

UREA DERIVATIVES OF TRICYCLIC COMPOUNDS, AND COMPOSITIONS AND METHODS THEREOF

Priority Claims and Related Applications

[0001] This application claims the benefit of priority to U.S. Provisional Application Nos. 63/627,117, filed January 31, 2024, and 63/729,148, filed December 6, 2024, 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 urea derivatives of 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 PDK1/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 H1047R, E542K, E545K and H1047X. (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.)

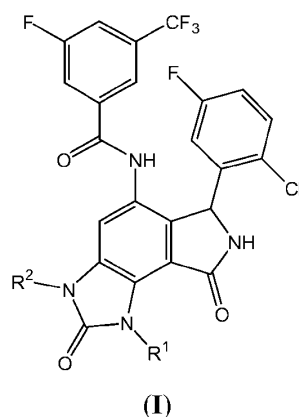
[0006] There remains an urgent and unmet need for potent and selective PI3K α inhibitors that are safe and effective in treating diseases and conditions associated with PI3K α , such as various types of cancer (*e.g.*, breast cancer, ovarian cancer, colorectal cancer, lung cancer).

Summary of the Invention

[0007] The invention provides novel urea derivatives of tricyclic compounds 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):



or a pharmaceutically acceptable form or an isotope derivative thereof, wherein

each of R¹ and R² is independently a C₁₋₆ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl group, substituted with 0-8 R^A, wherein R^A is independently selected from D, halogen, CN, OR, SR, NRR', an unsubstituted or substituted C₃₋₆ carbocyclic or heterocyclic group, and an unsubstituted or substituted 5- or 6-membered aryl or heteroaryl group; and

each of R and R' is independently H, unsubstituted or substituted C₁₋₄ alkyl, or unsubstituted or substituted 3- 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.

[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 modulating (*e.g.*, reducing) 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” 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, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxaliny, quinuclidinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 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.

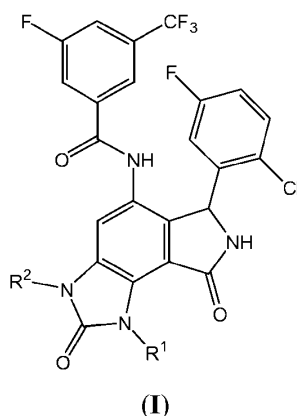
[0057] As used herein, the term “heterocycloalkyl” refers to a cycloalkyl radical, which have one or more skeletal chain atoms selected from an atom other than carbon, *e.g.*, O, N, S, P or combinations thereof. Unless stated otherwise in the specification, the term is intended to include both substituted 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-pyranyl, 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, aziridinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, piperazinyl, imidazolidinyl, imidazopyridinyl, thiazolidinyl, dithianyl, trithianyl, dioxolanyl, oxazolidinyl, oxazolidinonyl, decahydroquinolinyl, piperidinyl, 4-piperidinonyl, quinuclidinyl, thiomorpholinyl, thiomorpholinyl 1,1-dioxide, morpholinyl, azepanyl, oxazepanyl, azabicyclohexanyls, azabicycloheptanyl, azabicyclooctanyls, azabicyclononanyls (*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]oxazinyl, octahydroindoliziny, oxaazaspiroonanyls, oxaazaspirooctanyls, diazaspiroonanyls, oxaazabiocycloheptanyls, 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 urea derivatives of tricyclic compounds 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):

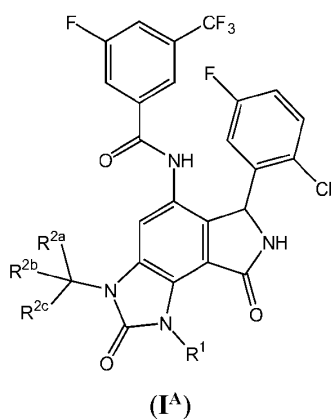


or a pharmaceutically acceptable form or an isotope derivative thereof,
wherein

each of R¹ and R² is independently a C₁₋₆ (*e.g.*, C₁₋₃) alkyl, C₂₋₅ (*e.g.*, C₂₋₃) alkenyl, or C₂₋₅ (*e.g.*, C₂₋₃) alkynyl group, substituted with 0-8 (*e.g.*, 0, 1, 2, 3, 4, 5, 6, 7 or 8) R^A, wherein each R^A is independently selected from D, halogen, CN, OR, SR, NRR', an unsubstituted or substituted C₃₋₆ carbocyclic or heterocyclic group, and an unsubstituted or substituted 5- or 6-membered aryl or heteroaryl group; and

each of R and R' is independently H, unsubstituted or substituted C₁₋₄ alkyl, or unsubstituted or substituted 3- to 6-membered (*e.g.*, 3-, 4-, 5- or 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 (*e.g.*, 4-, 5- or 6-membered) heterocyclic ring.

[0061] In certain embodiments of (I), R² is CR^{2a}R^{2b}R^{2c}, having the structural formula (I^A):



wherein

R^{2a} is H, D or halogen;

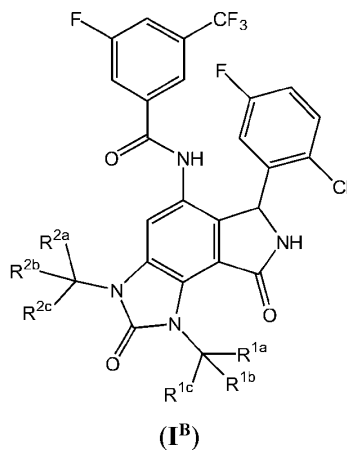
R^{2b} is H, D or halogen; and

R^{2c} is

H, D, halogen, CN, OR, SR, or NRR' ; or

an unsubstituted or substituted C_{1-5} (e.g., C_{1-3}) alkyl, C_{3-6} carbocyclic or heterocyclic group, or 5- or 6-membered aryl or heteroaryl group.

[0062] In certain embodiments of (I^A), R^1 is $CR^{1a}R^{1b}R^{1c}$, having the structural formula (I^B):



wherein

R^{1a} is H, D or halogen;

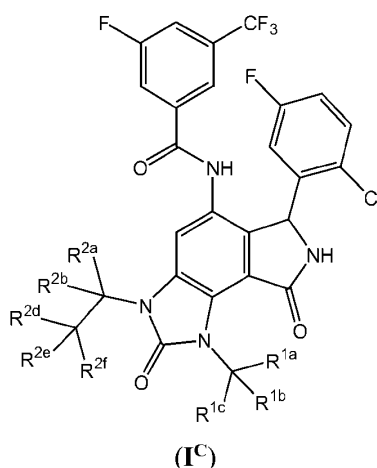
R^{1b} is H, D or halogen; and

R^{1c} is

H, D, halogen, CN, OR, SR, or NRR'; or

an unsubstituted or substituted C₁₋₅ (e.g., C₁₋₃) alkyl, C₃₋₆ carbocyclic or heterocyclic group, or 5- or 6-membered aryl or heteroaryl group.

[0063] In certain embodiments of (I^B), R^{2c} is CR^{2d}R^{2e}R^{2f}, having the structural formula (I^C):



wherein

R^{2d} is H, D or halogen; and

each of R^{2e} and R^{2f} is independently

H, D, halogen, CN, OR, SR, or NRR'; or

an unsubstituted or substituted C₁₋₅ (e.g., C₁₋₃) alkyl, C₃₋₆ carbocyclic or heterocyclic group, or 5- or 6-membered aryl or heteroaryl group.

[0064] In certain embodiments of (I^A)-(I^C), each of R^{2a} and R^{2b} is H.

[0065] In certain embodiments of (I^A)-(I^C), each of R^{2a} and R^{2b} is D.

[0066] In certain embodiments of (I^C), at least one of R^{2d}, R^{2e} and R^{2f} is a halogen atom. In certain embodiments of (I^C), one of R^{2d}, R^{2e} and R^{2f} is F. In certain embodiments of (I^C), two of R^{2d}, R^{2e} and R^{2f} is F. In certain embodiments of (I^C), each of R^{2d}, R^{2e} and R^{2f} is F.

[0067] In certain embodiments of (I^A)-(I^C), at least one of R^{2d}, R^{2e} and R^{2f} is a D. In certain embodiments of (I^C), one of R^{2d}, R^{2e} and R^{2f} is D. In certain embodiments of (I^C), two of R^{2d}, R^{2e} and R^{2f} is D. In certain embodiments of (I^C), each of R^{2d}, R^{2e} and R^{2f} is D.

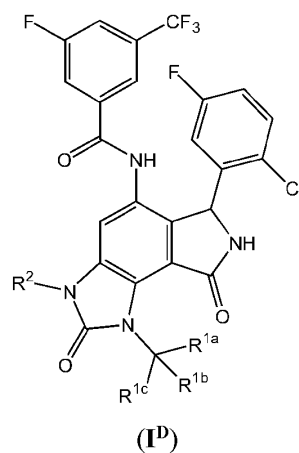
[0068] In certain embodiments of (I)-(I^C), R¹ is CH₃.

[0069] In certain embodiments of (I)-(I^C), R¹ is CD₃.

[0070] In certain embodiments of (I)-(I^C), R¹ is not CH₃.

[0071] In certain embodiments of (I)-(I^C), R¹ is not CD₃.

[0072] In certain embodiments of (I), R¹ is CR^{1a}R^{1b}R^{1c}, having the structural formula (I^D):



wherein

R^{1a} is H, D or halogen;

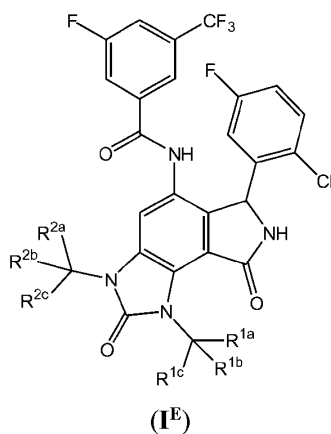
R^{1b} is H, D or halogen; and

R^{1c} is

H, D, halogen, CN, OR, SR, or NRR'; or

an unsubstituted or substituted C₁₋₅ (*e.g.*, C₁₋₃) alkyl, C₃₋₆ carbocyclic or heterocyclic group, or 5- or 6-membered aryl or heteroaryl group.

[0073] In certain embodiments of (I^D), R² is CR^{2a}R^{2b}R^{2c}, having the structural formula (I^E):



wherein

R^{2a} is H, D or halogen;

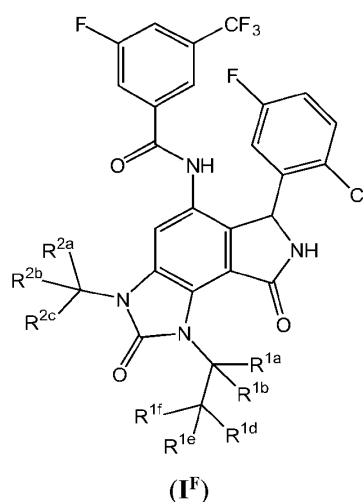
R^{2b} is H, D or halogen; and

R^{2c} is

H, D, halogen, CN, OR, SR, or NRR' ; or

an unsubstituted or substituted C_{1-5} (e.g., C_{1-3}) alkyl, C_{3-6} carbocyclic or heterocyclic group, or 5- or 6-membered aryl or heteroaryl group.

[0074] In certain embodiments of (I^E) , R^{1c} is $CR^{1d}R^{1e}R^{1f}$, having the structural formula (I^F) :



wherein

R^{1d} is H, D or halogen; and

each of R^{1e} and R^{1f} is independently

H, D, halogen, CN, OR, SR, or NRR' ; or

an unsubstituted or substituted C_{1-5} (e.g., C_{1-3}) alkyl, C_{3-6} carbocyclic or heterocyclic group, or a 5- or 6-membered aryl or heteroaryl group.

[0075] In certain embodiments of (I^D) – (I^F) , each of R^{1a} and R^{1b} is H.

[0076] In certain embodiments of (I^D) – (I^F) , each of R^{1a} and R^{1b} is D.

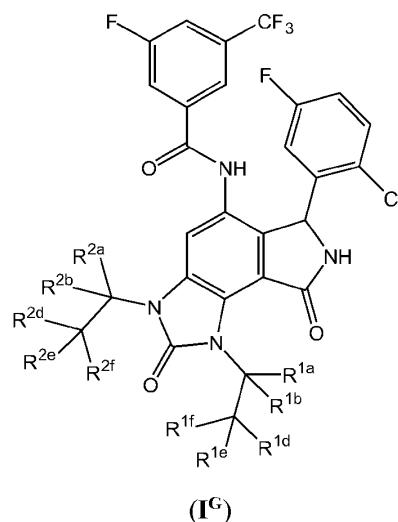
[0077] In certain embodiments of (I^D) – (I^F) , each of R^{1a} , R^{1b} and R^{1c} is D.

[0078] In certain embodiments of (I^F) , at least one of R^{1d} , R^{1e} and R^{1f} is a halogen atom. In certain embodiments of (I^F) , one of R^{1d} , R^{1e} and R^{1f} is F. In certain embodiments of (I^F) , two of R^{1d} , R^{1e} and R^{1f} is F.

[0079] In certain embodiments of (I^D) – (I^F) , R^2 is CH_3 or CD_3 .

[0080] In certain embodiments of (I^D) – (I^F) , R^2 is not CH_3 or CD_3 .

[0081] In certain embodiments of (I), (I^C) and (I^F), having the structural formula (I^G):



[0082] In certain embodiments of (I^G), each of R^{2a} and R^{2b} is H.

[0083] In certain embodiments of (I^G), each of R^{2a} and R^{2b} is D.

[0084] In certain embodiments of (I^G), at least one of R^{2d}, R^{2e} and R^{2f} is a halogen atom. In certain embodiments of (I^G), one of R^{2d}, R^{2e} and R^{2f} is F. In certain embodiments of (I^G), two of R^{2d}, R^{2e} and R^{2f} is F. In certain embodiments of (I^G), each of R^{2d}, R^{2e} and R^{2f} is F.

In certain embodiments of (I^G), at least one of R^{2d}, R^{2e} and R^{2f} is D.

[0085] In certain embodiments of (I^G), one of R^{2d}, R^{2e} and R^{2f} is D. In certain embodiments of (I^G), two of R^{2d}, R^{2e} and R^{2f} is D. In certain embodiments of (I^G), each of R^{2d}, R^{2e} and R^{2f} is D.

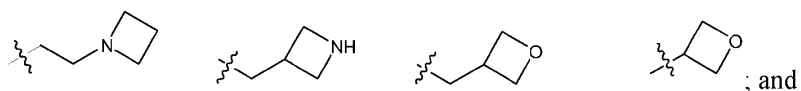
[0086] In certain embodiments of (I^G), each of R^{1a} and R^{1b} is H.

[0087] In certain embodiments of (I^G), each of R^{1a} and R^{1b} is D.

[0088] In certain embodiments of (I^G), each of R^{1d}, R^{1e} and R^{1f} is a H or D.

