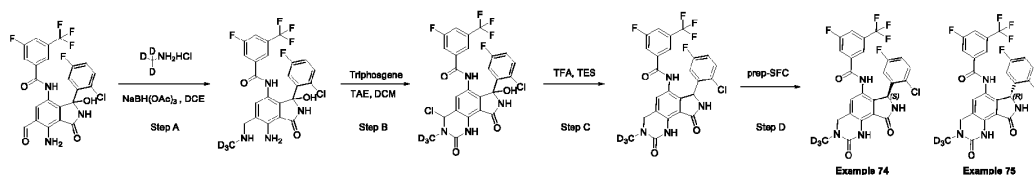
Wavelength: 220 nm

Cycle-time: 25 min

Eluted time: 3 H

Example 74 (S)-N-(7-(2-chloro-5-fluorophenyl)-3-(methyl-d₃)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 75 (R)-N-(7-(2-chloro-5-fluorophenyl)-3-(methyl-d₃)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00524] **Step A:** To a solution of N-[7-amino-3-(2-chloro-4-fluorophenyl)-6-formyl-3-hydroxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (300 mg, 0.571 mmol) and Methyl-D₃-amine hydrochloride (80.6 mg, 1.14 mmol) in THF (12 mL) was added TEA (116 mg, 1.14 mmol). The mixture was stirred at rt for 15min, then HOAc (68.6 mg,

1.14 mmol) was added. The mixture was stirred at rt for 1h, then NaBH(OAc)₃ (242 mg, 1.14 mmol) was added. The mixture was stirred for 1h, then another NaBH(OAc)₃ (242 mg, 1.14 mmol) was added. The mixture was stirred at rt for another 2h. The mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by column (eluted with (MeOH: DCM=10%) to give N-[7-amino-3-(2-chloro-4-fluorophenyl)-6-{(2,2-difluoroethyl)amino}methyl]-3-hydroxy-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (280 mg, 0.474 mmol, 83%) as a brown solid. LCMS: m/z 544 [M+H]⁺.

[00525] **Step B:** To a solution of N-[7-amino-3-(2-chloro-4-fluorophenyl)-3-hydroxy-1-oxo-6-{(trideuteriomethyl)amino}methyl]-2,3-dihydro-1H-isoindol-4-yl]-5-fluoro-3-(trifluoromethyl)benzamide (110 mg, 0.202 mmol) in THF (5 mL) was added triphosgene (19.8 mg, 67 μmol) in THF (5 mL) at 0 °C. The mixture was stirred at rt for 10min. The mixture was quenched with H₂O, extracted with EtOAc (10 mL*2). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo to give N-[7-(2-chloro-4-fluorophenyl)-7-hydroxy-2,9-dioxo-3-(trideuteriomethyl)-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (110 mg, 0.193 mmol, 95 %) (crude; 50%DP). LCMS: m/z 606 [M+H+2]⁺.

[00526] **Step C:** To a solution of N-[4-chloro-7-(2-chloro-4-fluorophenyl)-7-hydroxy-2,9-dioxo-3-(trideuteriomethyl)-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (100 mg, 0.165 mmol) in TFA (5 mL) was added Et₃SiH (0.5 mL). The reaction mixture was stirred at 60 °C for 30min. The cooled reaction mixture was concentrated. The residue was purified by prep-HPLC to give N-[7-(2-chloro-4-fluorophenyl)-2,9-dioxo-3-(trideuteriomethyl)-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (50 mg, 90 μmol, 55%) as a white solid. LCMS: m/z 554[M+H]⁺.

[00527] **Step D:** The N-[7-(2-chloro-4-fluorophenyl)-2,9-dioxo-3-(trideuteriomethyl)-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (50 mg) was separated by prep-SFC to give

[00528] P1: Example 74 (S)-N-(7-(2-chloro-5-fluorophenyl)-3-(methyl-d₃)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (19 mg, 34 μmol, 21%). (97% ee). LCMS: m/z 554 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ

7.68 – 7.60 (m, 3H), 7.28 – 7.24 (m, 2H), 7.13 – 6.94 (m, 1H), 6.69 (s, 1H), 6.13 (s, 1H), 4.65 (s, 2H).

[00529] P2: Example 75 (S)-N-(7-(2-chloro-5-fluorophenyl)-3-(methyl-d3)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (17.9 mg, 32 μ mol, 20%) as a white solid. (94% ee). LCMS: m/z 554 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.68 – 7.60 (m, 3H), 7.28 – 7.24 (m, 2H), 7.13 – 6.94 (m, 1H), 6.69 (s, 1H), 6.13 (s, 1H), 4.65 (s, 2H).

[00530] Preparative SFC separation method:

Instrument: SHIMADZU PREP SOLUTION SFC

Column: ChiralPak AS, 250×20mm I.D., 5 μ m

Mobile phase: A for CO₂ and B for MEOH

Gradient: B 30%

Flow rate: 40 mL/min

Back pressure: 100 bar

Column temperature: 35°C

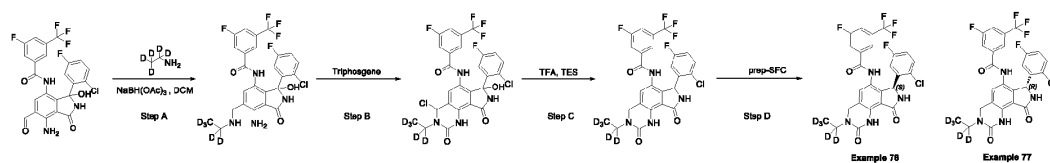
Wavelength: 220 nm

Cycle-time: 3.5 min

Eluted time: 2H

Example 76 (S)-N-(7-(2-chloro-5-fluorophenyl)-3-(ethyl-d5)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 77 (R)-N-(7-(2-chloro-5-fluorophenyl)-3-(ethyl-d5)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00531] **Step A:** To a solution of N-(7-amino-3-(2-chloro-5-fluorophenyl)-6-formyl-3-hydroxy-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (180 mg, 0.342 mmol) and ethan-d5-1-amine (17.8 mg, 0.342 mmol) in THF (5 mL) was added HOAc (41.1 mg, 0.684 mmol). The mixture was stirred at rt for 1h, then NaBH(OAc)₃ (145 mg, 0.684 mmol) was added. The mixture was stirred for 16h. The mixture was diluted with EA and H₂O. The organic

phase was concentrated to give a residue. The residue was purified by column (eluted with (MeOH: DCM=10%) to give N-(7-amino-3-(2-chloro-5-fluorophenyl)-6-(((ethyl-d5)amino)methyl)-3-hydroxy-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (100 mg, 0.179 mmol, 52%) as a brown solid. LCMS: m/z 560 [M+H]⁺.

[00532] **Step B:** To a solution of N-(7-amino-3-(2-chloro-5-fluorophenyl)-6-(((ethyl-d5)amino)methyl)-3-hydroxy-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (50 mg, 89 μ mol) in THF (2.5 mL) was added triphosgene (8.6 mg, 29 μ mol) in THF (2.5 mL) at 0 °C. The mixture was stirred for another 10min. The mixture was quenched with H₂O, extracted with EtOAc (10 mL*2). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo to give N-(4-chloro-7-(2-chloro-5-fluorophenyl)-3-(ethyl-d5)-7-hydroxy-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (50 mg, 85 μ mol, 96%) as a brown solid. The crude product (50%) was used directly in the next step. LCMS: ESI m/z 622 [M + 2 + H]⁺.

[00533] **Step C:** To a solution of N-(4-chloro-7-(2-chloro-5-fluorophenyl)-3-(ethyl-d5)-7-hydroxy-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (50 mg, 85 μ mol) in TFA (2 mL) was added Et₃SiH (0.2 mL). The reaction mixture was stirred at 60 °C for 30min. The cooled reaction mixture was concentrated to give a residue. The residue was purified by pre-HPLC to give N-(7-(2-chloro-5-fluorophenyl)-3-(ethyl-d5)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (20 mg, 35 μ mol, 43%) as a white solid. LCMS: m/z 570 [M+H]⁺.

[00534] **Step D:** The N-(7-(2-chloro-5-fluorophenyl)-3-(ethyl-d5)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide was purified by prep-SFC to give

[00535] P1: Example 76 (S)-N-(7-(2-chloro-5-fluorophenyl)-3-(ethyl-d5)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (5.1 mg, 9 μ mol, 11%) (99% ee) as a white solid. LCMS: m/z 570[M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.68 – 7.60 (m, 3H), 7.28 – 7.24 (m, 2H), 7.01 – 6.96 (m, 1H), 6.67 (s, 1H), 6.13 (s, 1H), 4.66 (s, 2H).

[00536] P2: Example 77 (R)-N-(7-(2-chloro-5-fluorophenyl)-3-(ethyl-d5)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (4.9 mg, 9 μ mol, 11%) (99% ee) as a white solid. LCMS: m/z 570 [M+H]⁺. ¹H NMR (400 MHz,

CD₃OD) δ 7.68 – 7.60 (m, 3H), 7.28 – 7.24 (m, 2H), 7.01 – 6.96 (m, 1H), 6.67 (s, 1H), 6.13 (s, 1H), 4.66 (s, 2H).

[00537] Preparative SFC separation method:

Instrument: SHIMADZU PREP SOLUTION SFC

Column: ChiralCel OX, 250×20mm I.D., 5 μ m

Mobile phase: A for CO₂ and B for MeOH

Gradient: B 40 %

Flow rate: 40mL /min

Back pressure: 100 bar

Column temperature: 35°C

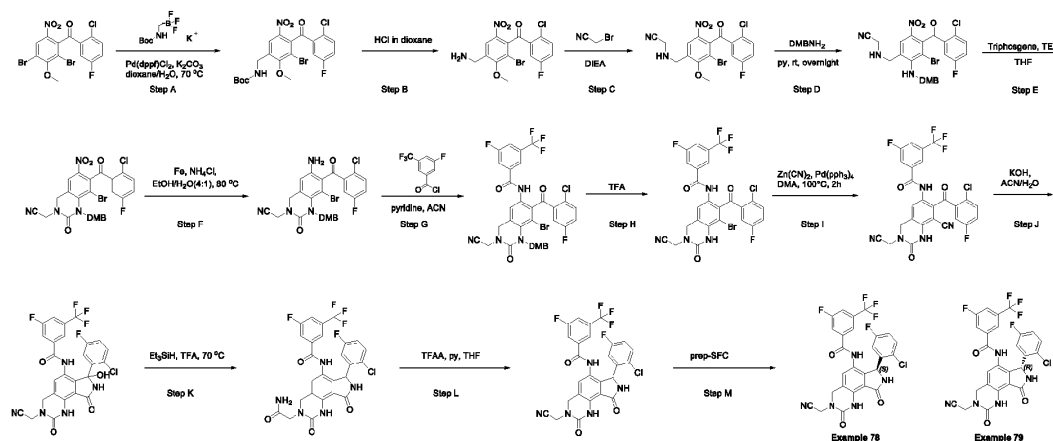
Wavelength: 220 nm

Cycle-time: 5 min

Eluted time: 2H

Example 78 (S)-N-(7-(2-chloro-5-fluorophenyl)-3-(cyanomethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 79 (R)-N-(7-(2-chloro-5-fluorophenyl)-3-(cyanomethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00538] **Step A:** To a stirred solution of (2-chloro-5-fluorophenyl)(2,4-dibromo-3-methoxy-6-nitrophenyl)methanone (10 g, 21.4 mmol) in dioxane (80 mL)/ H₂O (20 mL) was added (2,2-dimethyl-4-oxo-5-aza-3-oxahex-6-yl)trifluoro- λ^3 -boranuide (5 g, 25.7 mmol), Pd(dppf)Cl₂ (1.25 g, 1.71 mmol) and K₂CO₃ (5.91 g, 42.8 mmol) at rt. After stirred at 70 °C overnight,

the mixture was poured into ice-water (100 mL) and extracted with DCM (80 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-50%, EtOAc in PE) to give 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl]amino]methanoate (2.5 g, 4.83 mmol, 22%) as a brown solid. LCMS: m/z 517 [M+H]⁺.