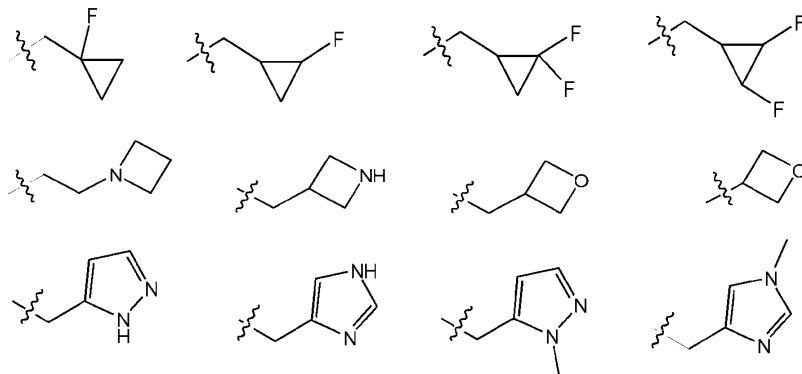
[0089] In certain embodiments of (I), R¹ and R² are independently selected from:

R¹: CH₃, CH₂D, CHD₂, CD₃, CH₂F, CHF₂, CD₂F, CDF₂, CF₃, CH₂CH₃, CD₂CH₃, CH₂CD₃, CD₂CD₃, CH₂CN, CH₂CH₂N(CH₃)₂,

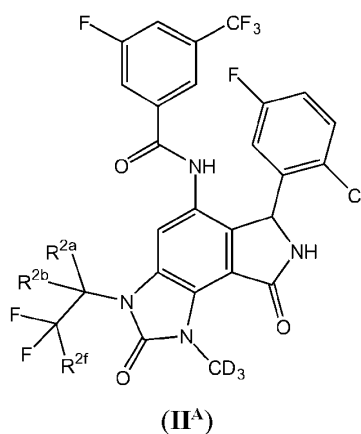


R²: CH₃, CH₂D, CHD₂, CD₃, CH₂CH₃, CH₂CH₂F, CD₂CH₂F, CH₂CD₂F, CD₂CD₃, CD₂CD₂F, CH₂CHF₂, CD₂CHF₂, CH₂CDF₂, CD₂CDF₂, CH₂CF₃, CD₂CF₃, CH₂CN, CH₂CH₂N(CH₃)₂, CH₂CH₂OH, CH₂CH₂OCH₃, CH₂CH₂CH₂F, CH₂CH₂CHF₂, CH₂CH₂CF₃,

propyl, isopropyl, n-butyl, isobutyl,



[0090] In certain embodiments of (I), the compound has a structural formula (II^A):



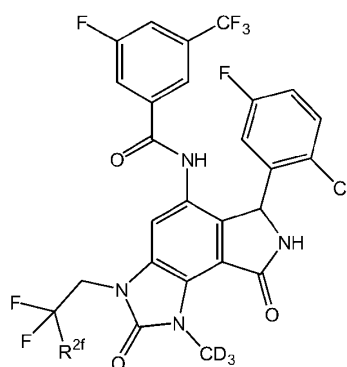
wherein

R^{2a} is H or D;

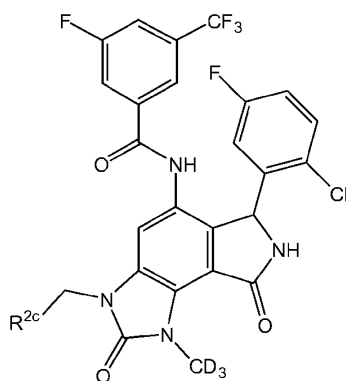
R^{2b} is H or D; and

R^{2f} is D, F, CN, OR, NRR', or an unsubstituted or substituted C₁₋₅ (*e.g.*, C₁₋₃) alkyl or C₃₋₅ carbocyclic or heterocyclic group.

[0091] In certain embodiments of (II^A), each of R^{2a} and R^{2b} is H, having the structural formula (II^B):

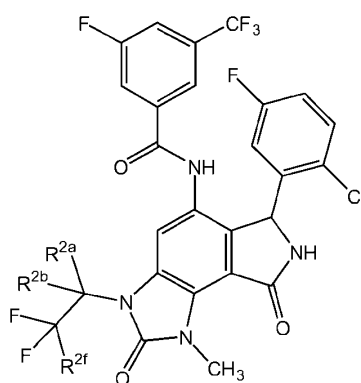
(II^B)

[0092] In certain embodiments of (I), the compound has the structural formula (II^C):

(II^C)

wherein R^{2c} is CN, OR, SR, NRR', unsubstituted or substituted C₃₋₆ carbocyclic or heterocyclic group, or a 5- or 6-membered aryl or heteroaryl group.

[0093] In certain embodiments of (I), the compound has the structural formula (II^E):



(II^E)

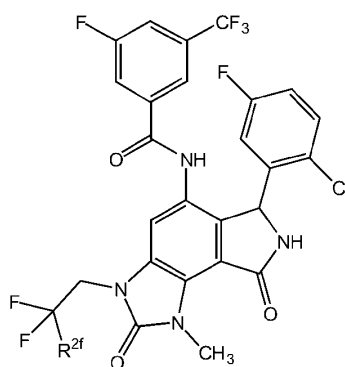
wherein

R^{2a} is H or D;

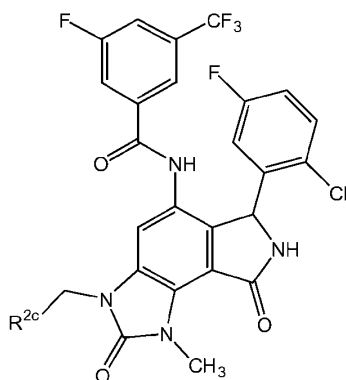
R^{2b} is H or D; and

R^{2f} is D, F, CN, OR, NRR', or an unsubstituted or substituted C₁₋₅ (*e.g.*, C₁₋₃) alkyl or C₃₋₅ carbocyclic or heterocyclic group.

[0094] In certain embodiments of (II^E), each of R^{2a} and R^{2b} is H, having the structural formula (II^F):

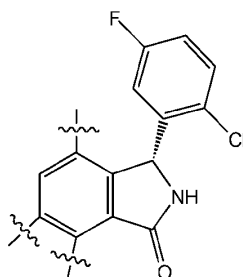
(II^F)

[0095] In certain embodiments of (I), the compound has the structural formula (II^G):

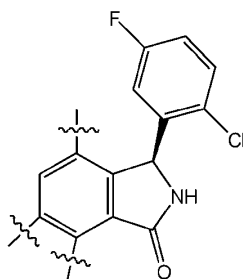
(II^G)

wherein R^{2c} is CN, OR, SR, NRR', unsubstituted or substituted C₃₋₆ carbocyclic or heterocyclic group, or a 5- or 6-membered aryl or heteroaryl group.

[0096] In certain embodiments of (I)-(II^G), the compound has the chirality shown in formula (III^A):

(III^A)

[0097] In certain embodiments of (I)-(II^G), the compound has the chirality shown in formula (III^B):

(III^B)

[0098] Non-limiting exemplary compounds of the invention can also be found in **Table 1** in the Examples section.

[0099] 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.

[00100] In another aspect, the invention generally relates to a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient, carrier, or diluent.

[00101] In certain embodiments, the pharmaceutical composition is suitable for oral administration.

[00102] In yet another aspect, the invention generally relates to a unit dosage form comprising a pharmaceutical composition disclosed herein.

[00103] In certain embodiments, the unit dosage form is in the form of a tablet or capsule.

[00104] 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.

[00105] 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).

[00106] 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.

[00107] 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.

[00108] 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.

[00109] 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.

[00110] In yet another aspect, the invention generally relates to a method for modulating PI3K α activity in a cell, comprising contacting the cell with a compound disclosed herein.

[00111] In yet another aspect, the invention generally relates to a method for reducing PI3K α activity in a cell, comprising contacting the cell with a compound disclosed herein.

[00112] 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.

[00113] In certain embodiments, the disease or disorder is a cellular proliferative disease.

[00114] 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.

[00115] In certain embodiments, the cancer is selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcoma, leukemia, neuroma, melanoma, and lymphoma.

[00116] 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.

[00117] 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.

[00118] In certain embodiments, the cancer is selected from the group consisting of acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and glioblastomas.

[00119] In certain embodiments, the subject has a mutated class IA PI3K p110 α .

[00120] In certain embodiments, the subject has at least one of the following PI3K α mutations: H1047R, E542K, E545K and H1047X.

[00121] In certain embodiments, the subject does not have a PI3K α mutant protein.

[00122] In certain embodiments, the subject being treated is further administered one or more of chemotherapy, radiotherapy, targeted therapy, immunotherapy, and hormonal therapy.

[00123] 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.

[00124] In yet another aspect, the invention generally relates to use of a compound disclosed herein for treating a disease or disorder.

[00125] 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.

[00126] 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.

[00127] 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.

[00128] 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.

[00129] 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.

[00130] 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.

[00131] 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.

[00132] 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.

[00133] 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.

[00134] 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.

[00135] 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.

[00136] 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.

[00137] 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.

[00138] 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.

[00139] 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.

[00140] 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.

[00141] 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.

[00142] In certain embodiments, the method further comprises administering a chemotherapeutic agent to the subject.

[00143] 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.

[00144] 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.

[00145] 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).

[00146] 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.

[00147] 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.

[00148] 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.

[00149] 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.

[00150] 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.

[00151] 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.)

[00152] 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.

[00153] 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.

[00154] 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.

[00155] 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.

[00156] 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.

[00157] 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.

[00158] 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.

[00159] 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.

[00160] 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

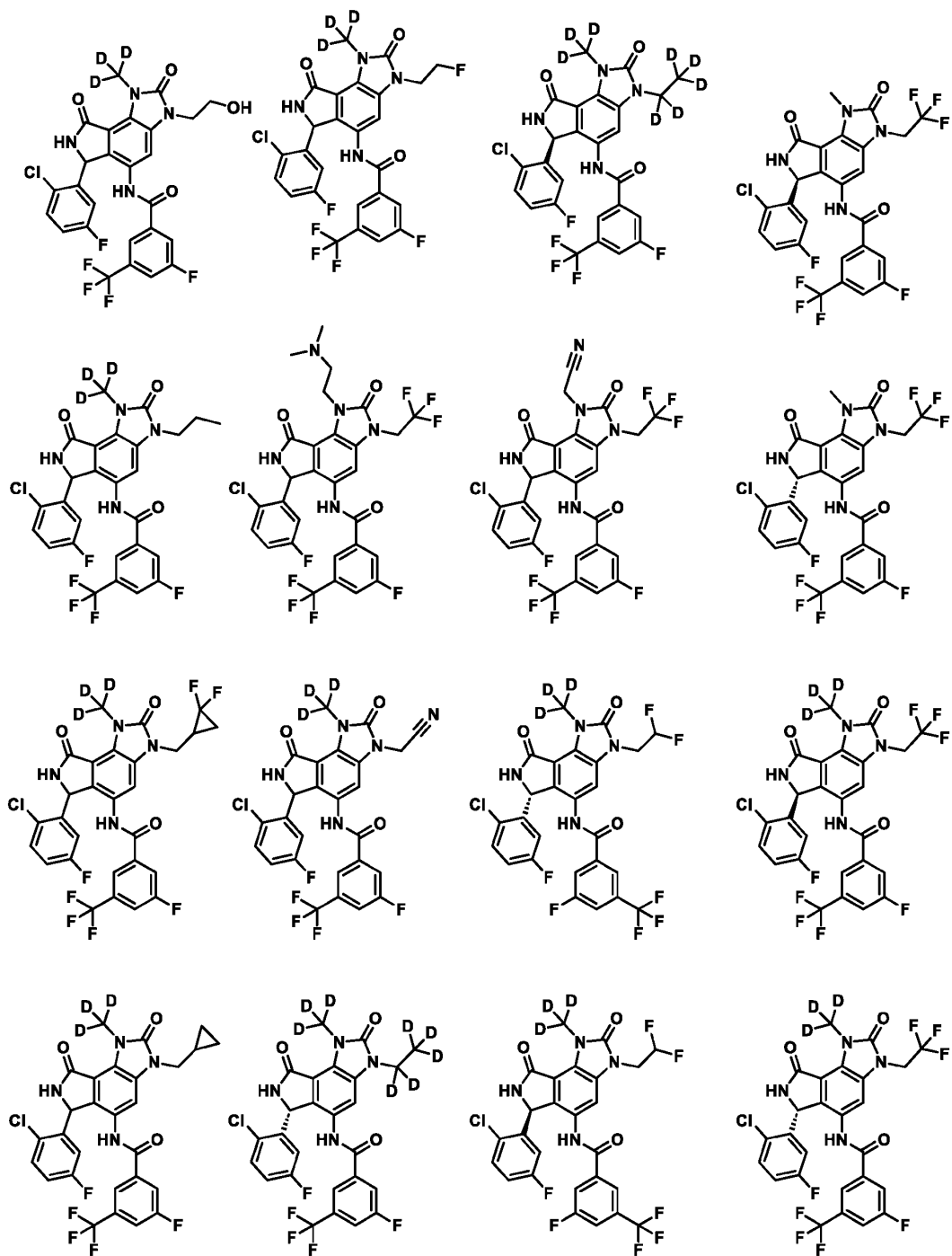
such combination or subset of combinations is specifically contemplated and should be considered disclosed.

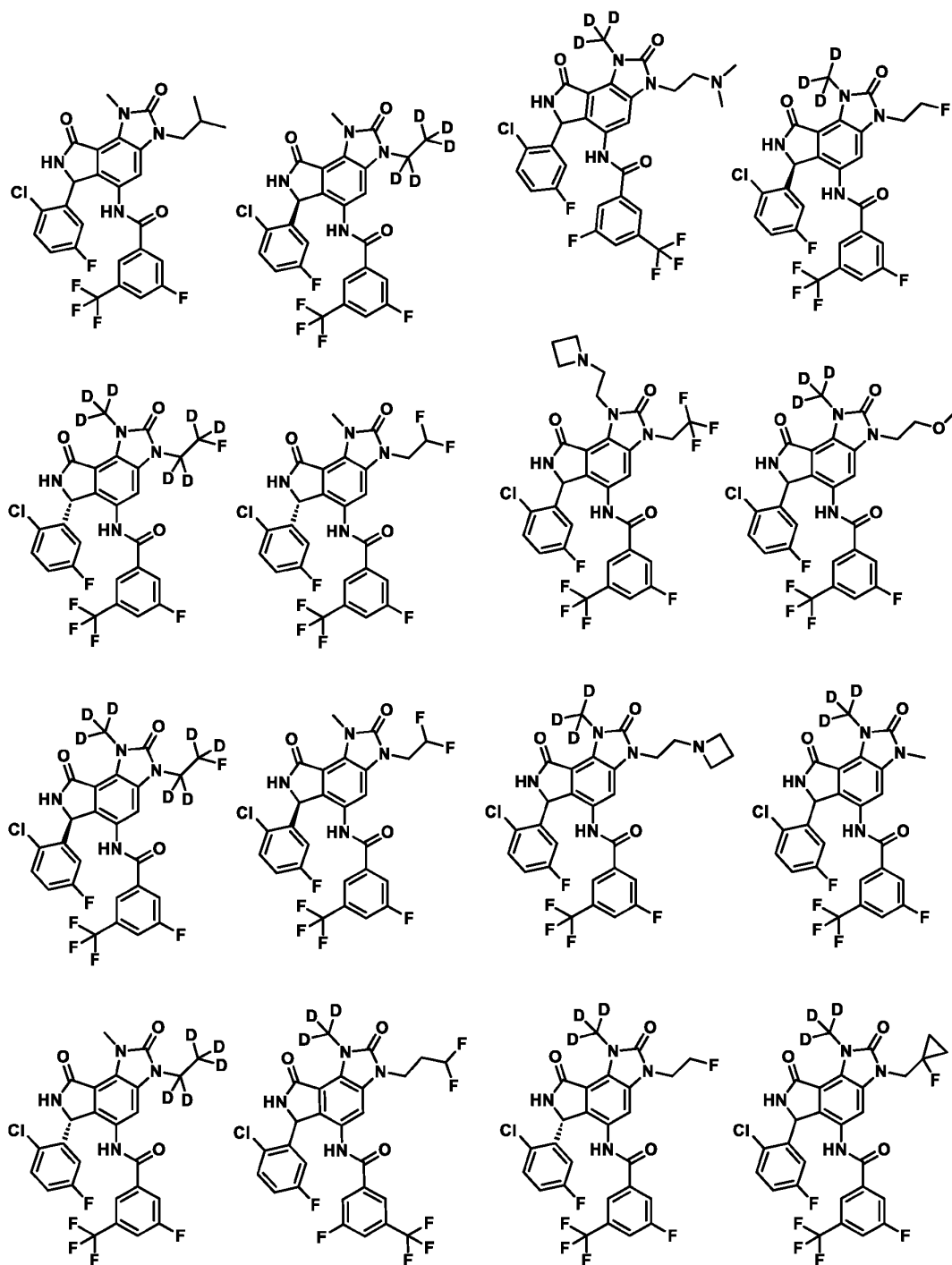
Examples

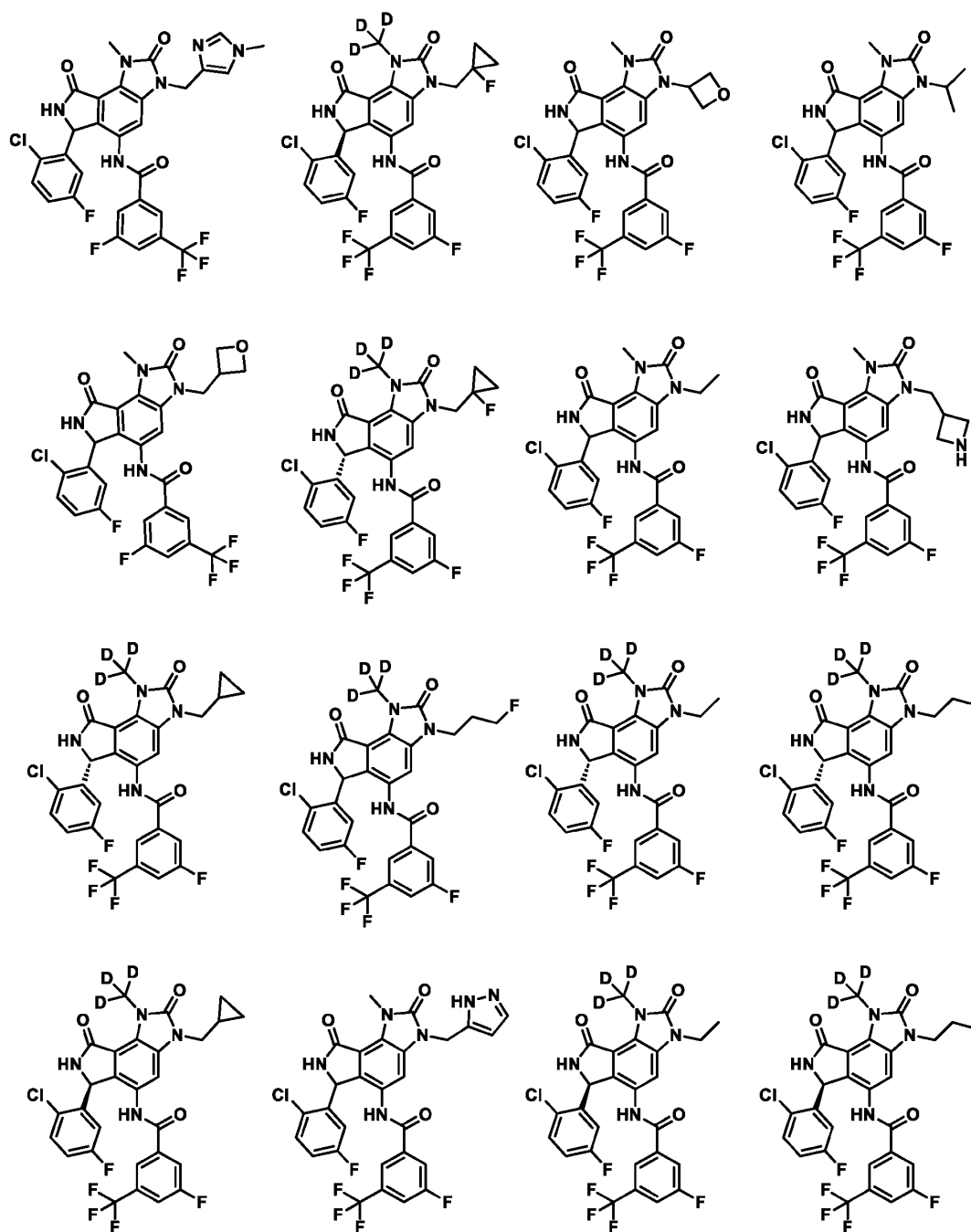
[00161] The following examples are given for the purpose of illustrating the invention, but not for limiting the scope or spirit of the invention.

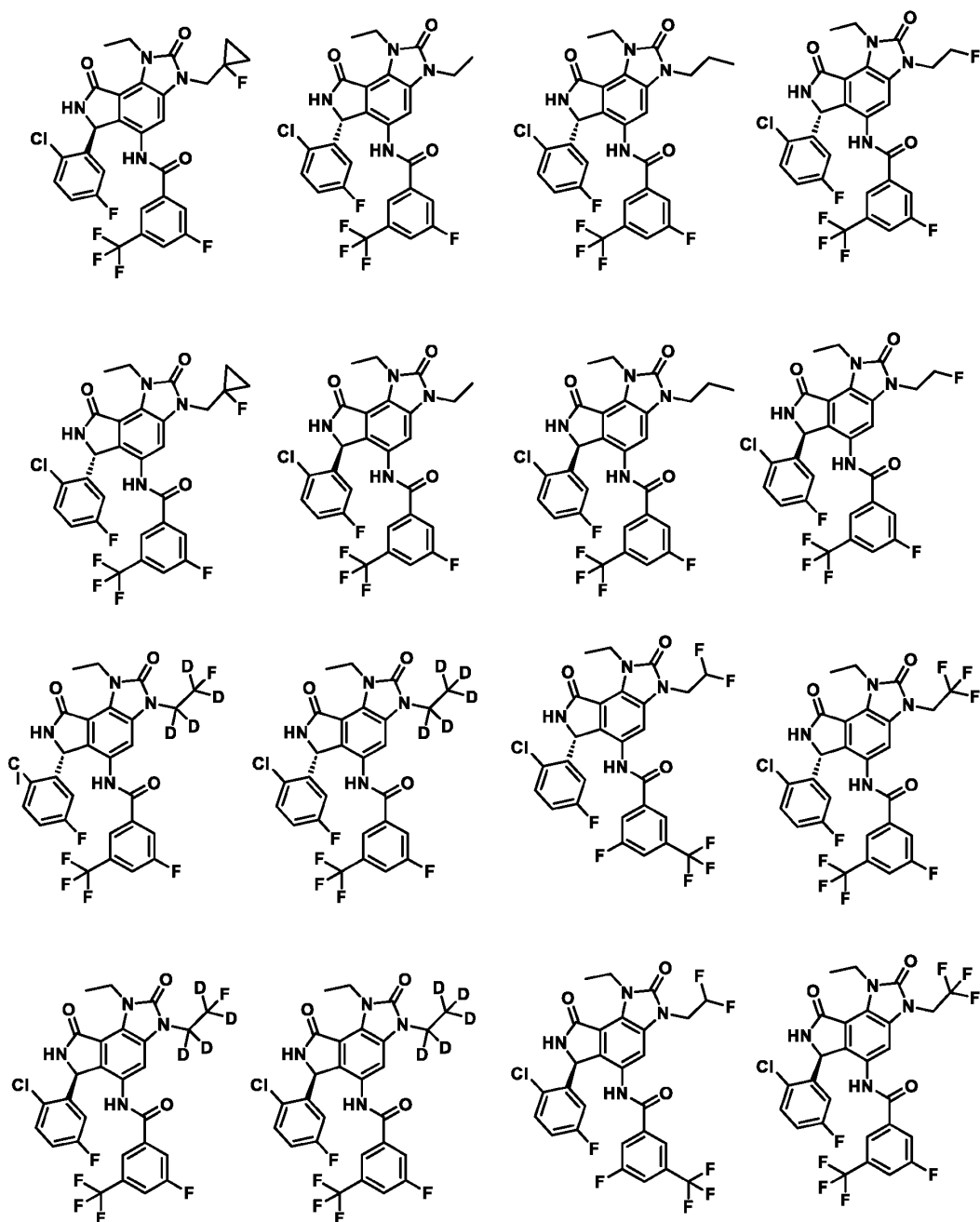
[00162] Compounds of the invention, including those specifically disclosed herein above and herein below, may be prepared as described in the following schemes. Although the present invention has been described in detail with preferred embodiments, those of ordinary skill in the art should understand 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.