[00539] **Step B:** A solution of 2-methylpropan-2-yl [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl]amino]methanoate (650 mg, 1.25 mmol) in HCl-dioxane (6 mL, 4M) was stirred at room temperature for 2 hr. The reaction was concentrated in vacuo to afford crude [4-(aminomethyl)-2-bromo-3-methoxy-6-nitrophenyl](2-chloro-5-fluorophenyl)methanone (500 mg, 1.197 mmol, 95%) as a yellow oil, which was used in next step without further purification. LCMS: ESI m/z 419 [M + H]⁺.

[00540] **Step C:** To a solution of [4-(aminomethyl)-2-bromo-3-methoxy-6-nitrophenyl](2-chloro-5-fluorophenyl)methanone (500 mg, 1.197 mmol) in ACN (5 mL) was added DIEA (309 mg, 2.395 mmol) and bromoacetonitrile (172 mg, 1.44 mmol). The reaction mixture was stirred at 25 °C for 1 h. The cooled reaction mixture was diluted with EA and water. The organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography eluted with PE in EA (gradient: 0~20%) to afford [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl]amino]acetonitrile (200 mg, 0.438 mmol, 36%) as a yellow oil. LCMS: ESI m/z 458 [M + H]⁺.

[00541] **Step D:** To a solution of [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-methoxy-5-nitrophenyl)methyl]amino]acetonitrile (200 mg, 0.438 mmol) in pyridine (5 mL) was added (2,4-dimethoxyphenyl)methanamine (219 mg, 1.31 mmol). The reaction mixture was stirred at 25 °C for 48 h. The reaction mixture was diluted with EA and water. The organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography eluted with PE in EA (gradient: 0~20%) to afford [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-[(2,4-dimethoxyphenyl)methyl]amino)-5-nitrophenyl)methyl]amino]acetonitrile (200 mg, 0.338 mmol, 77%) as a yellow oil. LCMS: ESI m/z 593 [M + H]⁺.

[00542] **Step E:** To a solution of [(3-bromo-4-[(2-chloro-5-fluorophenyl)carbonyl]-2-[(2,4-dimethoxyphenyl)methyl]amino)-5-nitrophenyl)methyl]amino]acetonitrile (200 mg, 0.338 mmol) in THF (5 mL) was added triethylamine (0.094 mL, 0.676 mmol) and trichloromethyl [(trichloromethyl)oxy]methanoate (40.1 mg, 0.135 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with EA and water. The organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography eluted with PE in EA (gradient: 0~23%) to afford {8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(2,4-dimethoxyphenyl)methyl]-6-nitro-2-oxo-1,2,3,4-tetrahydroquinazolin-3-yl}acetonitrile (150 mg, 0.243 mmol, 72%) as a yellow solid. LCMS: ESI m/z 619 [M + H]⁺.

[00543] **Step F:** To a solution of {8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(2,4-dimethoxyphenyl)methyl]-6-nitro-2-oxo-1,2,3,4-tetrahydroquinazolin-3-yl}acetonitrile (160 mg, 0.259 mmol) in ethanol (3 mL) and H₂O (1 mL), was added Fe (72.3 mg, 1.29 mmol) and NH₄Cl (69.2 mg, 1.29 mmol), and the resulting mixture was stirred at 90 °C for 2 h. The cooled reaction mixture was filtered, concentrated, diluted with EA and water. The organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography eluted with MeOH in DCM (gradient: 0~2%) to afford {6-amino-8-bromo-7-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(2,4-dimethoxyphenyl)methyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-3-yl}acetonitrile (110 mg, 0.187 mmol, 72%) as a yellow solid. LCMS: ESI m/z 589 [M + H]⁺.

[00544] **Step G:** To a solution of {6-amino-8-bromo-7-[(2-chloro-4-fluorophenyl)carbonyl]-1-[(2,4-dimethoxyphenyl)methyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-3-yl}acetonitrile (100 mg, 0.170 mmol) in ACN (5 mL) was added Py (67.3 mg, 0.851 mmol) and 5-fluoro-3-(trifluoromethyl)benzoyl chloride (46.3 mg, 0.204 mmol) at 0 °C. The reaction mixture was stirred at rt for 30min. Then the mixture was diluted with water (~20 mL) and extracted with ethyl acetate (~20 mL x 2). The combined organic phases were washed with brine (20 mL) dried over Na₂SO₄ and concentrated. The residue was purified by column (eluted with (MeOH: DCM=10%) to give N-{8-bromo-7-[(2-chloro-4-fluorophenyl)carbonyl]-3-(cyanomethyl)-1-[(2,4-dimethoxyphenyl)methyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl}-5-fluoro-3-(trifluoromethyl)benzamide (120 mg, 0.154 mmol, 91%) as a brown solid. LCMS: m/z 745 [M+H]⁺.

[00545] **Step H:** To a solution of N-{8-bromo-7-[(2-chloro-4-fluorophenyl)carbonyl]-3-(cyanomethyl)-1-[(2,4-dimethoxyphenyl)methyl]-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl}-5-fluoro-3-(trifluoromethyl)benzamide (120 mg, 0.154 mmol) in DCM (4 mL) was added TFA (1 mL). The mixture was stirred at rt for 30min. The mixture was quenched with aq. NaHCO₃, extracted with DCM (10 mL*2). The combined organic layers were dried over Na₂SO₄, filtered, concentrated, and purified by column to give N-{8-bromo-7-[(2-chloro-4-fluorophenyl)carbonyl]-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl}-5-fluoro-3-(trifluoromethyl)benzamide (90 mg, 0.143 mmol, 93%) as a brown solid. LCMS: m/z 627[M+H]⁺.

[00546] **Step I:** A sealed vial was charged with N-{8-bromo-7-[(2-chloro-4-fluorophenyl)carbonyl]-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl}-5-fluoro-3-(trifluoromethyl)benzamide (100 mg, 0.159 mmol), Zn(CN)₂ (56.1 mg, 0.48 mmol), Pd(PPh₃)₄ (18.4 mg, 0.02 mmol) and DMA (2 mL). The mixture was stirred at 100 °C under N₂ for 3h. The cooled mixture was diluted with water (~10mL) and extracted with EtOAc (~20 mL x 2). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by column (eluted with (MeOH: DCM=10%) to give N-{7-[(2-chloro-4-fluorophenyl)carbonyl]-8-cyano-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl}-5-fluoro-3-(trifluoromethyl)benzamide (80 mg, 0.139 mmol, 88%) as a brown solid. LCMS: m/z 574 [M+H]⁺.

[00547] **Step J:** To a solution of N-{7-[(2-chloro-4-fluorophenyl)carbonyl]-8-cyano-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl}-5-fluoro-3-(trifluoromethyl)benzamide (85 mg, 0.148 mmol) in H₂O (0.2 mL) and ACN (2 mL) was added KOH (42 mg, 0.741 mmol) at room temperature. The reaction mixture was stirred at rt for 30min. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic phases were washed with brine (20 mL x 2), dried over Na₂SO₄ and concentrated to give N-[7-(2-chloro-4-fluorophenyl)-3-(cyanomethyl)-7-hydroxy-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (60 mg, 0.101 mmol, 68%) as a brown solid. LCMS: m/z 592 [M+H]⁺.

[00548] **Step K:** To a solution of N-[7-(2-chloro-4-fluorophenyl)-3-(cyanomethyl)-7-hydroxy-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (55 mg, 93 μmol) in TFA (2 mL) was added TES (0.2 mL). The

reaction mixture was stirred at 60 °C for 30min. The cooled reaction mixture was concentrated to give a residue. The residue was purified by column (eluted with (MEOH: DCM=10%) to give 2-[7-(2-chloro-4-fluorophenyl)-6-([5-fluoro-3-(trifluoromethyl)phenyl]carbonyl)amino]-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-3-yl]acetamide (45 mg, 76 µmol, 82%) as a brown solid. LCMS: m/z 594 [M+H]⁺.

[00549] **Step L:** To a solution of 2-[7-(2-chloro-4-fluorophenyl)-6-([5-fluoro-3-(trifluoromethyl)phenyl]carbonyl)amino]-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-3-yl]acetamide (40 mg, 67 µmol) in THF (2 mL) was added py (11 mg, 0.135 mmol) and TFAA (28.3mg, 0.135 mmol) at 0°C. The mixture was stirred at rt for 2h. Then the reaction mixture was concentrated to give a residue. The residue was purified by pre-HPLC to give N-[7-(2-chloro-4-fluorophenyl)-3-(cyanomethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide (15 mg, 26 µmol, 39%) as a white solid. LCMS: m/z 576 [M+H]⁺.

[00550] **Step M:** The N-[7-(2-chloro-4-fluorophenyl)-3-(cyanomethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[4,3-h]quinazolin-6-yl]-5-fluoro-3-(trifluoromethyl)benzamide was pre by prep-SFC to afforded

[00551] P1 Example 78: (S)-N-(7-(2-chloro-5-fluorophenyl)-3-(cyanomethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (4.7 mg, 8 µmol, 12%) as a white solid. LCMS: m/z 576 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.68 – 7.63 (m, 3H), 7.30 (s, 1H), 7.26 (dd, J = 8.8, 5.0 Hz, 1H), 7.01 – 6.97 (m, 1H), 6.69 (s, 1H), 6.14 (s, 1H), 4.77 (s, 2H), 4.53 (d, J = 3.4 Hz, 2H).

[00552] P2 Example 78: (R)-N-(7-(2-chloro-5-fluorophenyl)-3-(cyanomethyl)-2,9-dioxo-2,3,4,7,8,9-hexahydro-1H-pyrrolo[3,4-h]quinazolin-6-yl)-3-fluoro-5-(trifluoromethyl)benzamide (5.7 mg, 10 µmol, 15%) as a white solid (99% ee). LCMS: m/z 576 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.68 – 7.63 (m, 3H), 7.30 (s, 1H), 7.26 (dd, J = 8.8, 5.0 Hz, 1H), 7.01 – 6.97 (m, 1H), 6.69 (s, 1H), 6.14 (s, 1H), 4.77 (s, 2H), 4.53 (d, J = 3.4 Hz, 2H).

[00553] Preparative separation method

Instrument: SHIMADZU PREP SOLUTION SFC

Column: ChiralPak IH, 250×20mm I.D., 5µm

Mobile phase: A for CO₂ and B for MEOH

Gradient: B 30%

Flow rate: 40 mL/min

Back pressure: 100 bar

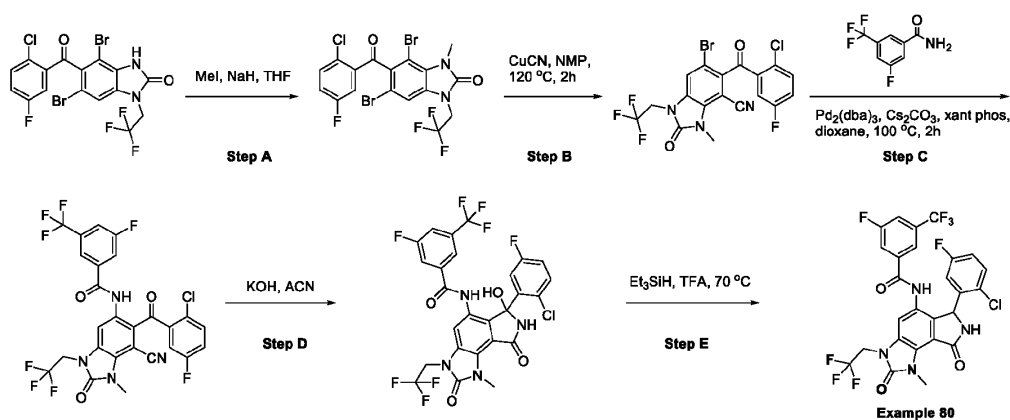
Column temperature: 35°C

Wavelength: 220 nm

Cycle-time: 3.5 min

Eluted time: 2H

Example 80 N-(6-(2-chloro-5-fluorophenyl)-1-methyl-2,8-dioxo-3-(2,2,2-trifluoroethyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00554] **Step A:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (600 mg, 1.13 mmol) in THF (15 mL) were added NaH (90 mg, 2.26 mmol, 60% in mineral oil) at 0 °C. After stirred at 0 °C for 1h, CH₃I (240 mg, 1.69 mmol) was added. The reaction mixture was stirred at rt for 2h. The reaction mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by chromatography (silica gel, 0-20 %, EtOAc in PE) to give 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (500 mg, 0.91 mmol, 81 %) as a white solid.

[00555] **Step B:** To a stirred solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (500 mg, 0.91 mmol) in NMP (8 mL) was added CuCN (90 mg, 1.01 mmol) at rt. After stirred at 120 °C under N₂ for 2h, the cooled mixture was poured into brine (50 mL) and extracted with EtOAc (30 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and

concentrated. The residue was purified by chromatography (silica gel, 0-50 %, EtOAc in PE) to give 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-2-oxo-1-(2,2,2-trifluoroethyl)benzo[d]imidazole-4-carbonitrile (160 mg, 0.32 mmol, 35 %) as a yellow solid. LCMS: m/z 491 $[M+H]^+$.

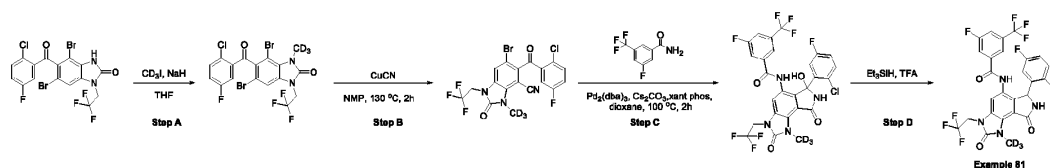
[00556] **Step C:** To a stirred solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-2-oxo-1-(2,2,2-trifluoroethyl)benzo[d]imidazole-4-carbonitrile (80 mg, 0.16 mmol) in dioxane (6 mL) was added 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (50 mg, 0.24 mmol), $Pd_2(dba)_3$ (29 mg, 0.03 mmol), Xant-PHOS (37 mg, 0.06 mmol) and Cs_2CO_3 (106 mg, 0.32 mmol) at rt. After stirred at 100 °C for 3h, the mixture was poured into ice-water (10 mL) and extracted with DCM (10 mL*3). The combined organic phase was washed with brine, dried with Na_2SO_4 , filtered and concentrated. The combined organic phase was washed with brine, dried with Na_2SO_4 , filtered and concentrated. The residue was purified by chromatography (silica gel, 0-50%, EtOAc in PE) to give N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-1-methyl-2-oxo-3-(2,2,2-trifluoroethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (60 mg, 0.09 mmol, 59 %) as a brown solid. LCMS: m/z 617 $[M+H]^+$.

[00557] **Step D:** To a stirred solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-1-methyl-2-oxo-3-(2,2,2-trifluoroethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (60 mg, 0.09 mmol) in ACN (3 mL)/ H_2O (1 mL) was added KOH (16 mg, 0.29 mmol) slowly at rt. After stirred at rt for 1h, the mixture was poured into water (10 mL) and extracted with EtOAc (10 mL*2). The combined organic phase was washed with brine, dried with Na_2SO_4 , filtered and concentrated to give crude N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-2,8-dioxo-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (40 mg, 0.06 mmol, 65 %) as a white solid. LCMS: m/z 635 $[M+H]^+$.

[00558] **Step E:** To a stirred solution of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-2,8-dioxo-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (40 mg, 0.06 mmol) in TFA (2 mL) was added Et_3SiH (0.5 mL) at rt. After stirred at 70 °C for 1h, the cooled mixture was concentrated. The residue was purified by chromatography (silica gel, 0-10%, MeOH in DCM) and then prep-TLC (DCM: MeOH= 20: 1) to give N-(6-(2-chloro-5-fluorophenyl)-1-methyl-2,8-dioxo-3-(2,2,2-trifluoroethyl)-1,2,3,6,7,8-

hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (25 mg, 0.04 mmol, 64 %) as a white solid. LCMS: m/z 619 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.35 (s, 1H), 9.20 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 7.48 (s, 1H), 7.28 (dd, J = 8.8, 5.2 Hz, 1H), 7.09 (t, J = 6.8 Hz, 1H), 6.59 (brs, 1H), 6.02 (brs, 1H), 4.87 (m, 2H), 3.92 (s, 3H).

Example 81 N-(6-(2-chloro-5-fluorophenyl)-1-(methyl-d3)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00559] **Step A:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (550 mg, 1.04 mmol) in THF (10 mL) was added NaH (82.9 mg, 2.07 mmol, 60% in mineral oil) at 0 °C. The mixture was stirred at 0 °C for 10min, then CD_3I (301 mg, 2.07 mmol) was added. The mixture was stirred at rt for 16h. The reaction mixture was quenched by water, and the mixture was extracted with EtOAc (15 mL*3). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 0%~20%) to afford 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-(trideuteriomethyl)-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (450 mg, 0.822 mmol, 79%) as a brown solid. LCMS: ESI m/z 546 $[M+H]^+$.

[00560] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-(trideuteriomethyl)-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (500 mg, 0.913 mmol) in NMP (10 mL) was added CuCN (85.9 mg, 0.959 mmol), and the mixture was stirred at 130 °C under N_2 for 3h. The cooled reaction mixture was diluted with H_2O , extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 0%~30%) to afford 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-3-(trideuteriomethyl)-1-(2,2,2-trifluoroethyl)benzo[d]imidazole-4-carbonitrile (140 mg, 0.284 mmol, 31%) as a brown solid. LCMS: ESI m/z 493 $[M+H]^+$.

[00561] **Step C:** A solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-3-(trideuteriomethyl)-1-(2,2,2-trifluoroethyl)benzo[d]imidazole-4-carbonitrile (50 mg, 0.101 mmol), 5-fluoro-3-(trifluoromethyl)benzene-1-carboxamide (22 mg, 0.106 mmol), Pd₂(dba)₃ (9.28 mg, 10 μmol), Xantphos (11.7 mg, 20 μmol), Cs₂CO₃ (99 mg, 0.304 mmol) and dioxane (2 mL) was stirred at 100 °C for 2h. The cooled reaction mixture was concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with MeOH in DCM (gradient: 0%~10%) to afforded N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-5-(difluoromethyl)-3-fluorobenzamide (50 mg, 40 μmol, 40%) as a brown solid. (50% DP). LCMS: ESI m/z 638 [M + H]⁺.

[00562] **Step D:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-5-(difluoromethyl)-3-fluorobenzamide (50 mg, 81 μmol) in TFA (2 mL) was added Et₃SiH (0.2 mL). The reaction mixture was stirred at 60 °C for 30 min. The cooled reaction mixture was concentrated. The residue was purified by prep-HPLC to give N-(6-(2-chloro-5-fluorophenyl)-1-(methyl-d₃)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (3 mg, 5 μmol, 6%) as a white solid. LCMS: ESI m/z 622 [M + H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.69-7.62 (m, 3H), 7.42 (s, 1H), 7.24 (dd, *J* = 8.8, 5.0 Hz, 1H), 6.99 (td, *J* = 8.4, 3.0 Hz, 1H), 6.59 (s, 1H), 6.21 (s, 1H), 4.74 (q, *J* = 8.8 Hz, 2H).

Table 2. Biochemical Potency for Exemplary Compounds

Example #	ADP-Glo IC ₅₀ PI3K α H1047R	ADP-Glo IC ₅₀ PI3K α E545K	ADP-Glo IC ₅₀ PI3K α E542K	ADP-Glo IC ₅₀ PI3K α WT
Example 1	A	A	A	B
Example 2	B	B	B	C
Example 3	A	A	A	B
Example 4	A	A	A	C

Example 5	A	A	A	B
Example 6	D			D
Example 7	D			D
Example 8	C			C
Example 9	A	A	A	B
Example 10	A	A	A	A
Example 11	D			D
Example 12	A	A	A	B
Example 13	D			D
Example 14	A	A	A	B
Example 15	D			D
Example 16	A	A	B	B
Example 17	A	A	B	B
Example 18	A	A	B	B
Example 19	A	A	B	A
Example 20	A	A	A	A
Example 21	A	B	B	B
Example 22	D			D
Example 23	C			D
Example 24	A	B	B	A
Example 25	D	C	C	D
Example 26	A	A	A	B
Example 27	B			C
Example 28	C			C
Example 29	A	B	B	B
Example 30	A	A	A	B
Example 32	A	A	A	B

Example 35	A	A	A	A
Example 36	A	A	A	B
Example 37	A	A	A	A
Example 38	A	A	A	A
Example 39	D	D	D	D
Example 40	D	C	C	D
Example 41	A	A	A	B
Example 42	C	D	D	C
Example 43	A	A	A	B
Example 44	A	A	A	B
Example 45	A	A	A	B
Example 46	A	A	B	B
Example 47	A	A	A	B
Example 48	D	D	C	D
Example 49	A	A	B	B
Example 50	A	A	B	B
Example 51	A	A	B	B
Example 52	A	A	A	B
Example 53	B	C	C	C
Example 54	B	B	B	B
Example 55	A	A	A	A
Example 56	C	D	C	C
Example 57	A	A	A	A
Example 58	A	A	A	B
Example 59	A	A	A	B
Example 60	D	D	C	D
Example 61	A	A	A	B

Example 62	A	A	A	B
Example 63	B	B	B	C
Example 64	A	A	A	B
Example 65	B	B	B	C
Example 66	D	C	D	D
Example 67	A	A	A	B
Example 68	C	C	C	C
Example 69	A	A	A	B
Example 70	C	B	B	C
Example 71	A	A	A	A
Example 72	A	A	A	A
Example 73	D	D	D	D
Example 74	B	B	C	C
Example 75	A	A	A	A
Example 76	D	C	C	C
Example 77	A	A	A	A
Example 78	D	C	C	C
Example 79	A	A	A	A
Example 80	A	A	A	C
Example 81	A	A	A	C

PI3K α enzymatic ADP-Glo assay

[00563] All the compounds were initially prepared as 10 mM stock solution in 100% DMSO. The stock solution was then serially diluted 3-fold in 100% DMSO to 10 concentrations. 50 nL of each compound dilution was subsequently added to 384-well plate in duplicate. To each well, 2.5 μ L of enzyme solution containing PI3K α protein (PI3K α WT, H1047R, E542K, E545K) with final concentrations 0.15 μ g/ml for WT, 0.05 μ g/ml for PI3K α H1047R, 0.07 μ g/ml for PI3K α E542K, and 0.07 μ g/ml for PI3K α E545K, respectively in 1 $\times$ Kinase buffer (50 mM HEPES pH

7.5, 3 mM MgCl₂, 2 mM DTT and 0.03% CHAPS, 100mM NaCl, 1mM EGTA). For negative control, 2.5 uL of assay buffer was added instead. The mixture was incubated at room temperature for 10 min. 2.5 μ L of substrate solution containing PIP2 peptide (final concentrations 50 μ g/ml) and ATP (final concentration 25 μ M for WT and H1047R, 68 μ M and 100 μ M for E542K and E545K, respectively) in 1 $\times$ Kinase buffer was added into each well to initiate each reaction. All the reactions were incubated at room temperature for 60 min. Then 5 μ L of ADP-Glo reagent 1 was subsequently added to stop the reactions. After equilibrating for 120 min at room temperature, 10 μ L ADP-Glo reagent 2 was added to each well, followed by shaking for 1 min and equilibrating for 30 min at room temperature. All the samples were then subjected to analysis using Envision to read luminescence RLU values. IC₅₀ values were then calculated by plotting dose-response curves and then using the XLfit application in Excel software.

[00564] Results of the ADP-Glo Biochemical PI3K α enzymatic assays using PI3K α H1047R, E545K, E542K and WT enzymes are presented in **Table 2**. Compounds having an IC₅₀ less than or equal to 200 nM are represented as “A”; Compounds having an IC₅₀ greater than 200 nM but less than or equal to 1 μ M are represented as “B”; Compounds having an IC₅₀ greater than 1 μ M but less than 10 μ M are represented as “C”; Compounds having an IC₅₀ greater than or equal to 10 μ M are represented as “D”.