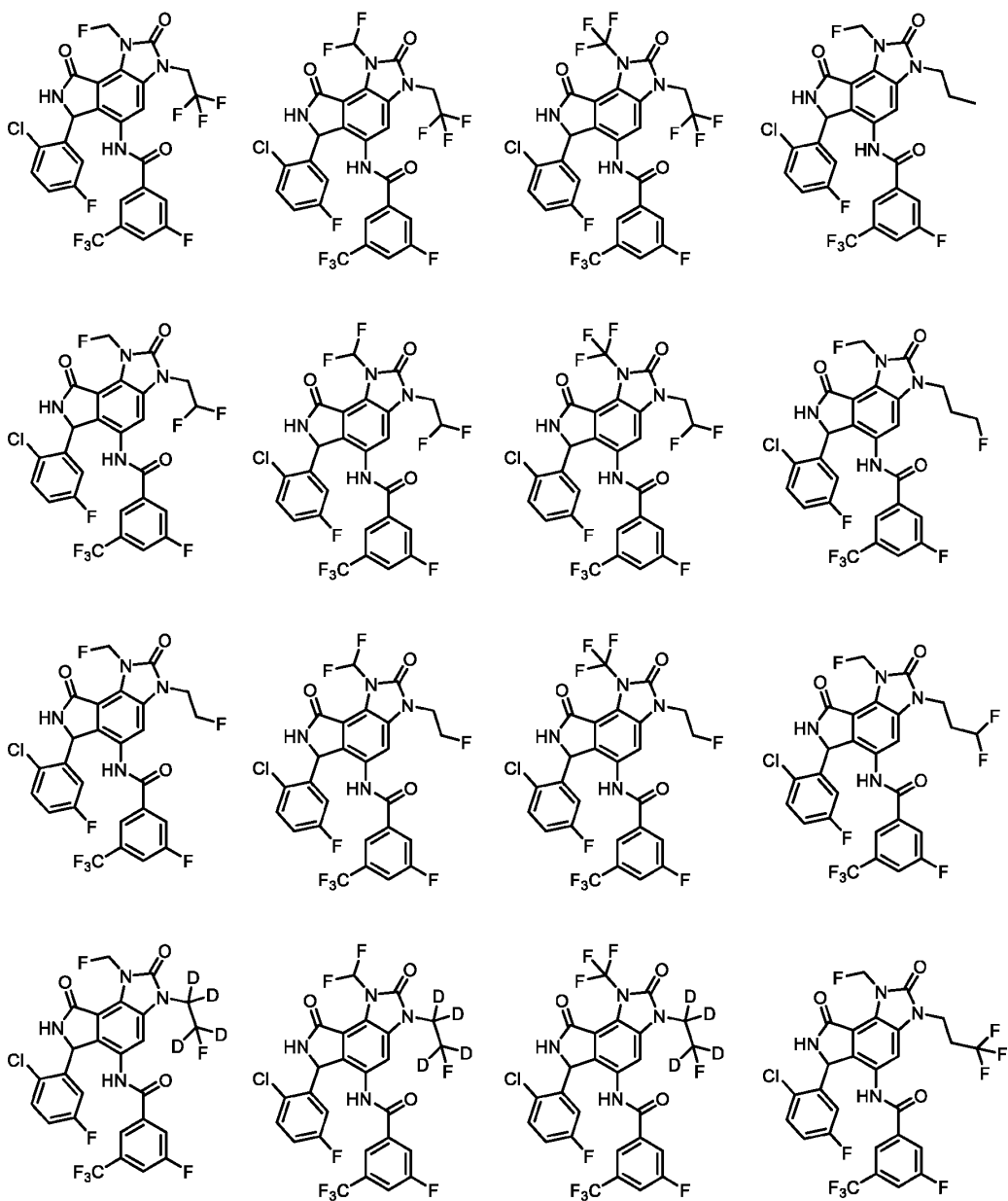
Table 1. Exemplary Compounds

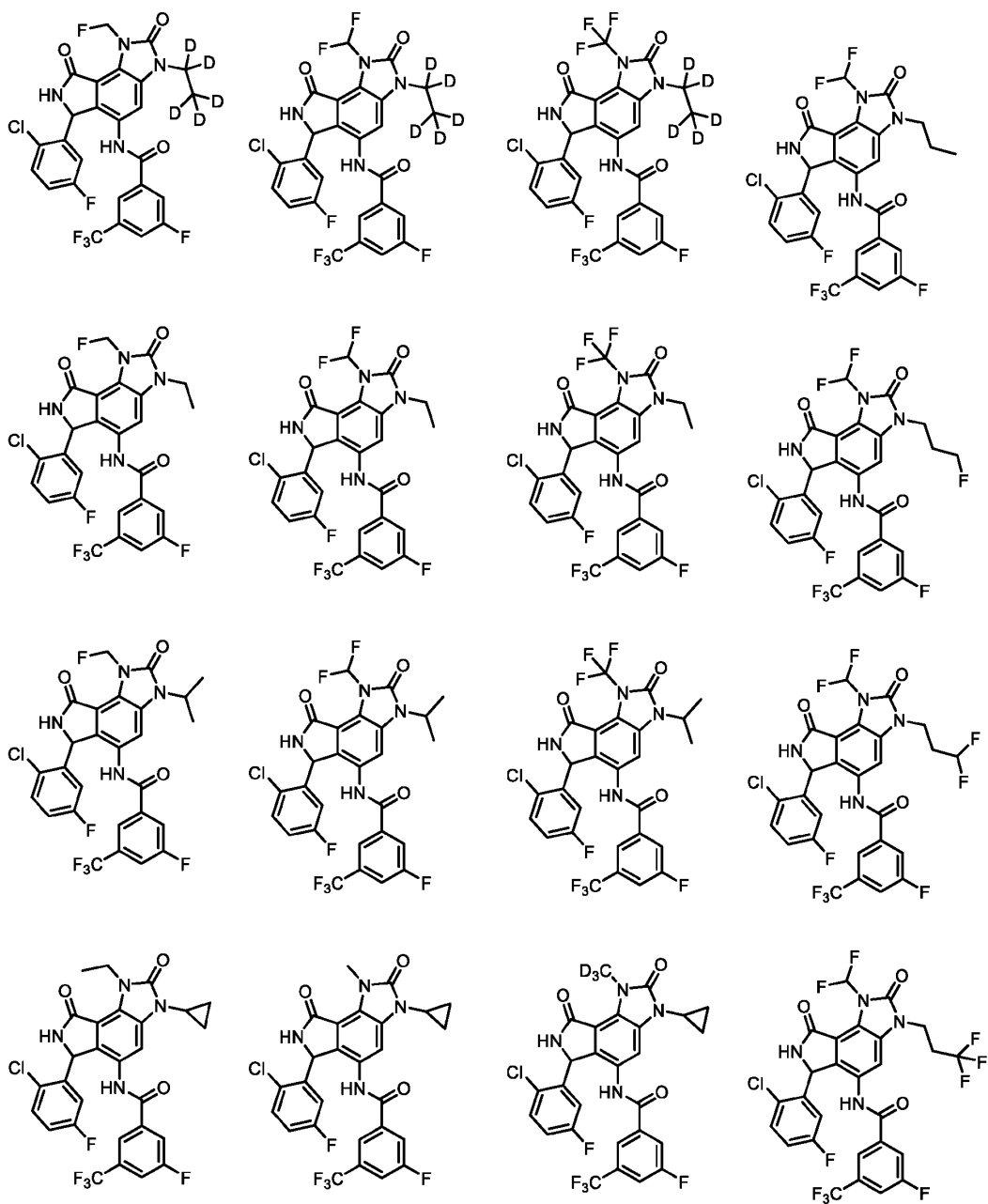


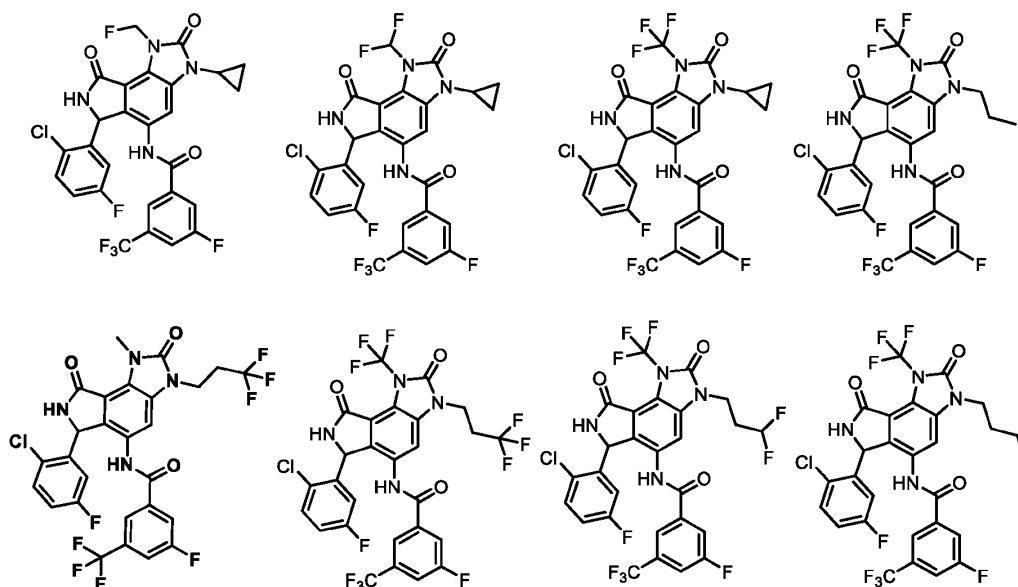












List of Abbreviations

aq: aqueous

Ac = Acetyl

AcO = Acetate

Ac₂O = Acetic anhydride

AIBN = a,a'-Azobisisobutyronitrile

$$\text{All} = \text{Allyl}$$

Alloc = Allyloxycarbonyl

Am = Amyl (Pentyl)

$$\text{Ar} = \text{Aryl}$$

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 = Dihydropiran

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
DP	= Desired product
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
Et ₂ O	= 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
Na₂SO₄ = Sodium Sulphate
NaHMDS = Sodium bis(trimethylsilyl)amide
NaCNBH₃ = 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-toluenesulphonate
n-Pr = n-Propyl
Pr = Propyl
i-Pr or iPr = iso-propilo
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 = Tetrahydrofuran
THP = Tetrahydropyranyl
TIPS = Triisopropylsilyl
TMEDA = N,N,N',N'-Tetramethylethylenediamine
TMG = Tetramethylguanidine
TMS = Trimethylsilyl
Tol = p-Tolyl
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: ultra violet

General LCMS Method:

[00163] Shimadzu LCMS2020, Reverse-phase column (Shim-Pack Scepter C18, 33 x 3.0 mm, 3µm), 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:

[00164] Instrument = Shimadzu FRC-40; Shimadzu LH-40; Shimadzu LC-8A; GX-281.
Column = YMC-Triart C18, 250*20 mm, 5µm; Welch Ultimate XB-C18, 250*21.2 mm, 5µm.

Detection wavelength = 220, 254 nM. Flow rate = 15ml/min-20ml/min; Run time = 8 min;
Column temperature = 25 °C.

Exemplary chiral prep-SFC conditions and methods for racemic compounds separation:

[00165] Preparative separation method 1:

Instrument: SHIMADZU PREP SOLUTION SFC

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

Mobile phase: A for CO₂ and B for MeOH

Gradient: B 35%

Flow rate: 60 mL/min

Back pressure: 100 bar

Column temperature: 35 °C

Wavelength: 220 nm

Cycle-time: 5 min

Eluted time: 2 H

[00166] Preparative separation method 2:

Instrument: SHIMADZU PREP SOLUTION SFC

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

Mobile phase: A for CO₂ and B for MeOH

Gradient: B 40%

Flow rate: 60 mL/min

Back pressure: 100 bar

Column temperature: 35 °C

Wavelength: 220 nm

Cycle-time: 5 min

Eluted time: 2 H

[00167] Preparative separation method 3:

Instrument: SHIMADZU PREP SOLUTION SFC

Column: ChiralPak IH, 150×20mm I.D., 5µm

Mobile phase: A for CO₂ and B for MEOH

Gradient: B 15%

Flow rate: 40mL /min

Back pressure: 100 bar

Column temperature: 35°C

Wavelength: 220nm

Cycle-time: 10 min

Eluted time: 3 H

[00168] Preparative separation method 4:

Instrument: SHIMADZU PREP SOLUTION SFC

Column: ChiralPak AD, 250×30mm 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: 220nm

Cycle-time: 7 min

Eluted time: 2 H

[00169] Preparative separation method 5:

Instrument: SHIMADZU PREP SOLUTION SFC

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

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: 220nm

Cycle-time: 7 min

Injection volume: 3.4 mL

Eluted time: 2 H

[00170] Preparative separation method 6:

Instrument: SHIMADZU PREP SOLUTION SFC

Column: ChiralPak IH, 150×20mm I.D., 5μm

Mobile phase: A for CO₂ and B for MEOH

Gradient: B 10%

Flow rate: 40mL /min

Back pressure: 100 bar

Column temperature: 35°C

Wavelength: 220nm

Cycle-time: 15 min

Eluted time: 2 H

[00171] **Preparative separation method 7:**

Instrument: Waters Thar 80 preparative SFC

Column: ChiralPak IA, 250×30mm 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

Run time: 10 min

Cycle-time: 6 min

Injection volume: 1.5 mL

Eluted time: 2 H

[00172] **Preparative separation method 8:**

Instrument: SHIMADZU PREP SOLUTION SFC

Column: ChiralPakC-IG, 250×30mm I.D., 5μm

Mobile phase: A for CO₂ and B for MEOH

Gradient: B 30%

Flow rate: 60mL/min

Back pressure: 100 bar

Column temperature: 35°C

Wavelength: 220nm

Cycle-time: 6min

Injection volume: 2 mL

Eluted time: 2 H

[00173] Preparative separation method 9:

Instrument: SHIMADZU PREP SOLUTION SFC

Column: ChiralPak C-IG, 250×30mm I.D., 5μm

Mobile phase: A for CO₂ and B for MEOH

Gradient: B 30%

Flow rate: 60 mL/min

Back pressure: 100 bar

Column temperature: 35°C

Wavelength: 220nm

Cycle-time: 5 min

Injection volume: 3 mL

Eluted time: 2 H

[00174] Preparative separation method 10:

Instrument: SHIMADZU PREP SOLUTION SFC

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

Mobile phase: A for CO₂ and B for MEOH

Gradient: B 30%

Flow rate: 40mL /min

Back pressure: 100 bar

Column temperature: 35°C

Wavelength: 220nm

Cycle-time: 10min

Eluted time: 2 H

[00175] Preparative separation method 11:

Instrument: Waters Thar 80 preparative SFC

Column: (R,R)-WHELK, 250×20mm I.D., 5μm

Mobile phase: A for CO₂ and B for MeOH

Gradient: B 50%

Flow rate: 35mL/min

Back pressure: 100 bar

Column temperature: 35°C

Wavelength: 220nm

Cycle-time: 5 min

Run time: 10 min

Injection volume: 3 mL

Eluted time: 2 H

[00176] Preparative separation method 12:

Instrument: Waters Thar 80 preparative SFC

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

Mobile phase: A for CO₂ and B for MEOH

Gradient: B 25%

Flow rate: 40 mL/min

Back pressure: 100 bar

Column temperature: 35°C

Wavelength: 220 nm

Run time: 15 min

Cycle-time: 9 min

Eluted time: 3 H

[00177] Preparative separation method 13:

Instrument: SHIMADZU PREP SOLUTION SFC

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

Mobile phase: A for CO₂ and B for MeOH

Gradient: B 13%

Flow rate: 40 mL/min

Back pressure: 100 bar

Column temperature: 35 °C

Wavelength: 220nm

Cycle-time: 7 min

Injection volume: 1.5 mL

Number of injection needles: 10

Eluted time: 2 H

[00178] **Preparative separation method 14:**

Instrument: Waters Thar 80 preparative SFC

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

Mobile phase: A for CO₂ and B for MeOH

Gradient: B 20%

Flow rate: 60 mL/min

Back pressure: 100 bar

Column temperature: 35 °C

Wavelength: 220nm

Run time: 8min

Cycle-time: 8min

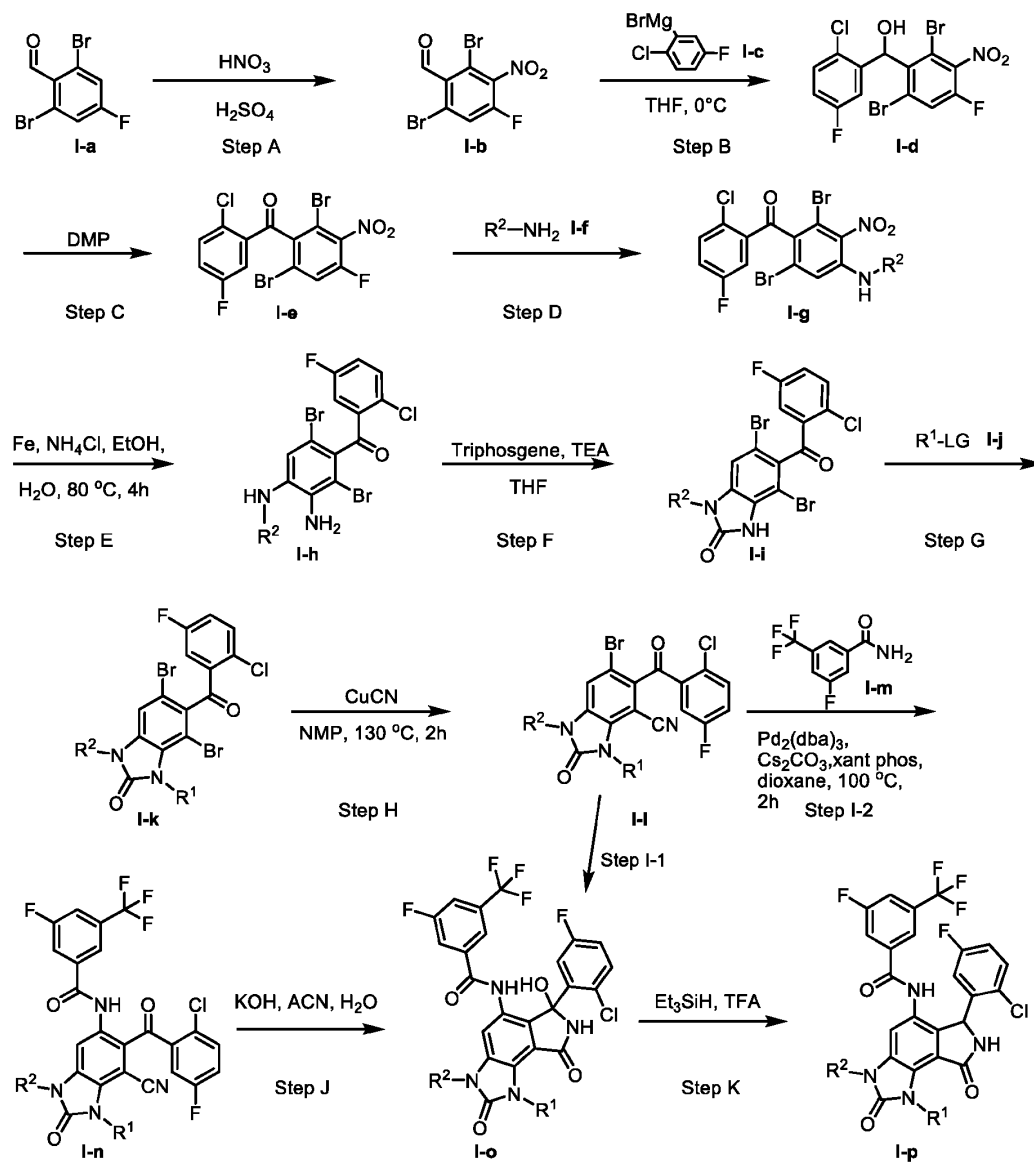
Injection volume: 3 mL

Number of injection needles: 3

Eluted time: 2H

Exemplary synthetic procedures:

General synthetic route I:

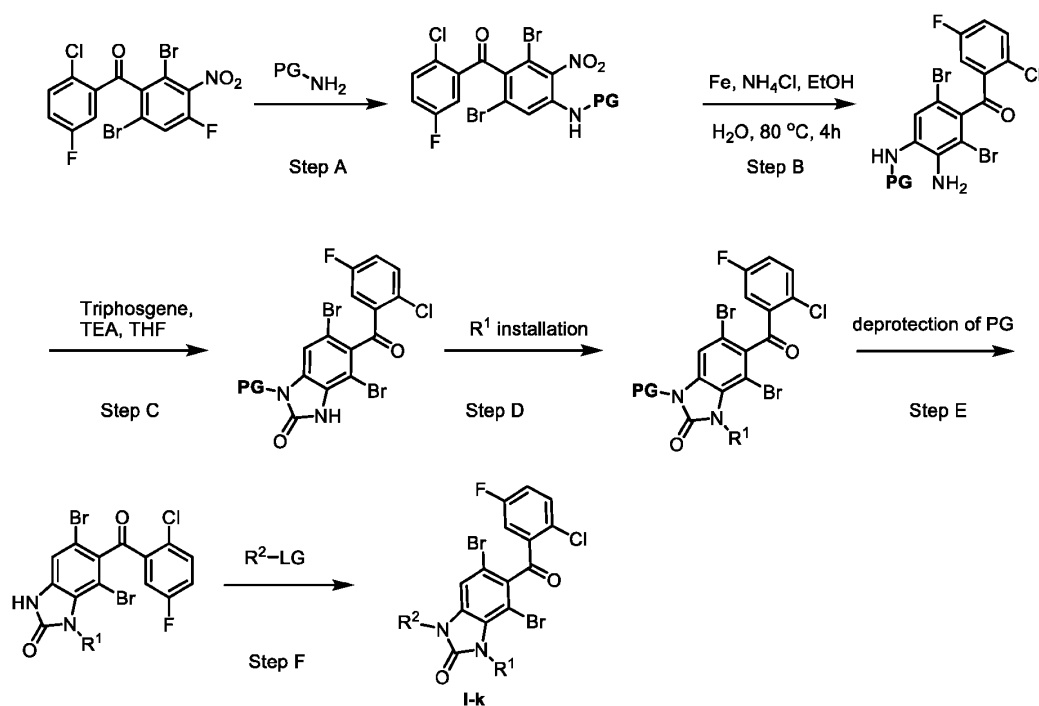


LG = leaving group. i.e., Br, I, OMs, OTs, OTf ...

[00179] With this general route I, different R^1 's were introduced at step G, while R^2 's were installed by $\text{S}_{\text{N}}\text{Ar}$ reaction with different amines at earlier step D. In some cases, product **I-o** was obtained from intermediate **I-l** at step I-1 directly. While in other cases, intermediate **I-o** was

generated in a two-step sequence to form **I-n** first at step I-2, for instance, when the step I-2 was carried out in more diluted conditions, **I-n** was isolated and then cyclized to form **I-o** under basic conditions at step J.

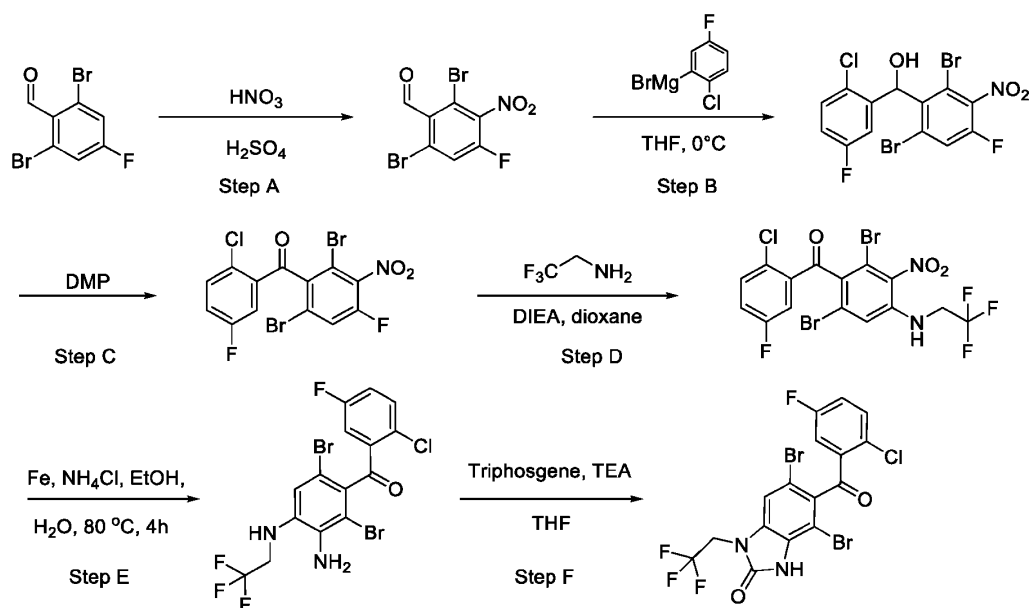
[00180] General synthetic route II to synthesize intermediate **I-k**:



PG = Protecting group, i.e., DMB, PMB...

[00181] With this general route II, with protecting group (PG) as R², different R¹s were installed at earlier step D and R² was installed later at step F after deprotection of PG.

Synthesis of intermediate 4,6-dibromo-5-[(2-chloro-4-fluorophenyl)carbonyl]-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one



[00182] **Step A:** To a solution of 2,6-dibromo-4-fluorobenzene-1-carbaldehyde (110 g, 390 mmol) in con. H_2SO_4 (550 mL) was added dropwise con. HNO_3 (43.4 g, 468 mmol) at 0°C . The reaction mixture was stirred at rt for 4 hr. The reaction mixture was poured into ice water and filtrated. The resulting solid was dissolved in EtOAc, and washed with water to remove the remaining acid, dried over Na_2SO_4 and concentrated in vacuo to afford 2,6-dibromo-4-fluoro-3-nitrobenzene-1-carbaldehyde (115 g, 352 mmol, 90%) as a black solid. LCMS: ESI m/z 328 $[\text{M} + \text{H}]^+$.

[00183] **Step B:** To a solution of 2,6-dibromo-4-fluoro-3-nitrobenzene-1-carbaldehyde (40 g, 122 mmol) in THF (400 mL) was added 2-chloro-5-fluorophenyl)magnesium bromide (734 mL, freshly made, 0.5 M in THF) at 0°C . The mixture was stirred at rt for 1h. The reaction mixture was quenched with aqueous solution of NH_4Cl , extracted with EA. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (eluted with EA/PE = 0-20%) to afford (2-chloro-4-fluorophenyl)(2,6-dibromo-4-fluoro-3-nitrophenyl)methanol (50 g, 109mmol, 89%) as a brown oil. (crude). LCMS: ESI m/z 458 $[\text{M} + \text{H}]^+$.

[00184] **Step C:** To a solution of (2-chloro-4-fluorophenyl)(2,6-dibromo-4-fluoro-3-nitrophenyl)methanol (122 g, 267 mmol) in DCM (1500 mL) was added DMP (170 g, 400 mmol) at 0°C . The reaction was stirred at rt for 1h. The reaction mixture was diluted with water,

extracted with EA. 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: 0-20%) to afford crude (2-chloro-4-fluorophenyl)(2,6-dibromo-4-fluoro-3-nitrophenyl)methanone as a brown solid. The crude was triturated with 500 ml (EA: PE=1: 10). The suspension was filtered to get (2-chloro-4-fluorophenyl)(2,6-dibromo-4-fluoro-3-nitrophenyl)methanone (88 g, 193 mmol, 72%) as a white solid. LCMS: ESI m/z 456 [M + H]⁺.

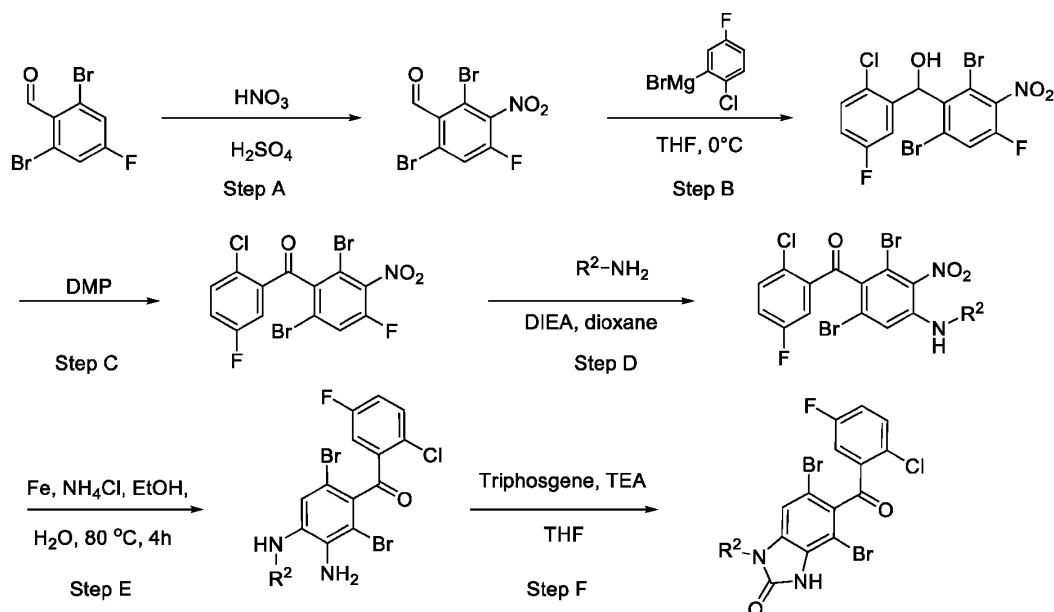
[00185] **Step D:** To a solution of (2-chloro-4-fluorophenyl)(2,6-dibromo-4-fluoro-3-nitrophenyl)methanone (45 g, 98.8 mmol) in tetrahydrofuran (450 mL) was added DIEA (38.3 g, 296 mmol) and 2,2,2-trifluoroethan-1-amine hydrochloride (26.8 g, 198 mmol). The mixture was stirred at 65 °C for 16 h. The reaction mixture was diluted with water, extracted with EA. 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: 0-10%, with 5% of DCM) to afford the title compound (2-chloro-4-fluorophenyl){2,6-dibromo-3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}methanone (22 g, 41.2 mmol, 41%) as a yellow solid.

[00186] **Step E:** To a solution of (2-chloro-4-fluorophenyl){2,6-dibromo-3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}methanone (30 g, 56.1 mmol) in EtOH (300 mL) and H₂O (75 mL) was added Fe (15.7 g, 281 mmol) and NH₄Cl (15.2 g, 281 mmol). The reaction was stirred at 80 °C for 2h. The cooled reaction mixture was filtered. The filtrate was concentrated, diluted with water and 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: 0-20%) to afford {3-amino-2,6-dibromo-4-[(2,2,2-trifluoroethyl)amino]phenyl}(2-chloro-4-fluorophenyl)methanone (26 g, 51.5 mmol, 92%) as an orange solid. LCMS: ESI m/z 505 [M + H]⁺.

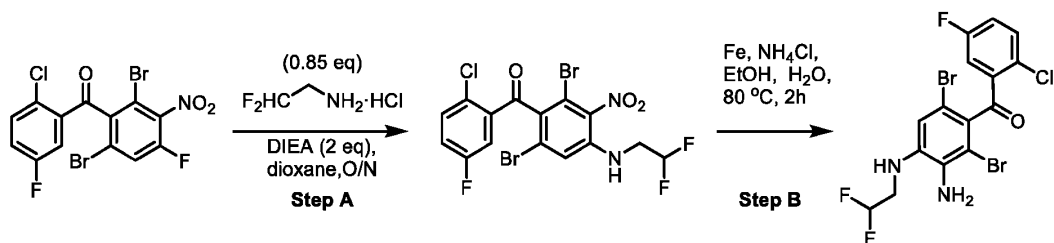
[00187] **Step F:** To a solution of {3-amino-2,6-dibromo-4-[(2,2,2-trifluoroethyl)amino]phenyl}(2-chloro-4-fluorophenyl)methanone (5 g, 9.91 mmol), TEA (2.76 mL, 19.8 mmol) in THF (50 mL) was added triphosgene (1.47 g, 4.96 mmol) at 0 °C. The reaction was stirred at rt for 2h. Aqueous solution of NaHCO₃ 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

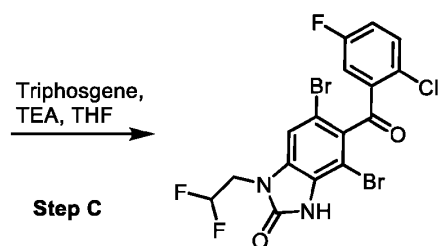
eluted with ethyl acetate in petroleum ether (gradient: 0~30%) to afford 4,6-dibromo-5-[(2-chloro-4-fluorophenyl)carbonyl]-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (5 g, 9.43 mmol, 95%) as a white solid. LCMS: m/z 531 $[M+H]^+$.

[00188] Intermediate with different R^2 were synthesized via the same general route with different amines at step D below:



[00189] For example, synthesis of intermediate 4,6-dibromo-5-[(2-chloro-4-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one was achieved via the same sequence with similar conditions.





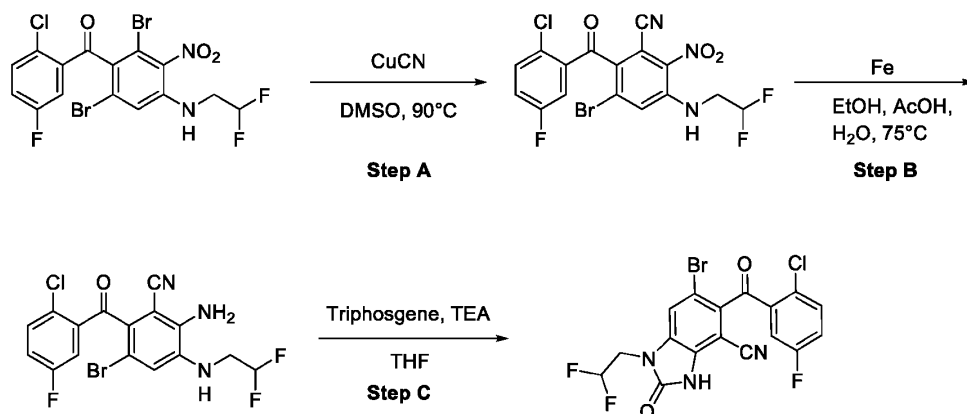
[00190] **Step A:** To a solution of (2-chloro-5-fluorophenyl)(2,6-dibromo-4-fluoro-3-nitrophenyl)methanone (18.0 g, 39.5 mmol) in 1,4-dioxane (200 mL) was added ethyl[di(prop-2-yl)]amine (13.7 mL, 79.0 mmol) and 2,2-difluoroethan-1-amine hydrochloride (3.95 g, 33.6 mmol). The mixture was stirred at r.t. for 72 h. The reaction mixture was concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with PE/EA/DCM=100/5/5 to give the starting material (2-chloro-5-fluorophenyl)(2,6-dibromo-4-fluoro-3-nitrophenyl)methanone (3.8 g), then eluted with DCM/EA=50/50 to afford (2-chloro-5-fluorophenyl){2,6-dibromo-4-[(2,2-difluoroethyl)amino]-3-nitrophenyl}methanone (14.0 g, 27.1 mmol, 69%) as a yellow solid. LCMS: ESI m/z 517 $[M + H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 7.71 (dd, $J = 9.6, 4.8$ Hz, 1H), 7.63 – 7.56 (m, 2H), 7.51 (s, 1H), 7.02 (s, 1H), 6.15 (tt, $J = 55.6, 3.6$ Hz, 1H), 3.74 (t, $J = 15.4$ Hz, 2H).

[00191] **Step B:** To a solution of (2-chloro-5-fluorophenyl){2,6-dibromo-4-[(2,2-difluoroethyl)amino]-3-nitrophenyl}methanone (17.5 g x 2, 33.9 mmol x 2, parallel) in EtOH (170 mL) and H₂O (34 mL) was added Fe (9.46 g, 169.4 mmol) and NH₄Cl (9.1 g, 169.4 mmol). The reaction was stirred at 80 °C for 2h. The cooled reaction mixture was filtrated, concentrated, diluted with water and extracted with EtOAc (100 mL x 2). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was triturated with (PE/EA=4/1) to afford {3-amino-2,6-dibromo-4-[(2,2-difluoroethyl)amino]phenyl}(2-chloro-5-fluorophenyl)methanone (26.0 g, 53.4 mmol, 79%) as an orange solid. LCMS: ESI m/z 487 $[M + H]^+$.

[00192] **Step C:** To a solution of {3-amino-2,6-dibromo-4-[(2,2-difluoroethyl)amino]phenyl}(2-chloro-4-fluorophenyl)methanone (26.0 g, 53.4 mmol), TEA (10.8 g, 106 mmol) in THF (260 mL L) was added triphosgene (7.93 g, 26.7 mmol) at 0 °C. The reaction was stirred at rt for 2h. Water was added, and the mixture was extracted with EtOAc (1000 mL*3). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The crude was triturated with DCM/EA=10/1 to afford 4,6-dibromo-5-[(2-chloro-

4-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (21.3 g, 41.6 mmol, 78%) as a brown solid. LCMS: ESI m/z 513 $[M + H]^+$.

Synthesis of Intermediate 6-bromo-5-[(2-chloro-4-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-2-oxo-3H-benzo[d]imidazole-4-carbonitrile



[00193] **Step A:** To a solution of (2-chloro-5-fluorophenyl) {2,6-dibromo-4-[(2,2-difluoroethyl) amino]-3-nitrophenyl} methanone (300.0 g, 581.0 mmol) in DMSO (500 mL) were added CuCN (53.1 g, 592.0 mmol) at 90°C. The reaction was stirred at 90°C for 30 min. LCMS showed the reaction was completed. The cooled reaction was poured into EA and water was added. The suspension was filtered through celite, the filtrate was diluted with water and EA. The organic layer was separated and washed with brine, dried over Na₂SO₄ and concentrated. The residue was triturated with PE: EA=15:1 and IPA to afford 5-bromo-6-[(2-chloro-5-fluorophenyl) carbonyl]-3-[(2,2-difluoroethyl) amino]-2-nitrobenzene-1-carbonitrile (252 g, 545 mmol, 94%) as a yellow solid.

LCMS: ESI m/z 462.61 $[M+H]^+$.

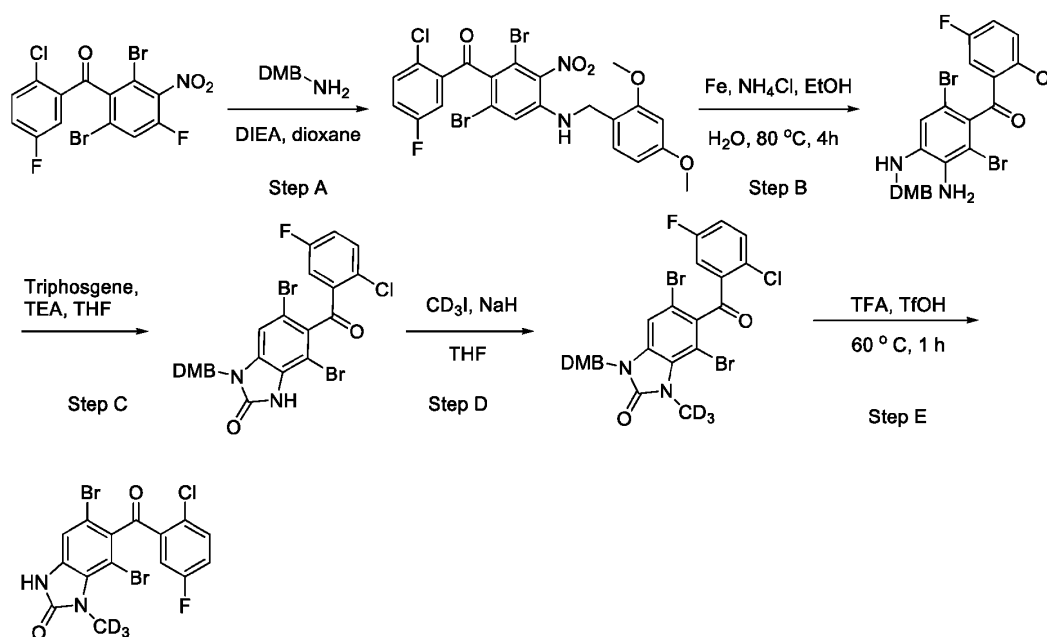
[00194] **Step B:** To a solution of 5-bromo-6-[(2-chloro-5-fluorophenyl) carbonyl]-3-[(2,2-difluoroethyl) amino]-2-nitrobenzene-1-carbonitrile (320.0 g, 692.0 mmol) in EtOH (2.4 L), Acetic acid (600 mL) and H₂O (480 mL) was added Fe (212.0 g, 3804.0 mmol). The reaction was stirred at inner temp 75°C for 30 min. LCMS showed the reaction was completed. The reaction mixture was filtered and the filtrate was concentrated, the residue was diluted with water and extracted with EtOAc (1500 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:0-50%) to give a crude product which was triturated with PE: DCM=1:1 to afford 2-amino-5-bromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-3-[(2,2-difluoroethyl) amino] benzene-1-carbonitrile (190.0 g, 439.2 mmol, 63.5%) as a yellow solid.

[00195] LCMS: ESI m/z 432.63 [M+H]⁺.

[00196] **Step C:** To a solution of 6-amino-3-bromo-2-[(2-chloro-4-fluorophenyl)carbonyl]-5-[(2,2-difluoroethyl)amino]benzene-1-carbonitrile (1 g, 2.31 mmol) in THF (10 mL) was added triphosgene (0.69 g, 2.31 mmol) at 0 °C. The reaction mixture was stirred at rt for 6 h. The mixture was diluted with H₂O, extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was triturated with EA: PE=5: 1 to afford 6-bromo-5-[(2-chloro-4-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-2-oxo-3H-benzo[d]imidazole-4-carbonitrile (1 g, 2.18 mmol, 94%) as a brown solid. LCMS: ESI m/z 458.0 [M – H]⁺.

Synthesis of intermediate 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one



[00197] **Step A:** To a solution of (2-chloro-5-fluorophenyl)(2,6-dibromo-4-fluoro-3-nitrophenyl)methanone (9.45 g, 20.7 mmol) in dioxane (100 mL) was added DIEA (5.36 g, 41.4

mmol) and (2,4-dimethoxyphenyl)methanamine (2.78 g, 16.6 mmol). The mixture was stirred at 100 °C for 2 hours. The cooled mixture was concentrated and the residue was purified by silica gel chromatography (20 g column) using 0 - 10% EtOAc/hexane to afford (2-chloro-5-fluorophenyl)(2,6-dibromo-4-{[(2,4-dimethoxyphenyl)methyl]amino}-3-nitrophenyl)methanone (8.8 g, 14.6 mmol, 70 %) as a yellow solid. LCMS: ESI m/z 601 [M - H]⁻.

[00198] **Step B:** To a solution of (2-chloro-5-fluorophenyl)(2,6-dibromo-4-{[(2,4-dimethoxyphenyl)methyl]amino}-3-nitrophenyl)methanone (8.8 g, 14.6 mmol) in EtOH (80 mL) and H₂O (20 mL) was added Fe (4.89 g, 87.6 mmol) and NH₄Cl (3.91 g, 73.0 mmol). The mixture was stirred at 80 °C for 2 hours. The mixture was filtrated and concentrated in vacuo to remove EtOH. The mixture was poured into saturation NaHCO₃, extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated in vacuum to give (3-amino-2,6-dibromo-4-{[(2,4-dimethoxyphenyl)methyl]amino}phenyl)(2-chloro-5-fluorophenyl)methanone (8.3 g, 14.5 mmol, 99 %) as a brown solid. LCMS: ESI m/z 573 [M + H]⁺.

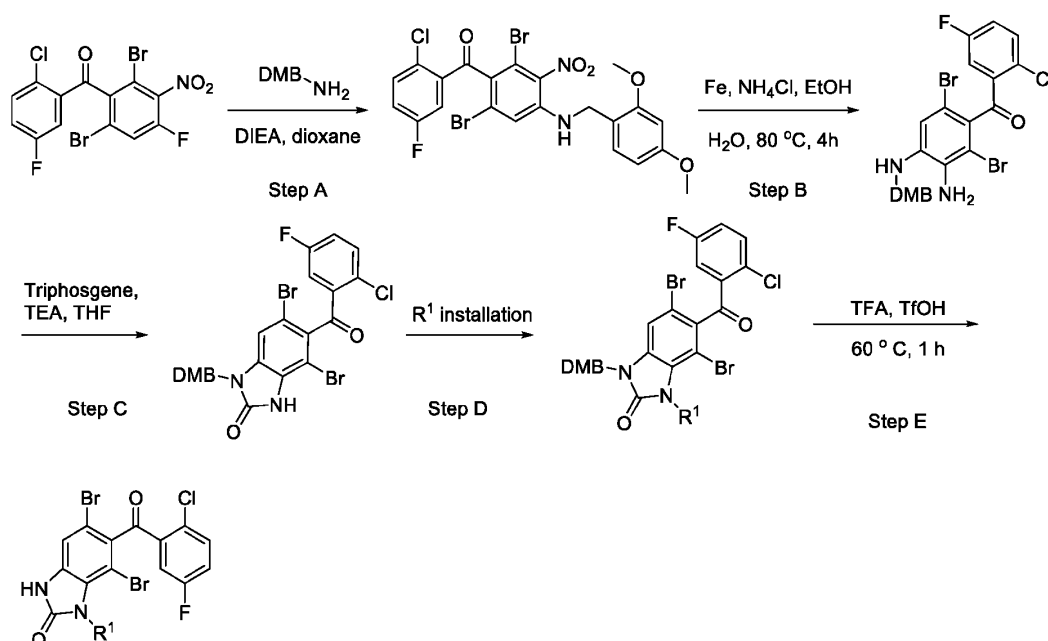
[00199] **Step C:** To a solution of (3-amino-2,6-dibromo-4-{[(2,4-dimethoxyphenyl)methyl]amino}phenyl)(2-chloro-5-fluorophenyl)methanone (8.4 g, 14.7 mmol) in THF (100 mL) was added TEA (4.45 g, 44.0 mmol) and trichloromethyl [(trichloromethyl)oxy]methanoate (4.35 g, 14.7 mmol) at 0 °C and the mixture was stirred for 1 hour. The mixture was diluted with water, extracted with EA. The organic phase was dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (20 g column) using 0 - 30% EtOAc/hexane to afford 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(2,4-dimethoxyphenyl)methyl]-2,3-dihydro-1H-benzo[d]imidazol-2-one (8.6 g, 14.3 mmol, 98%) as a brown solid. LCMS: ESI m/z 599 [M + H]⁺.

[00200] **Step D:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(2,4-dimethoxyphenyl)methyl]-2,3-dihydro-1H-benzo[d]imidazol-2-one (2 g, 3.34 mmol) in THF (30 mL) was added NaH (0.27 g, 6.68 mmol, 60% in mineral oil) at 0 °C. The mixture was stirred for 10 min. Then trideuterio(iodo)methane (0.97 g, 6.68 mmol) was added and the mixture was stirred at 0 °C for 1 hour. The mixture was quenched with MeOH. The mixture was concentrated under vacuum and the residue was purified by silica gel chromatography (30 g column) using 0 - 30% EtOAc/hexane to afford 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(2,4-dimethoxyphenyl)methyl]-3-(trideuteriomethyl)-2,3-dihydro-1H-

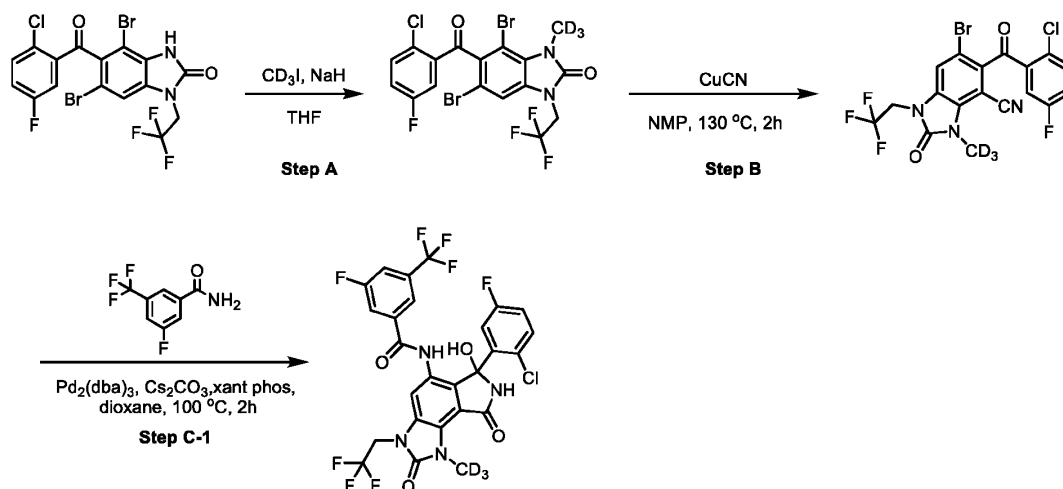
benzo[d]imidazol-2-one (2 g, 3.25 mmol, 97 %) as a yellow solid. LCMS: ESI m/z 616 $[M + H]^+$.