Table 3. Cellular Potency for Exemplary Compounds

Example #	HTRF pAKT IC ₅₀ HCC1954	CTG cell proliferation IC ₅₀ NCI-H1048
Example 1	B	
Example 2	C	
Example 3	C	
Example 4		A
Example 5		A
Example 9	A	A
Example 10	B	

Example 11		
Example 12	A	A
Example 14		C
Example 16	A	A
Example 17		C
Example 18	B	B
Example 19	A	A
Example 20	B	B
Example 21	A	A
Example 22	D	C
Example 23		C
Example 24	B	C
Example 26	B	A
Example 27		C
Example 28		C
Example 29	C	D
Example 30	A	
Example 32	A	A
Example 35	A	A
Example 36	A	A
Example 37	A	A
Example 38	A	A
Example 39	D	D
Example 40	D	C
Example 41	B	C
Example 42	D	D
Example 43	A	C

Example 44	A	A
Example 45	A	A
Example 46	C	B
Example 47	A	A
Example 48	D	C
Example 49	A	A
Example 50	A	A
Example 51	A	A
Example 52	A	A
Example 53	C	C
Example 54	D	D
Example 55	A	A
Example 56	C	A
Example 57	A	A
Example 58	B	B
Example 59	A	A
Example 60	D	B
Example 61	A	A
Example 62	A	A
Example 63	D	D
Example 64	A	A
Example 65	C	B
Example 66	D	B
Example 67	A	A
Example 68	D	C
Example 69	A	A
Example 70	C	A

Example 71	A	A
Example 72	A	A
Example 73	D	A
Example 74	D	B
Example 75	A	A
Example 76	D	C
Example 77	A	A
Example 78	D	B
Example 79	A	A
Example 80	A	
Example 81	A	

HTRF PHOSPHO-AKT (SER473) assay

[00565] HCC1954 cells (American Type Culture Collection) are maintained by culturing in the medium recommended by the provider. To each well of a flat-bottom 384-well plate, 10,000 cells were added in a volume of 35 μ L of culture medium. Cells were allowed to recover overnight. On the following day, the plated cells were treated with 9 concentrations of compounds in 3-fold serial dilution or with DMSO. Compounds were prepared as 10 mM DMSO stock solution, and 100 μ L of the diluted compounds were added to the cells, with a final concentration of 0.1% DMSO. Cells were treated for 2 h and the culture medium was removed by aspiration. To each well, 20 μ L of lysis buffer were added (Perkin Elmer phospho-AKT Ser473 kit) and the plates were incubated for 30 minutes at room temperature. AKT phosphorylation at Ser473 was detected using a pair of donor and acceptor antibodies specific for the total and phosphorylated protein provided in the assay kit. A pre-mixed antibody solution was added to each well of cell lysate and the plates were incubated at room temperature for 16h. Fluorescence emission by the two antibodies was measured at 665 and 620 nm in a plate reader. Data analysis:

Calculate the ratio of the acceptor and donor emission signals for each individual well.

$$\text{Ratio} = \frac{\text{Signal 665 nm}}{\text{Signal 620 nm}} \times 10^4$$

Protocol for Cell Proliferation Assay

[00566] Cancer cells were grown in culture media according to vendors' instructions. Cells were plated in clear bottom tissue culture treated 96-well plates at a density of 1250-5000 cells/well in a volume of 100 μ L and allowed to recover overnight. The edge wells were filled with cell culture media only. The plated cells were treated with a 3-fold 9-point serial dilution doses of test compounds, or DMSO control. Compounds were prepared as 10 mM DMSO stock solution and added to the cells with a HP D300 digital dispenser. The top final concentration varied from 10 to 1 μ M depending on the potency of the compounds, with the final concentration of DMSO to be 0.1%. Following 7 days of drug treatment, 100 μ L of CellTiter-Glo (CTG) (Promega, G7570) reagent was added to the cells using a Multidrop Combi instrument and the plates were placed on an orbital shaker for 15 minutes. The luminescence signal was read on an Envision plate reader with a measurement time of 0.1 s.

[00567] Cell proliferation percent inhibition values were calculated using the following equation:

$$\text{Inhibition\%} = [1 - (\text{T168}_{\text{compound}} - \text{T168}_{\text{blank}}) / (\text{T168}_{\text{DMSO}} - \text{T168}_{\text{blank}})] \times 100\%.$$

T168_{compound}: the signals from compound-treated wells;

T168_{blank}: the signals from blank wells;

T168_{DMSO}: the signals from 0.1%DMSO-treated wells.

[00568] XLfit software (Fit model: Dose response one site/ $\frac{A + (B-A)/(1 + ((C/x)^D))}{1 + ((C/x)^D)}$) was used for curve fitting and IC₅₀ calculation.

[00569] Results of the HTRF pAKT assay on HCC1954 cell line and CTG cell proliferation assay on NCI-H1048 cell line are presented in **Table 3**. Compounds having an IC₅₀ less than or equal to 500 nM are represented as "A"; Compounds having an IC₅₀ greater than 500 nM but less than or equal to 1 μ M are represented as "B"; Compounds having an IC₅₀ greater than 1 μ M but less than 10 μ M are represented as "C"; Compounds having an IC₅₀ greater than or equal to 10 μ M are represented as "D"

[00570] Although the present invention has been described in detail with preferred embodiments, those of ordinary skill in the art should understand that modifications, variations, and equivalent replacements made to the present invention within the scope of the present invention belong to the protection of the present invention.

[00571] 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.

[00572] 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.

[00573] 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. 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

[00574] 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.

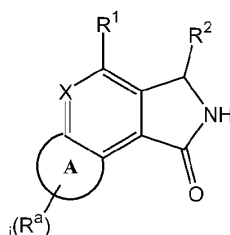
Equivalents

[00575] 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 is:

CLAIMS

1. A compound having the structural formula I:



I

or a pharmaceutically acceptable form or an isotope derivative thereof,
wherein

Ring A is a 4- to 7-membered monocyclic non-aromatic ring, substituted with 0-10 R^a s;

R^1 is Z^B-R^B ;

R^2 is Z^C-R^C ;

X is N, CH or CR^X ;

R^X is $Z^X-R^{X'}$;

each of Z^B , Z^C and Z^X is independently a covalent bond, O, S, NR, $NRC(O)$, $C(O)NR$, $C(O)$, $C(O)O$, $OC(O)$, $S(O)_2$, $NRS(O)_2$, $S(O)_2NR$, or a linking group selected from C_{1-4} saturated or unsaturated bivalent hydrocarbon radicals, wherein one or more carbons are optionally and independently substituted with a heteroatom selected from the group consisting of N, S and O;

each of R^B , R^C and R^X is independently

H, deuterium, oxo, halogen, -CN, -NO₂, -OR, -SR, -NRR', -S(O)₂R, -S(O)₂NRR', -S(O)R, -S(O)NRR', -S(O)(NR)R, -C(O)R, -C(O)OR, -C(O)NRR', -C(O)N(R)OR, -OC(O)R, -OC(O)NRR', -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NRR', -N(R)C(NR)NRR', -N(R)S(O)₂NRR', or -N(R)S(O)₂R; or

a C_{1-6} aliphatic chain, a 5- to 10-membered monocyclic, bicyclic or bridged carbocyclyl, heterocyclic, aryl or heteroaryl ring with 0-4 ring heteroatoms

independently selected from N, O and S, optionally substituted with one or more R^b, R^c or R^x, respectively;

each of R^a, R^b, R^c and R^x is independently

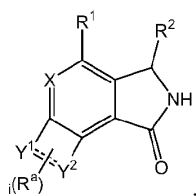
H, deuterium, oxo, halogen, -CN, -NO₂, -OR, -SR, -NRR', -S(O)₂R, -S(O)₂NRR', -S(O)R, -S(O)NRR', -S(O)(NR)R, -C(O)R, -C(O)OR, -C(O)NRR', -C(O)N(R)OR, -OC(O)R, -OC(O)NRR', -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NRR', -N(R)C(NR)NRR', -N(R)S(O)₂NRR' or -N(R)S(O)₂R; or

a substituted or unsubstituted group selected from C₁₋₆ alkyl or 4- to 6-membered carbocyclic ring;

each of R and R' is independently selected from H, unsubstituted or substituted C₁₋₄ alkyl, or unsubstituted or substituted 4- to 6-membered carbocyclic ring, or where R and R' are attached to the same C or N atom, together form an unsubstituted or substituted 4- to 6-membered heterocyclic ring; and

i is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

2. The compound of claim 1, wherein Ring A is a 4- to 7-membered carbocyclic ring with no ring heteroatoms, substituted with 0-10 R^as.
3. The compound of claim 1, wherein Ring A is a 4- to 7-membered heterocyclic ring with 1-4 ring heteroatoms selected from N, O and S, substituted with 0-10 R^as.
4. The compound of any one of claims 1-3, wherein Ring A is a 4-membered non-aromatic ring, substituted with 0-4 R^as, having the structural formula **I_a**:

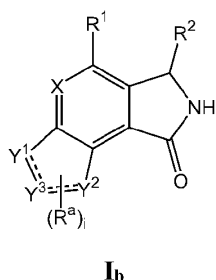


I_a

wherein

each of Y¹ and Y² is independently CH, CH₂, N, NH, O or S, *provided that* at least one of Y¹ and Y² is C or CH.

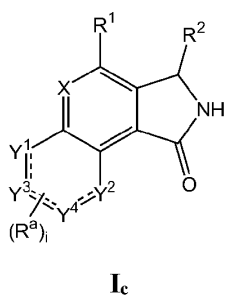
5. The compound of any one of claims 1-3, wherein Ring A is a 5-membered non-aromatic ring, substituted with 0-6 R^as, having the structural formula **I_b**:



wherein

each of Y¹, Y² and Y³ is independently CH, CH₂, N, NH, O, S or C(O), *provided that* at least one of Y¹, Y² and Y³ is not N or NH and at least one of Y¹, Y² and Y³ is C, CH or C(O).

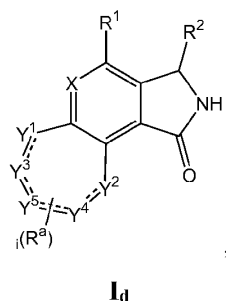
6. The compound of any one of claims 1-3, wherein Ring A is a 6-membered non-aromatic ring, substituted with 0-8 R^as, having the structural formula **I_c**:



wherein

each of Y¹, Y², Y³ and Y⁴ is independently CH, CH₂, N, NH, O, S, S(O)₂, or C(O), *provided that* at least two of Y¹, Y², Y³ and Y⁴ is not N or NH and at least two of Y¹, Y², Y³ and Y⁴ is C, CH or C(O).

7. The compound of any one of claims 1-3, wherein Ring A is a 7-membered non-aromatic ring, substituted with 0-8 R^as, having the structural formula **I_d**:



wherein

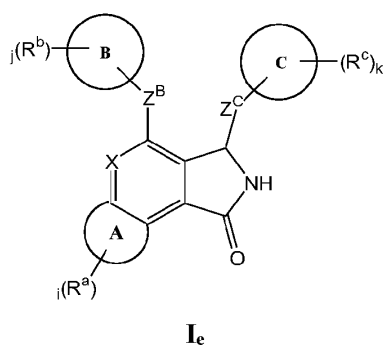
each of Y^1 , Y^2 , Y^3 , Y^4 and Y^5 is independently CH, CH_2 , N, NH, O, S or C(O),
provided that at least two of Y^1 , Y^2 , Y^3 , Y^4 and Y^5 is not N or NH and at least two of Y^1 , Y^2 , Y^3 , Y^4 and Y^5 is C, CH or C(O).