[00201] **Step E:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(2,4-dimethoxyphenyl)methyl]-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (2 g, 3.25 mmol) in TFA (30 mL) was added TfOH (50 mg, 0.325 mmol). The mixture was stirred at 50 °C for 2 hours. The mixture was concentrated under vacuum to remove TFA. The residue was poured into saturated NaHCO_3 and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuum to give 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (1.5 g, 3.22 mmol, 99%) as a yellow solid. LCMS: ESI m/z 466 $[M + H]^+$.

[00202] Intermediate with different R^1 are synthesized via the same general route with different R^1 's at step D below:



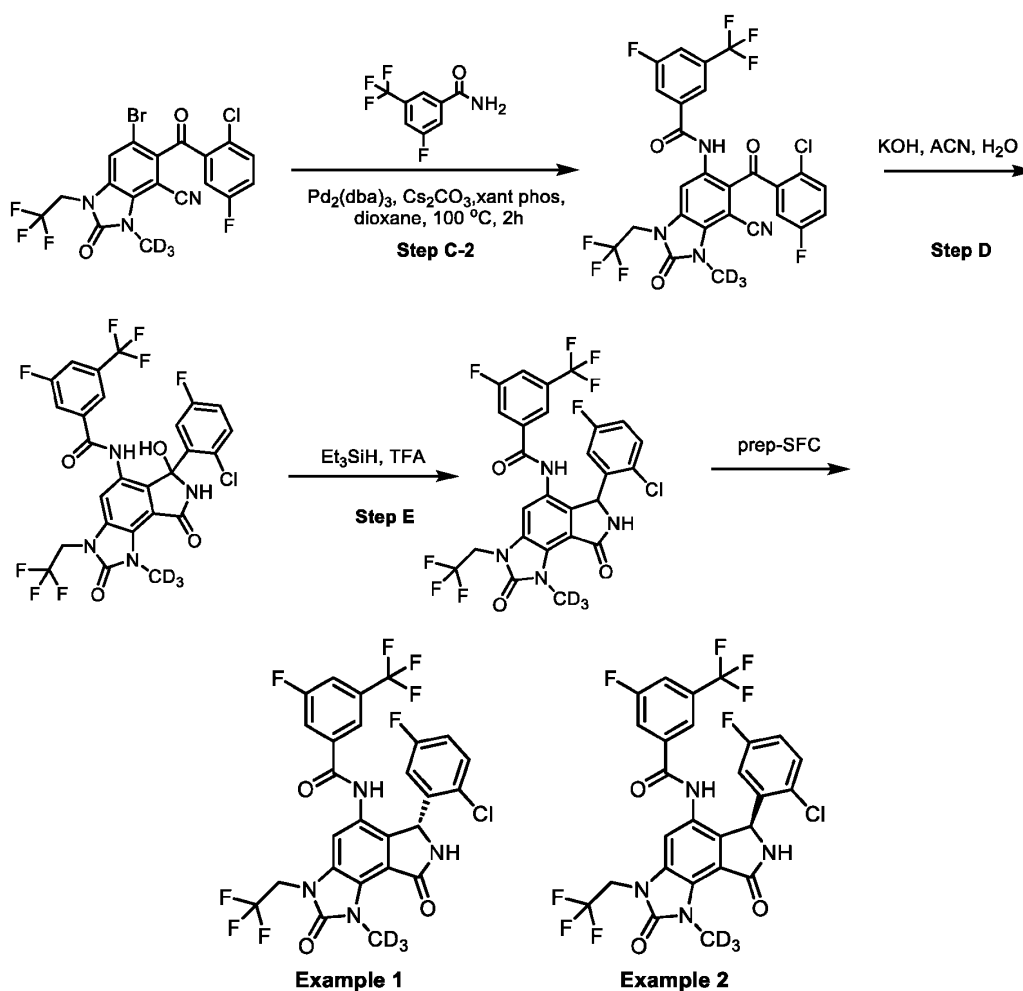
Example 1: (R)-N-(6-(2-chloro-5-fluorophenyl)-1-(methyl-d3)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide & **Example 2:** (S)-N-(6-(2-chloro-5-fluorophenyl)-1-(methyl-d3)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)be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



[00203] **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 CD₃I (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 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]-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]⁺.

[00204] **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 N₂ for 3h. The cooled reaction 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 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]⁺.

[00205] **Step C-1:** 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), $\text{Pd}_2(\text{dba})_3$ (9.28 mg, 10 μmol), Xantphos (11.7 mg, 20 μmol), Cs_2CO_3 (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 afford 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 $[\text{M} + \text{H}]^+$.



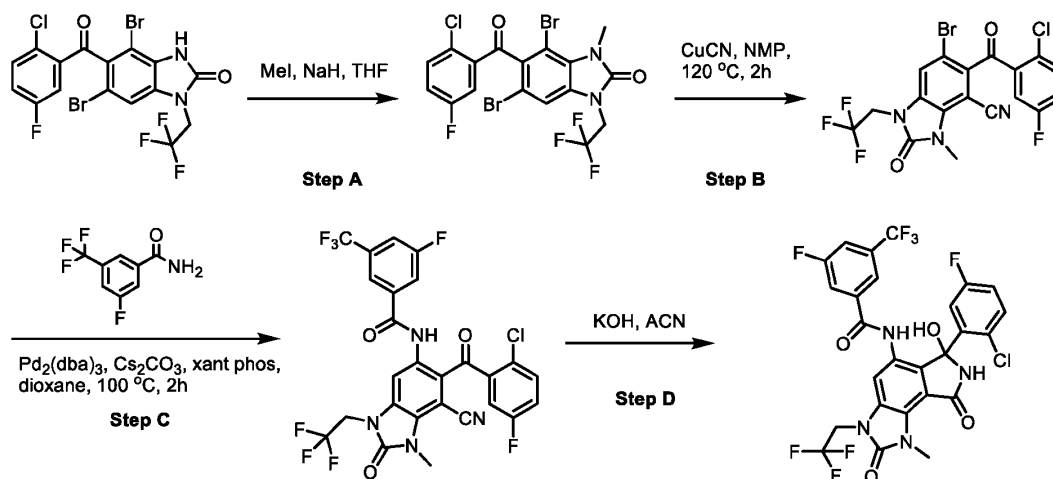
[00206] **Step C-2:** A solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-3-(trideuteriomethyl)-1-(2,2,2-trifluoroethyl)benzo[d]imidazole-4-carbonitrile (5.6 g, 11.3 mmol), 5-fluoro-3-(trifluoromethyl)benzene-1-carboxamide (2.35 g, 11.3 mmol), $\text{Pd}_2(\text{dba})_3$ (1.04 g, 1.13 mmol), xantphos (1.31 g, 2.26 mmol), Cs_2CO_3 (11.1 g, 34.0 mmol) in dioxane (300 mL) was stirred at 100 °C under N_2 for 2 h. The cooled reaction mixture was concentrated. The residue was purified using silica gel column chromatography eluted with MeOH in DCM (gradient: 0%~10%) to afford N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-2-oxo-1-(trideuteriomethyl)-3-(2,2,2-trifluoroethyl)benzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (5.9 g, 9.52 mmol, 84%) as a crude product. (70% DP). LCMS: ESI m/z 620 $[\text{M} + \text{H}]^+$.

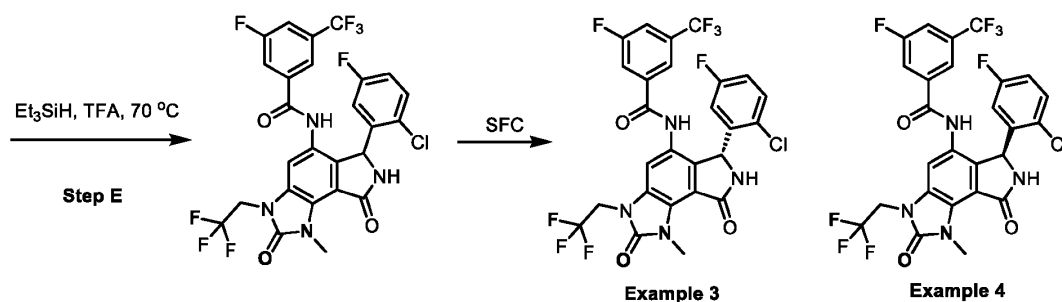
[00207] **Step D:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-2-oxo-1-(trideuteriomethyl)-3-(2,2,2-trifluoroethyl)benzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (6.3 g, 10.2 mmol) in ACN (60 mL) and H_2O (6 mL) was added KOH (2.85 g, 50.8 mmol) at room temperature. The reaction mixture was stirred at rt for 30 min. The mixture was diluted with water (20 mL) and extracted with EtOAc (50 mL x 2). The combined organic phases were washed with brine (50 mL x 2), dried over Na_2SO_4 and concentrated to give 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]-3-fluoro-5-(trifluoromethyl)benzamide (5 g, 7.84 mmol, 77%) as a brown solid. LCMS: ESI m/z 638 $[\text{M} + \text{H}]^+$.

[00208] **Step E:** 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 Et_3SiH (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 $[\text{M} + \text{H}]^+$. ^1H NMR (400 MHz, CD_3OD) 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).

[00209] N-[6-(1-chloro-4-fluorobenzen-2-yl)-2,8-dioxo-1-(trideuteriomethyl)-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (83 mg) was separated by prep-SFC method 1 to give (R)-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 (12.4 mg, 21 μmol, 15%) as a white solid. LCMS: 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). And (S)-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 (11.7 mg, 19 μmol, 14%) as a white solid. LCMS: 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).

Example 3: N-[(6R)-6-(2-chloro-5-fluorophenyl)-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 & Example 4: N-[(6S)-6-(2-chloro-5-fluorophenyl)-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





[00210] **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.

[00211] **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]⁺.

[00212] **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), Pd₂(dba)₃ (29 mg, 0.03 mmol), Xant-PHOS (37 mg, 0.06 mmol) and Cs₂CO₃ (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 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 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]⁺.

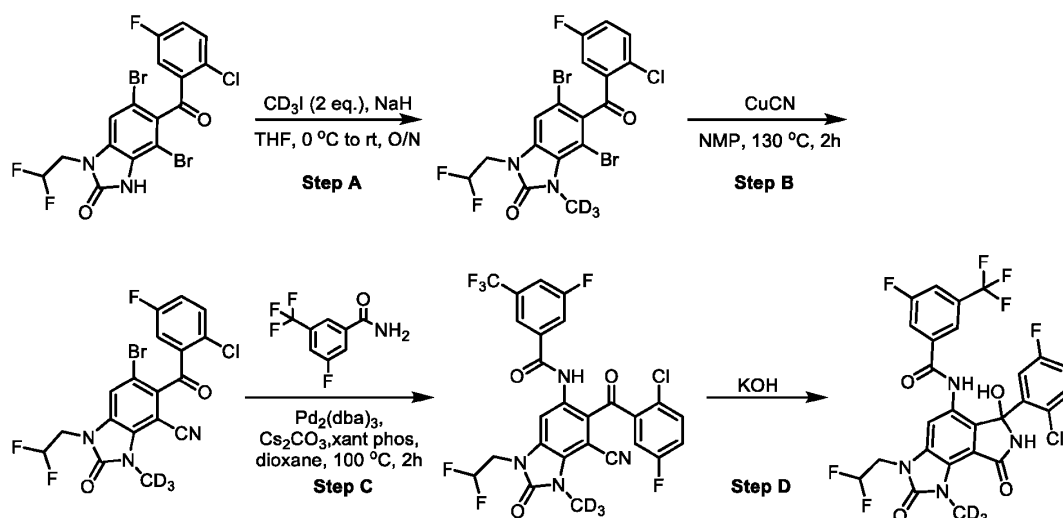
[00213] **Step D:** To a stirred solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-1-methyl-2-oxo-3-(2,2,2-trifluoroethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (60 mg, 0.09 mmol) in ACN (3 mL)/ H₂O (1 mL) was added KOH (16 mg, 0.29 mmol) slowly at rt. After stirred at 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 Na₂SO₄, 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]⁺.

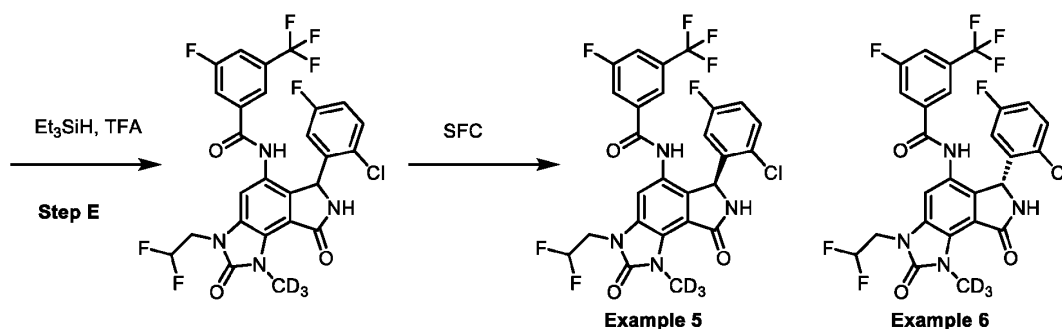
[00214] **Step E:** To a stirred solution of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-2,8-dioxo-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (40 mg, 0.06 mmol) in TFA (2 mL) was added Et₃SiH (0.5 mL) at rt. After stirred at 70 °C 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), 7.13 – 7.05 (m, 1H), 6.59 (brs, 1H), 6.02 (brs, 1H), 4.96 – 4.77 (m, 2H), 3.92 (s, 3H).

[00215] 19 mg of the racemic 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 was then separated by chiral prep-SFC method 2 to give N-[(6R)-6-(2-chloro-5-fluorophenyl)-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 (3.6 mg, 0.006 mmol,

19 %) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.36 (s, 1H), 9.20 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.71 (s, 1H), 7.48 (s, 1H), 7.28 (dd, J = 8.8, 5.2 Hz, 1H), 7.13 – 7.05 (m, 1H), 6.58 (brs, 1H), 6.02 (brs, 1H), 4.96 – 4.77 (m, 2H), 3.92 (s, 3H). And N-[(6S)-6-(2-chloro-5-fluorophenyl)-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 (3.9 mg, 0.006 mmol, 21 %) as a white solid. LCMS: m/z 619 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.36 (s, 1H), 9.20 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.71 (s, 1H), 7.49 (s, 1H), 7.28 (dd, J = 8.8, 5.2 Hz, 1H), 7.13 – 7.04 (m, 1H), 6.64 (brs, 1H), 6.01 (brs, 1H), 4.96 – 4.74 (m, 2H), 3.92 (s, 3H).