8. The compound of any one of claims 1-7, wherein

R^B is Ring B, a 5- to 10-membered monocyclic or bicyclic carbocyclyl, heterocyclic, aryl or heteroaryl ring with 0-4 ring heteroatoms independently selected from N, O and S, substituted with 0-6 R^b s; and

R^C is Ring C, a 5- to 10-membered monocyclic or bicyclic aryl or heteroaryl ring with 0-4 ring heteroatoms independently selected from N, O and S, substituted with 0-6 R^c s,

having the structural formula **I_e**:

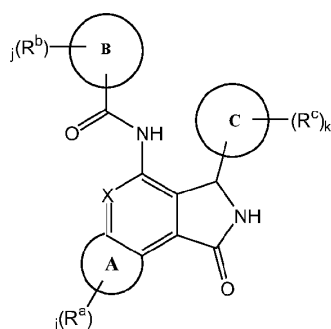


wherein

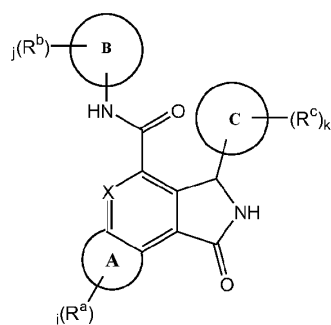
j is 0, 1, 2, 3, 4, 5 or 6; and

k is 0, 1, 2, 3, 4, 5 or 6.

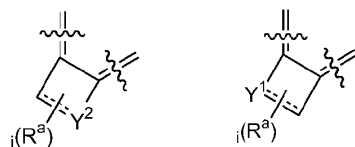
9. The compound of claim 8, wherein Z^B is NH-C(O) and Z^C is a single bond, having the structural formula **I_f**:

**I_f**

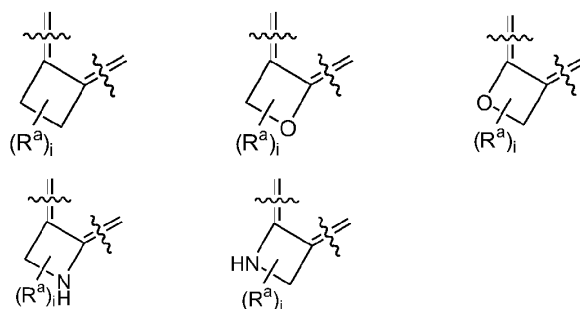
10. The compound of claim 8, wherein Z^B is C(O)-NH and Z^c is a single bond, having the structural formula **I_g**:

**I_g**

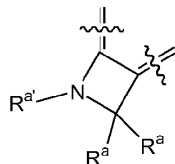
11. The compound of any one of claims 1-4 and 8-10, wherein Ring A is selected from:



12. The compound of any one of claims 1-4 and 8-10, wherein Ring A is selected from:

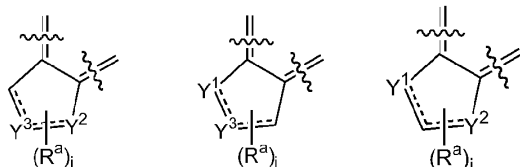


13. The compound of any one of claims 1-4 and 8-10, wherein Ring A is:

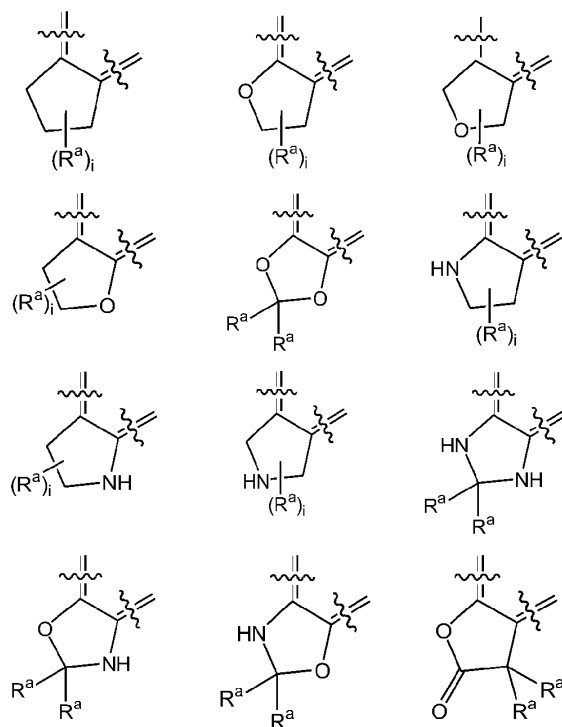


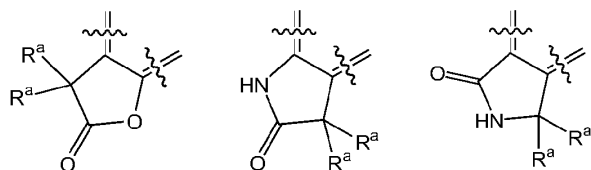
wherein $R^{a'}$ is CH_2CH_3 , CD_2CD_3 , CH_2CHF_2 , CH_2CF_3 and CH_2CN .

14. The compound of claim 13, wherein $R^{a'}$ is CH_2CHF_2 .
15. The compound of claim 13 or 14, wherein each R^a is independently H, Cl, F, CN or CH_3 .
16. The compound of any one of claims 1-3, 5 and 8-10, wherein Ring A is selected from:

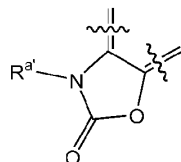


17. The compound of any one of claims 1-3, 5 and 8-10, wherein Ring A is selected from:





18. The compound of any one of claims 1-3, 5 and 8-10, wherein Ring A is selected from:

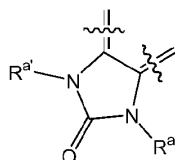


wherein

R^a is CH_2CHF_2 or CH_2CF_3 ; and

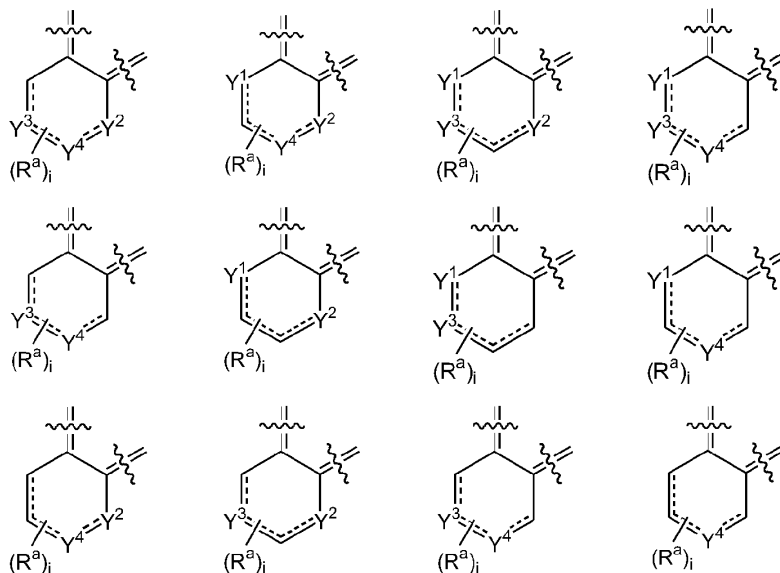
each R^a is independently H, Cl, F, CN or CH_3 .

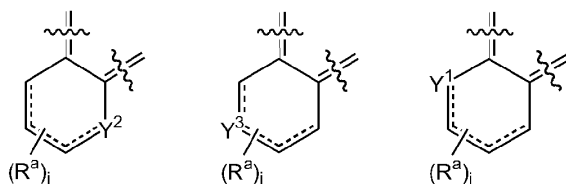
19. The compound of any one of claims 1-3, 5 and 8-10, wherein Ring A is



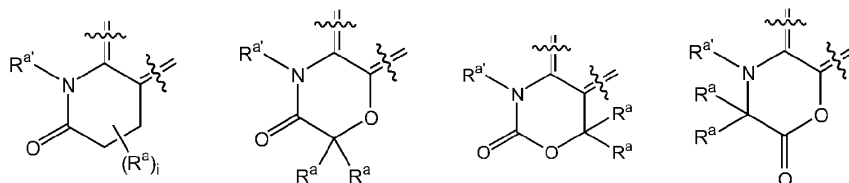
wherein one of R^a is CH_2CHF_2 or CH_2CF_3 , and the other R^a is H, CH_3 or CD_3 .

20. The compound of any one of claims 1-3, 6 and 8-10, wherein Ring A is selected from:



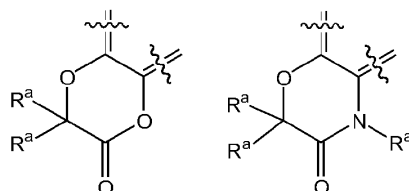


21. The compound of any one of claims 1-3, 6 and 8-10, wherein Ring A is selected from:



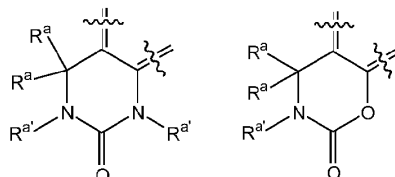
wherein $R^{a'}$ is CH_2CHF_2 or CH_2CF_3 , and R^a is H.

22. The compound of any one of claims 1-3, 6 and 8-10, wherein Ring A is selected from:



wherein one of R^a and $R^{a'}$ is selected from H, CH_3 , CD_3 , CD_2CD_3 , CH_2CN and CH_2CHF_2 , CH_2CF_3 and CH_2CN ; and the other R^a and/or $R^{a'}$ is H.

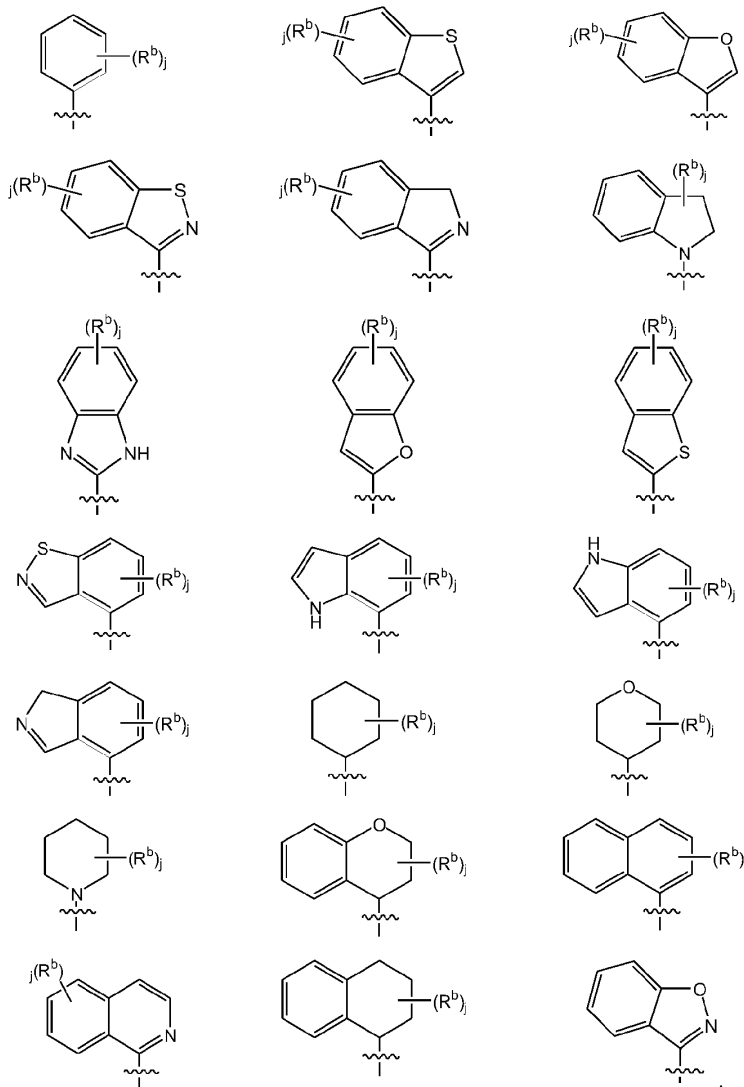
23. The compound of any one of claims 1-3, 6 and 8-10, wherein Ring A is selected from:



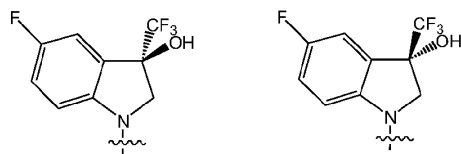
wherein each $R^{a'}$ is independently selected from H, CH_3 , CD_3 , CD_2CD_3 , CH_2CN and CH_2CHF_2 , CH_2CF_3 and CH_2CN .

24. The compound of any one of claims 1-3 and 7-10, wherein Ring A comprises one or more of O, NR, C(O), S(O)₂, C(O)O, C(O)NR, and NRC(O)NR, wherein each R is independently H, CH_3 , CH_2CH_3 , CD_2CD_3 , CH_2CHF_2 , CH_2CF_3 or CH_2CN .
25. The compound of claim any one of 1-24, wherein X is N.
26. The compound of claim any one of 1-24, wherein X is CH.
27. The compound of claim any one of 1-24, wherein X is CR^X , wherein R^X is C₁₋₃ alkyl.

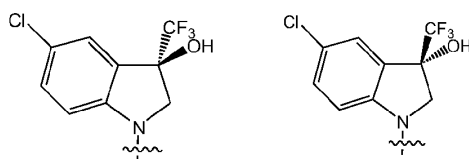
28. The compound of any one of claims 1-27, wherein Ring B is selected from:



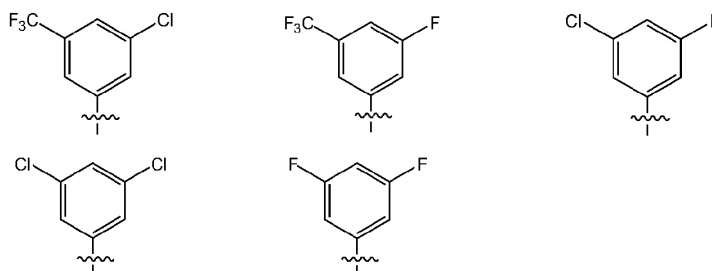
29. The compound of any one of claims 1-27, wherein Ring B is selected from:



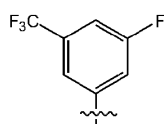
30. The compound of any one of claims 1-27, wherein Ring B is selected from:



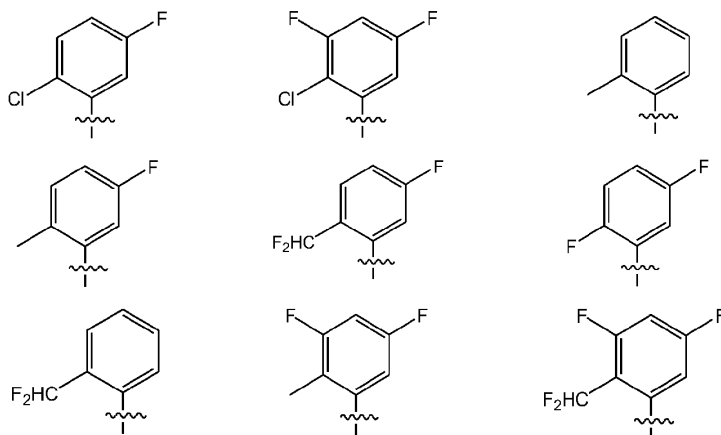
31. The compound of any one of claims 1-27, wherein Ring B is selected from:



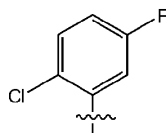
32. The compound of claim 31, wherein Ring B is:



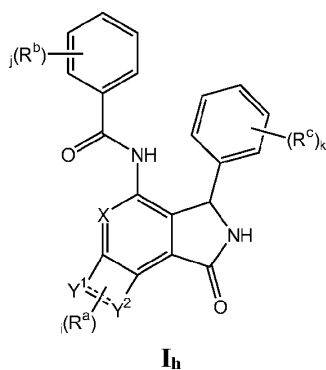
33. The compound of any one of claims 1-27, wherein Ring B is a substituted or unsubstituted phenyl, pyridyl, pyridazinyl or pyrazinyl.
34. The compound of claim 33, wherein Ring B is a substituted or unsubstituted phenyl.
35. The compound of claim 33, wherein Ring B is a substituted or unsubstituted pyridyl.
36. The compound of claim 33, wherein Ring B is a substituted or unsubstituted pyridazinyl.
37. The compound of claim 33, wherein Ring B is a substituted or unsubstituted pyrazinyl.
38. The compound of any one of claims 1-9 and 11-27, wherein Z^B is NH-C(O) .
39. The compound of any one of claims 1-38, wherein Ring C is a substituted or unsubstituted phenyl, pyridyl, pyridazinyl or pyrazinyl.
40. The compound of claim 39, wherein Ring C is a substituted or unsubstituted phenyl.
41. The compound of claim 39, wherein Ring C is a substituted or unsubstituted pyridyl.
42. The compound of claim 39, wherein Ring C is a substituted or unsubstituted pyridazinyl.
43. The compound of claim 39, wherein Ring C is a substituted or unsubstituted pyrazinyl.
44. The compound of claim 34 or 40, wherein each of Ring B and Ring C is independently a substituted or unsubstituted phenyl.
45. The compound of any one of claims 1-34, 40 and 44, wherein Ring C is selected from:



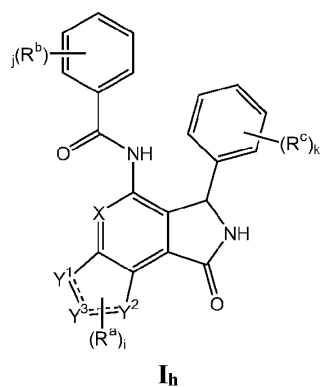
46. The compound of claim 45, wherein Ring C is:



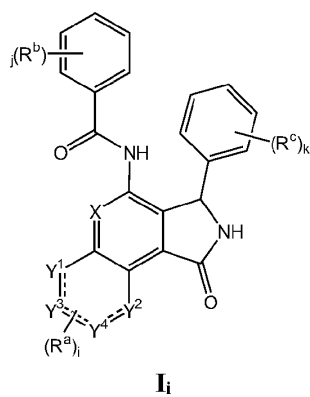
47. The compound of claim 1, having the structural formula **I_h**:



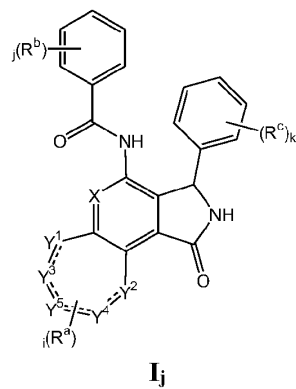
48. The compound of claim 1, having the structural formula **I_h**:



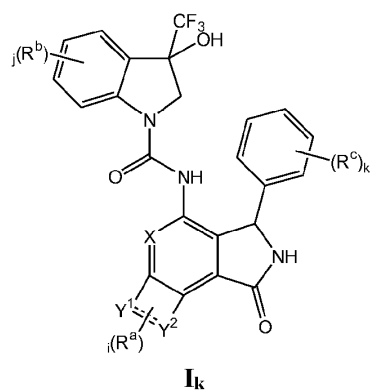
49. The compound of claim 1, having the structural formula **I_i**:



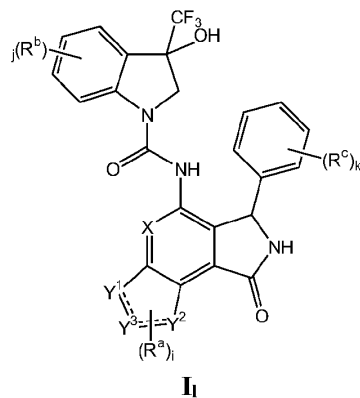
50. The compound of claim 1, having the structural formula **I_j**:



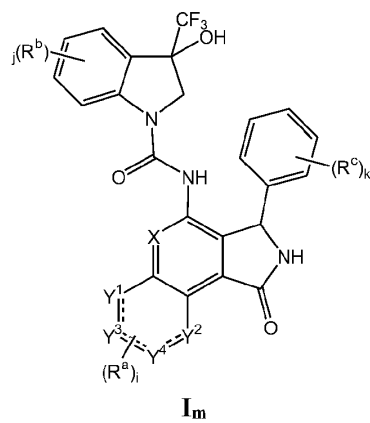
51. The compound of claim 1, having the structural formula **I_k**:



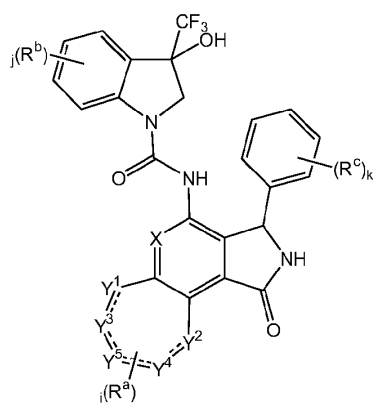
52. The compound of claim 1, having the structural formula **I_k**:



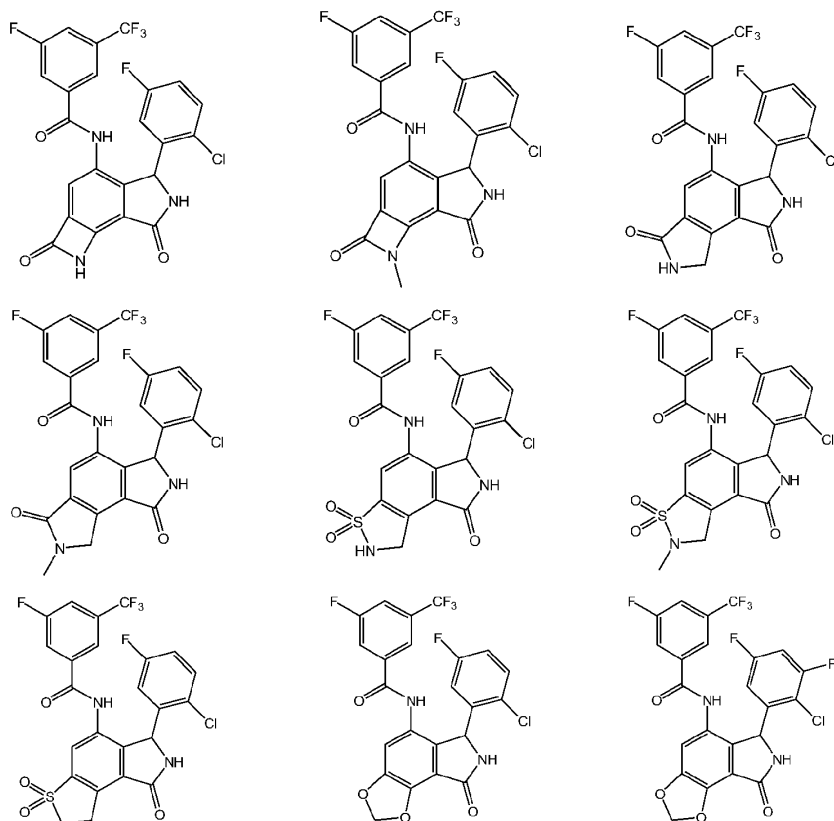
53. The compound of claim 1, having the structural formula **I_m**:

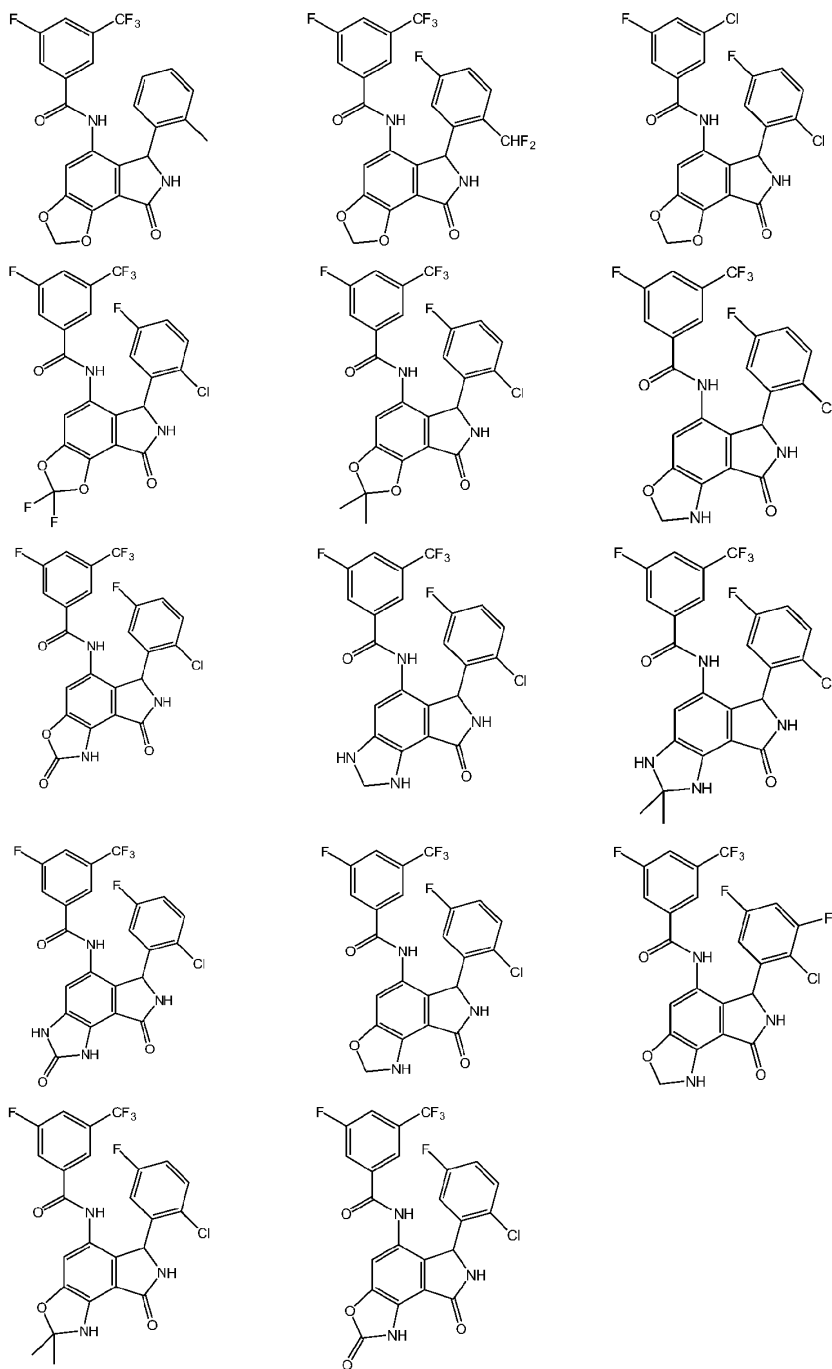


54. The compound of claim 1, having the structural formula **I_n**:

**I_n**

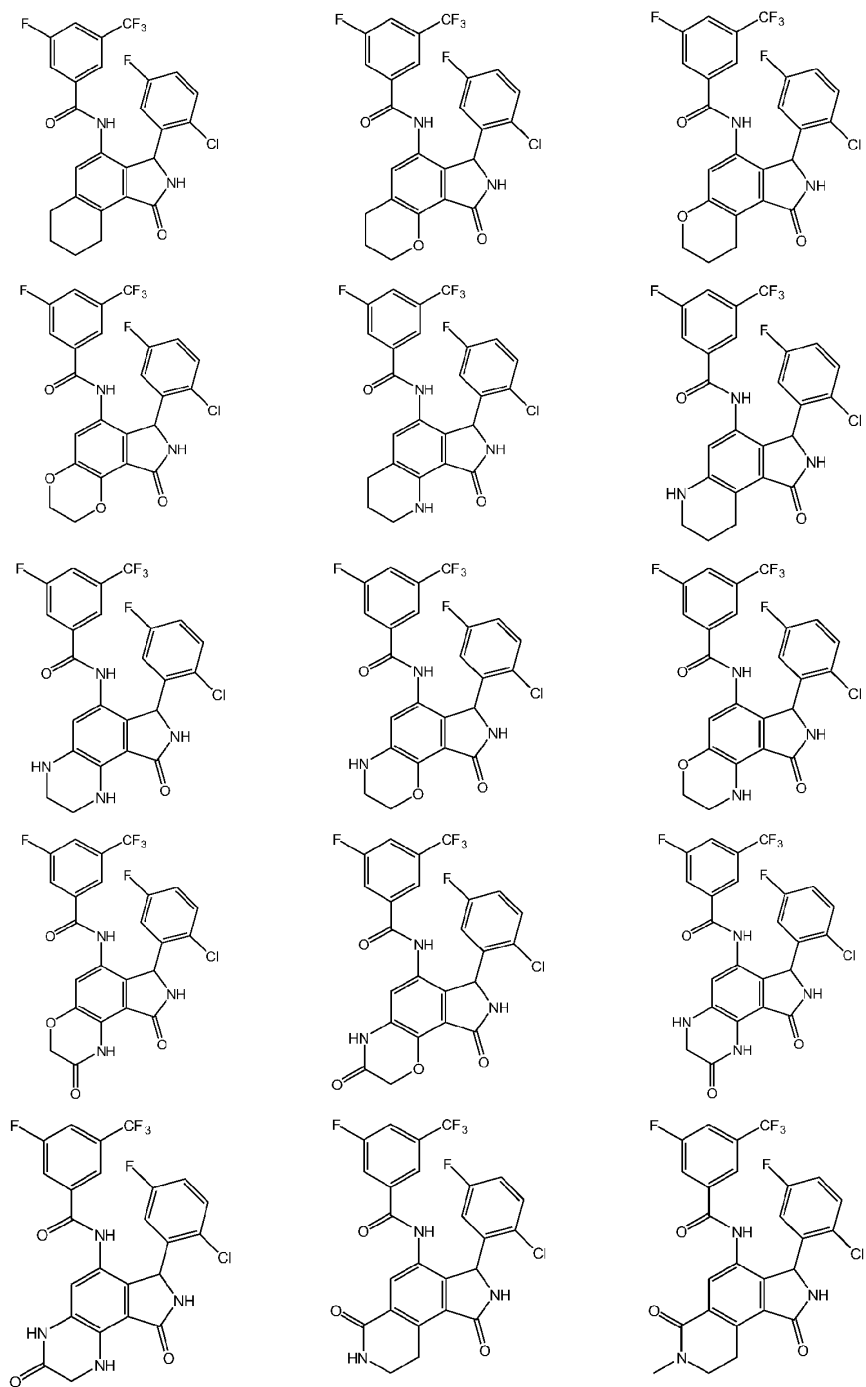
55. A compound having a structural formula selected from:

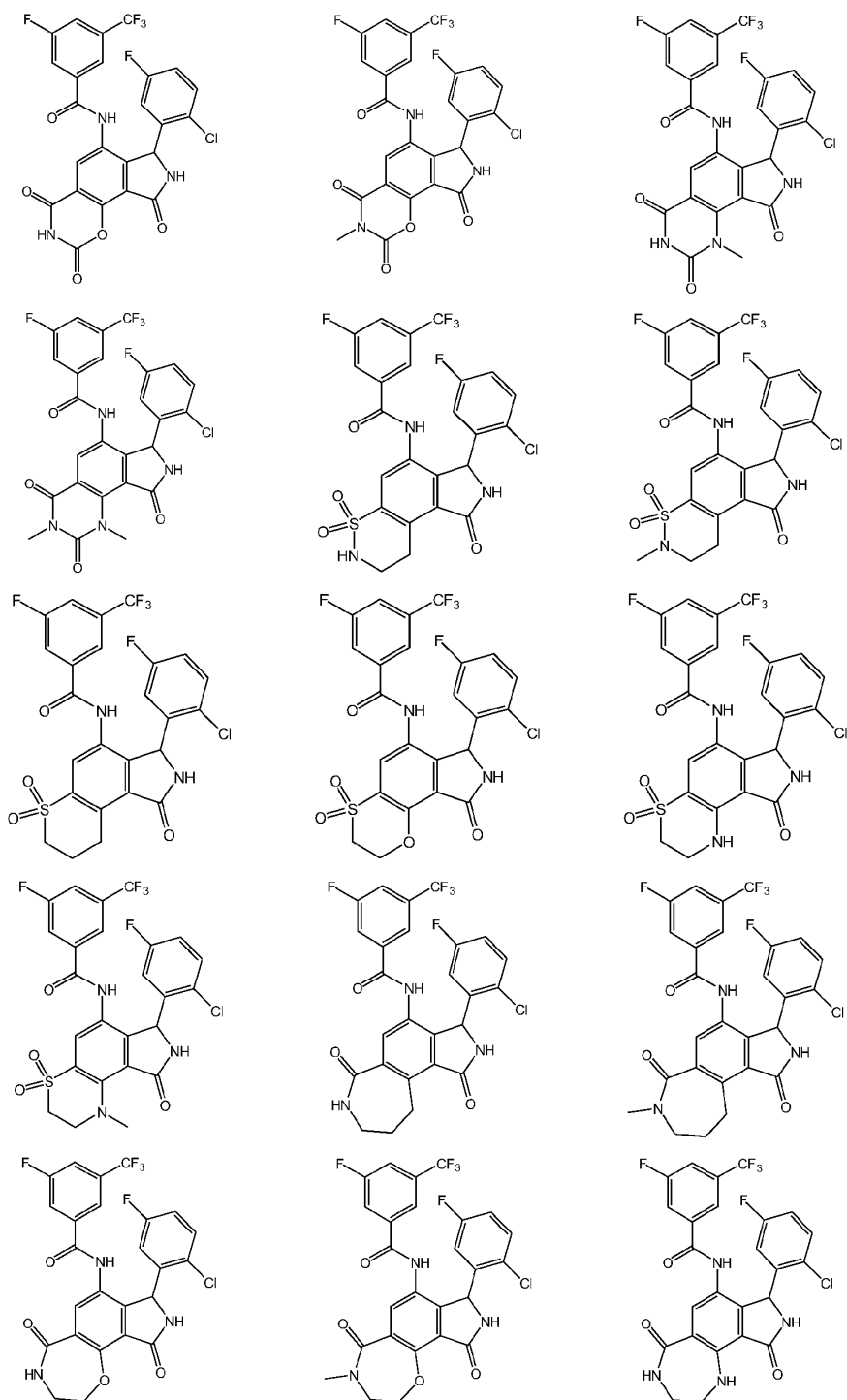


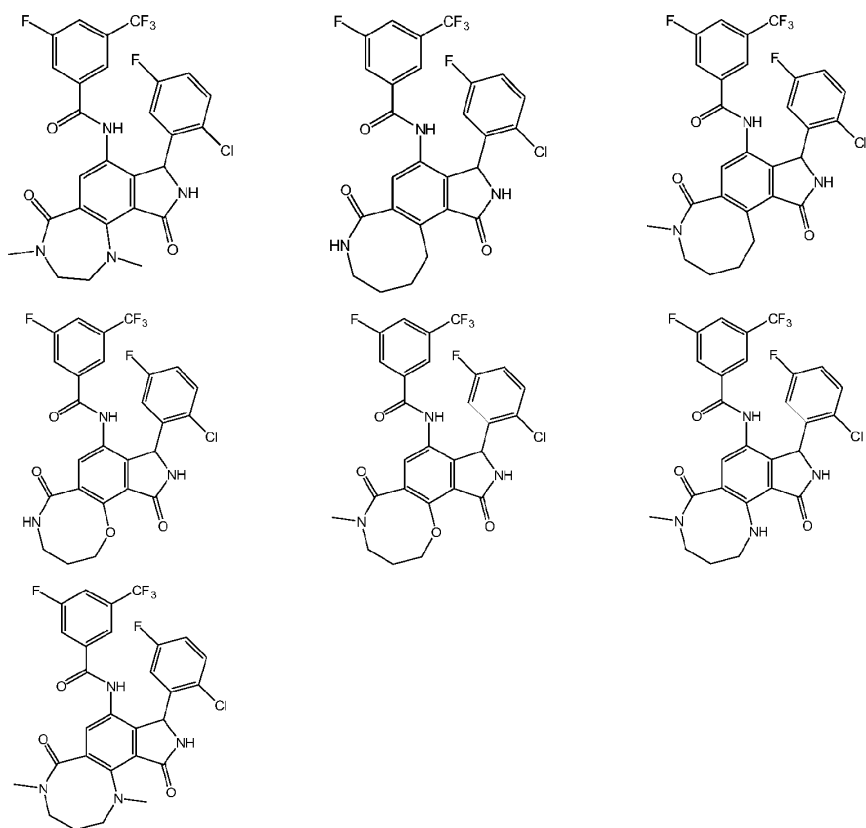


or a pharmaceutically acceptable form or an isotope derivative thereof.

56. A compound having a structural formula selected from:

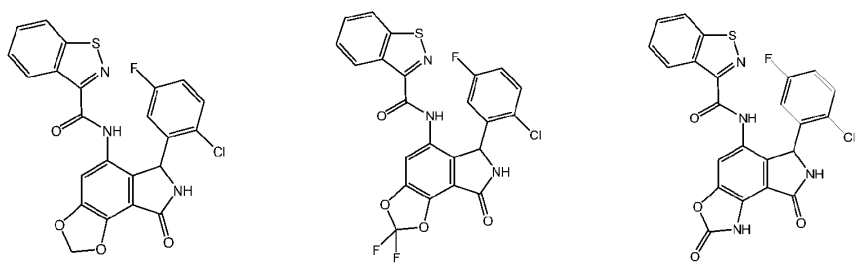


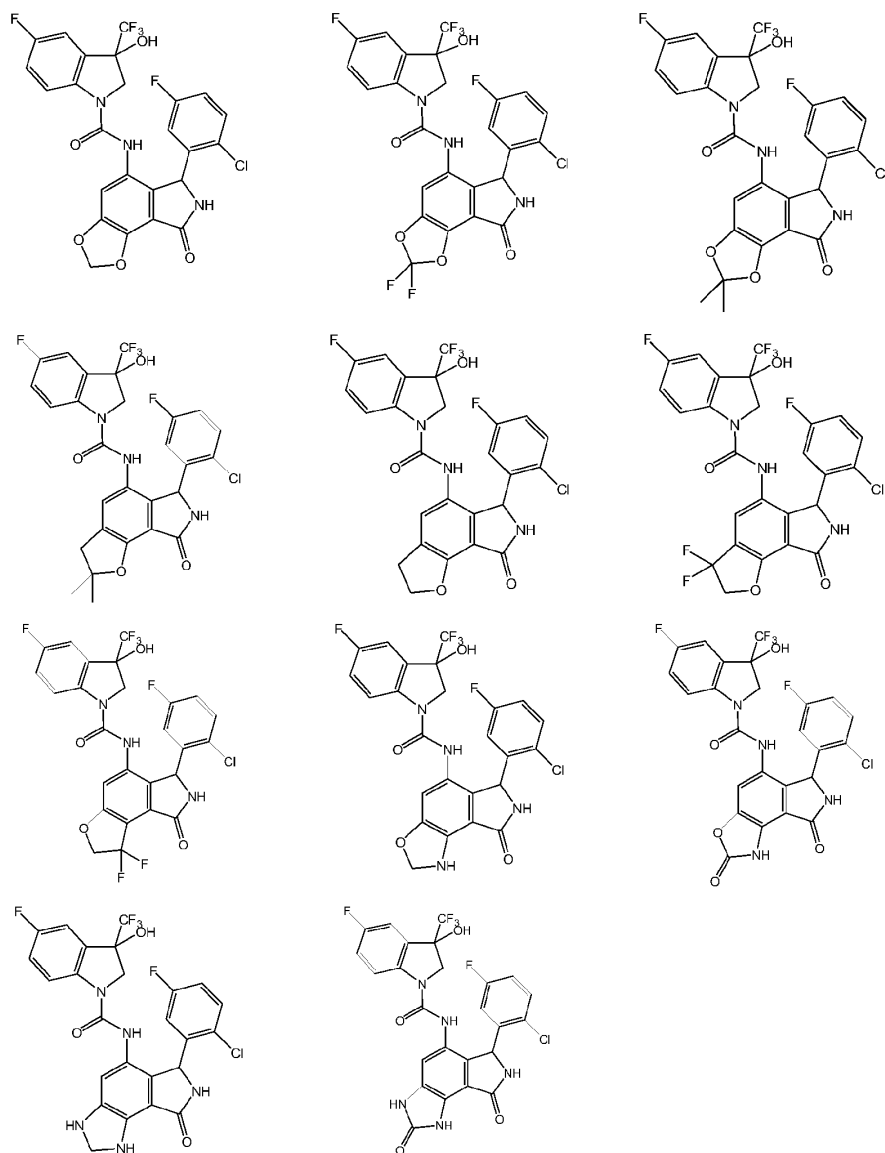




or a pharmaceutically acceptable form or an isotope derivative thereof.

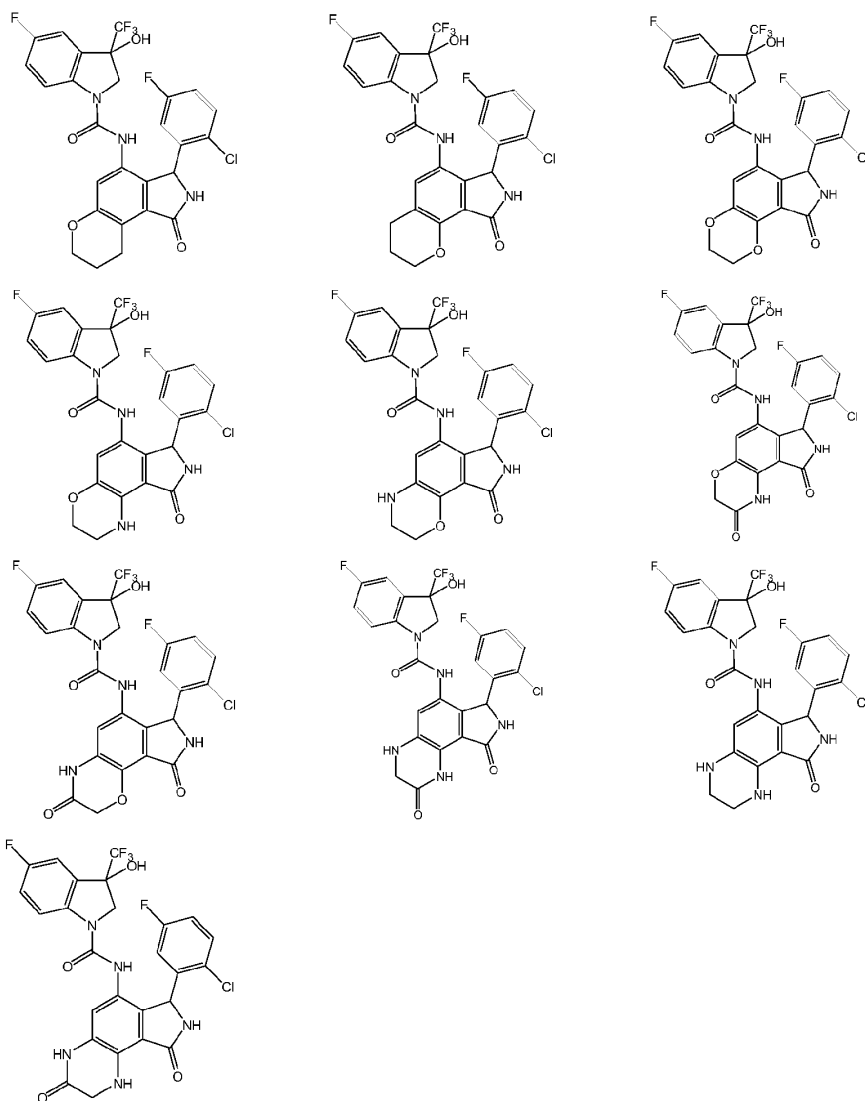
57. A compound having a structural formula selected from:





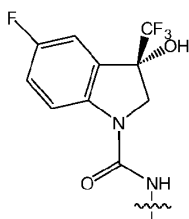
or a pharmaceutically acceptable form or an isotope derivative thereof.

58. A compound having a structural formula selected from:

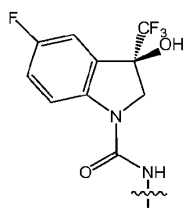


or a pharmaceutically acceptable form or an isotope derivative thereof.

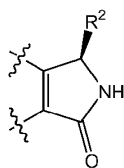
59. The compound of any one of claims 51-54, 57 and 58, having the following chirality in R¹:



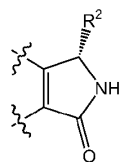
60. The compound of any one of claims 51-54, 57 and 58, having the following chirality in R^1 :



61. The compound of any one of claims 1-60, having the following chirality at the carbon to which R^2 is bond:



62. The compound of any one of claims 1-60, having the following chirality at the carbon to which R^2 is bond:



63. A compound selected from **Table 1**, or a pharmaceutically acceptable form or an isotope derivative thereof.
64. The compound of any of claims 1-63, having one or more deuterium atoms in place of hydrogen.
65. The compound of any of claims 1-64, having one deuterium atom in place of a hydrogen atom.
66. A pharmaceutical composition comprising a compound according to any one of claims 1-65 and a pharmaceutically acceptable excipient, carrier, or diluent.

67. The pharmaceutical composition of claim 66, being suitable for oral administration.
68. A unit dosage form comprising a pharmaceutical composition according to claim 66 or 67.
69. The unit dosage form of claim 68, being in the form of a tablet or capsule.
70. A method for inhibiting cellular proliferation *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound according to any one of claims 1-65.
71. A method for inhibiting phosphoinositide 3-kinase α (PI3K α) activity in a cell, comprising contacting the cell with a compound according to any one of claims 1-65.
72. A method for treating a disease or disorder mediated by phosphoinositide 3-kinase α (PI3K α), comprising administering to a subject in need thereof a therapeutically effective amount of the compound according to any one of claims 1-65.
73. The method of claim 72, wherein the disease or disorder is a cellular proliferative disease.
74. A method for treating or reducing cancer, or a related disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of the compound according to any one of claims 1-65.
75. The method of claim 74, wherein the cancer is selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcoma, leukemia, neuroma, melanoma, and lymphoma.
76. The method of claim 74 or 75, wherein the cancer is selected from the group consisting of breast cancer, ovarian cancer, pancreatic cancer, colorectal cancer, lung cancer, endometrial cancer, appendix cancer, cholangiocarcinoma, bladder urothelial cancer, gastric cancer, bile duct cancer, and a hematologic malignancy.
77. The method of any one of claims 74-76, wherein the subject has a mutated class IA PI3K p110 α .
78. The method of any one of claims 74-77, wherein the subject has at least one of the following PI3K α mutations: H1047R, E542K, and E545K.
79. The method of any one of claims 74-78, wherein the subject being treated is further administered one or more of chemotherapy, radiotherapy, targeted therapy, immunotherapy, and hormonal therapy.
80. Use of the compound according to any one of claims 1-65, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a

disease or disorder.

81. The use of claim 80, wherein the disease or disorder is a cellular proliferative disease.
82. The use of claim 81, wherein the disease or disorder is cancer.
83. The use of claim 82, wherein the cancer is selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcoma, leukemia, neuroma, melanoma, and lymphoma.
84. The use of claim 82, wherein the cancer is selected from the group consisting of ovarian cancer, cervical cancer, breast cancer, pancreatic cancer, colorectal cancer, small and non-small cell lung cancer, endometrial cancer, appendix cancer, cholangiocarcinoma, bladder urothelial cancer, gastric carcinomas, bile duct cancer, hepatocellular carcinoma, thyroid carcinoma, and a hematologic malignancy.
85. The use of claim 82, wherein the cancer is selected from the group consisting of acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and glioblastomas.