Example 5: (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-(methyl- d_3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide and Example 6: (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-(methyl- d_3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide





[00216] **Step A:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (10.1 g x 2, 19.8 mmol x 2, parallel) in THF (150 mL) was added NaH (1.58 g, 39.61 mmol, 60% purity in mineral oil) at 0 °C. The mixture was stirred at 0 °C for 10 min, then CD_3I (3.70 mL, 59.41 mmol) was added. The mixture was stirred at rt for 16h. The reaction mixture was quenched by ice-water, and the mixture was extracted with EtOAc (1000 mL*3). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was triturated with (PE/EA=10/1) and filtered to afford 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (19.1 g, 36.0 mmol, 91%) as a white solid. LCMS: ESI m/z 530 $[\text{M} + \text{H}]^-$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.77 (s, 1H), 7.73 (dd, $J = 8.8, 4.8$ Hz, 1H), 7.63 – 7.56 (m, 1H), 7.48 (dd, $J = 8.8, 2.8$ Hz, 1H), 6.36 (tt, $J = 54.8, 3.2$ Hz, 1H), 4.42 (td, $J = 15.6, 3.2$ Hz, 2H).

[00217] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (10 g x 2, 18.9 x 2 mmol, parallel) in NMP (150 mL) was added CuCN (1.77 g, 39.6 mmol). The reaction mixture was stirred at 120 °C under N_2 for 3h. The cooled reaction mixture was diluted with EA, filtered through a pad of celite. The filtrate was extracted with EtOAc (100 mL*3). The organic phase was washed with brine for 5 times, dried over Na_2SO_4 and concentrated. The residue was triturated with MeOH three times, then triturated with MeCN two times and filtered to afford 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (5.5 g, 11.5 mmol, 31%) as a white solid. LCMS: ESI m/z 530 $[\text{M} + \text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.97 (s, 1H), 7.74 (dd, $J = 8.8, 4.8$ Hz, 1H), 7.65 – 7.45 (m, 2H), 6.63 – 6.14 (m, 1H), 4.46 (td, $J = 15.6, 2.8$ Hz, 2H).

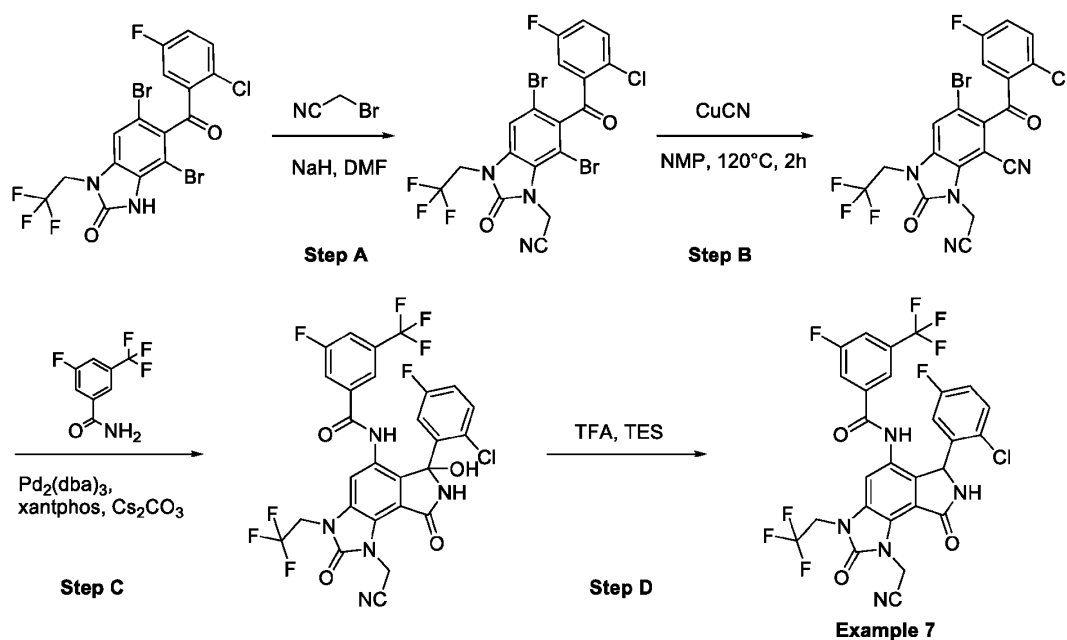
[00218] **Step C:** A solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (500 mg, 1.05 mmol), 5-fluoro-3-(trifluoromethyl)benzene-1-carboxamide (218 mg, 1.05 mmol), Pd₂(dba)₃ (96.3 mg, 0.105 mmol), Xantphos (122 mg, 0.210 mmol), Cs₂CO₃ (1.03 g, 3.15 mmol) in dioxane (25 mL) was stirred at 100 °C under N₂ for 2 h. The reaction mixture was concentrated to give a residue. The residue was purified using silica gel column chromatography eluted with MeOH in DCM (gradient: 0%~10%) to afford N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-(2,2-difluoroethyl)-2-oxo-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (500 mg, 0.831 mmol, 79%) as a brown solid. LCMS: ESI m/z 602 [M + H]⁺.

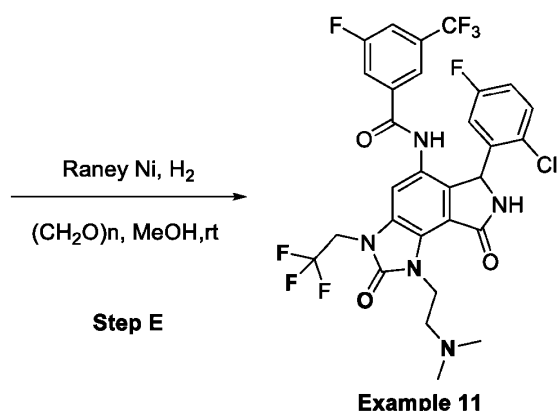
[00219] **Step D:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-(2,2-difluoroethyl)-2-oxo-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (90 mg, 0.150 mmol) in CH₃CN (8 mL) and H₂O (2 mL) was added KOH (25.2 mg, 0.449 mmol). The mixture was stirred at 20 °C for 30 min. The mixture was diluted with water, extracted with EA. The organic phase was dried over Na₂SO₄ and concentrated to give N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (90 mg, 0.145 mmol, 97 %) as a brown solid. LCMS: ESI m/z 618 [M - H]⁻.

[00220] **Step E:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (40 mg, 0.065 mmol) in TFA (1 mL) was added Et₃SiH (0.25 mL) and the mixture was stirred at 70 °C for 30 min. The mixture was concentrated and the residue was purified by prep-TLC (PE/EA=1: 1) to afford a crude product, which was separated by chiral prep-SFC method 3 to give (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (12.1 mg, 0.020 mmol, 31%) as a white solid. LCMS: ESI m/z 604.2 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.33 (s, 1H), 9.18 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.80 – 7.66 (m, 2H), 7.40 (s, 1H), 7.30 – 7.23 (m, 1H), 7.11 – 7.06 (m, 1H), 6.65 (brs, 1H), 6.36 (t, *J* = 54.7 Hz, 1H), 6.00 (brs, 1H), 4.54 – 4.22 (m, 2H). And (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-

e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (12.7 mg, 0.021 mmol, 32%) as a white solid. LCMS: ESI m/z 604.2 $[M + H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.33 (s, 1H), 9.18 (s, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.80 – 7.66 (m, 2H), 7.40 (s, 1H), 7.30 – 7.23 (m, 1H), 7.11 – 7.06 (m, 1H), 6.65 (brs, 1H), 6.36 (t, $J = 54.7$ Hz, 1H), 6.00 (brs, 1H), 4.54 – 4.22 (m, 2H)

Example 7: N-(6-(2-chloro-5-fluorophenyl)-1-(cyanomethyl)-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 and Example 11: N-[6-(2-chloro-5-fluorophenyl)-1-[2-(dimethylamino)ethyl]-2,8-dioxo-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide





[00221] **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 (500 mg, 0.943 mmol) in DMF (5 mL) were added bromoacetonitrile (136 mg, 1.13 mmol) and NaH (33.9 mg, 1.41 mmol, 60% in mineral oil). The reaction was stirred at 0 °C-RT for ON. The reaction 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 (gradient:0-30%) to afford {5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-3-(2,2,2-trifluoroethyl)benzo[d]imidazol-1-yl}acetonitrile (500 mg, 0.878 mmol, 93%) as a white solid. LCMS: ESI m/z 536.79 [M + H]⁺.

[00222] **Step B:** To a solution of {5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-3-(2,2,2-trifluoroethyl)benzo[d]imidazol-1-yl}acetonitrile (500 mg, 0.878 mmol) in NMP (5 mL) was added CuCN (78.6 mg, 0.878 mmol). The reaction was stirred at 130 °C for 4 hr. The cooled reaction 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 (gradient: 0-30%) to afford the title compound 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-(cyanomethyl)-2-oxo-1-(2,2,2-trifluoroethyl)benzo[d]imidazole-4-carbonitrile (100 mg, 0.194 mmol, 22%) as a white solid. LCMS: ESI m/z 515.65 [M + H]⁺.

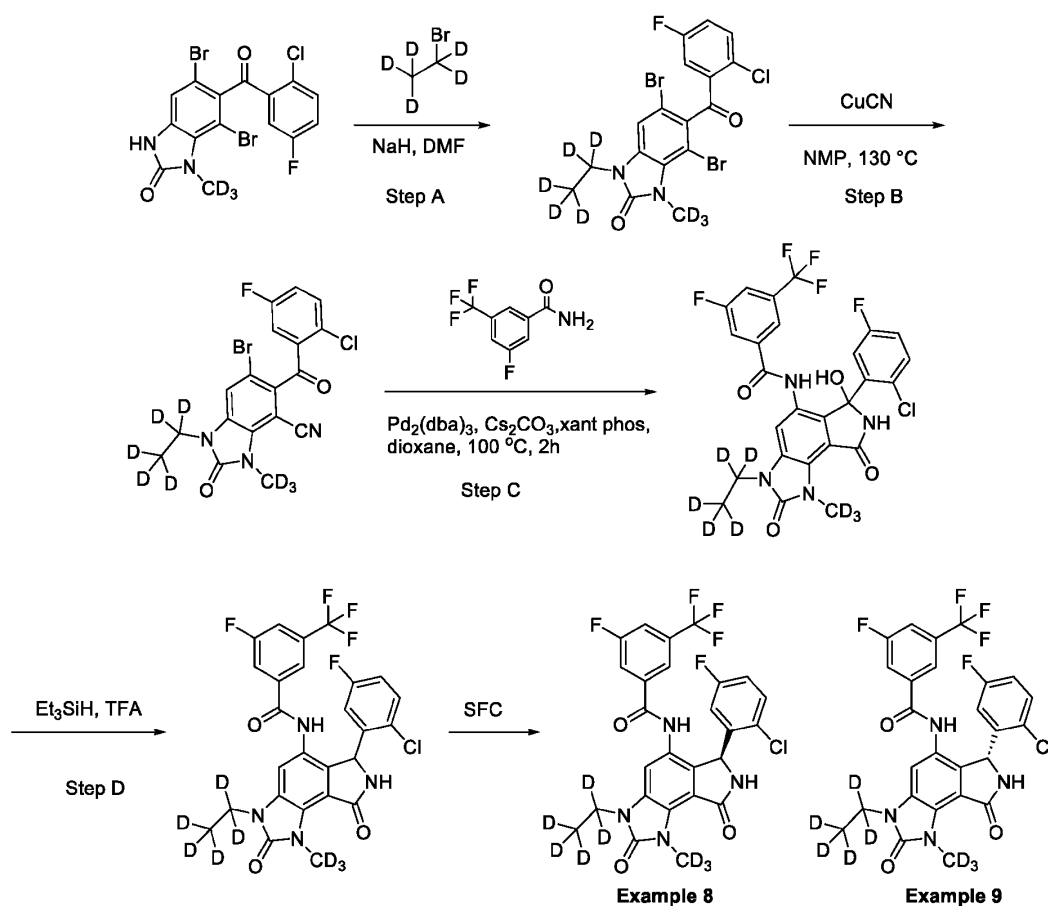
[00223] **Step C:** To a solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-(cyanomethyl)-2-oxo-1-(2,2,2-trifluoroethyl)benzo[d]imidazole-4-carbonitrile (100 mg, 0.194 mmol) in dioxane (5 mL) were added 2-methylpropan-2-yl aminomethanoate (4.22 mg, 0.036 mmol), Pd₂(dba)₃ (17.8 mg, 0.019 mmol), XANT PHOS (22.4 mg, 0.039 mmol) and Cs₂CO₃

(190 mg, 0.582 mmol). The reaction was stirred at 100 °C for 2 hr. The cooled reaction 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 (gradient:0-30%) to afford the title compound N-(6-(2-chloro-5-fluorophenyl)-1-(cyanomethyl)-6-hydroxy-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 (30 mg, 0.045 mmol, 23%) as a yellow solid. LCMS: ESI m/z 659.88 [M + H]⁺.

[00224] **Step D:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-1-(cyanomethyl)-6-hydroxy-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 (30 mg, 0.045 mmol) in TFA (3 mL) was added Et₃SiH (1 mL). The reaction was stirred at 50°C for 2 hr. The reaction was concentrated in vacuo. The residue was purified by prep-HPLC (C18, 0–80 % acetonitrile in H₂O) to afford N-(6-(2-chloro-5-fluorophenyl)-1-(cyanomethyl)-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 (2.5 mg, 0.004 mmol, 9%) as a white solid. LCMS: ESI m/z 643.88 [M + H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.45 (s, 1H), 9.42 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 7.58 (s, 1H), 7.34 – 7.23 (m, 1H), 7.14 – 7.05 (m, 1H), 6.82 – 6.44 (m, 1H), 6.08 (s, 1H), 5.86 – 5.72 (m, 2H), 5.03 – 4.82 (m, 2H).

[00225] **Step E:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-1-(cyanomethyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (15 mg, 0.023 mmol) in MeOH (3 mL) were added Raney Ni (0.13 mg, 0.002 mmol) and Paraformaldehyde (13.8 mg, 0.460 mmol). The reaction mixture was stirred at room temperature under H₂ for 4 hr. LCMS showed the reaction was 30% DP. The reaction mixture was filtered. The filtrate was concentrated. The residue was purified by prep-HPLC to afford N-[6-(2-chloro-5-fluorophenyl)-1-[2-(dimethylamino)ethyl]-2,8-dioxo-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (1 mg, 0.001 mmol, 6 %) as a white solid. LCMS: ESI m/z 676 [M + H]⁺. ¹H NMR (400 MHz, MeOD-*d*₄) δ 7.71 – 7.62 (m, 3H), 7.48 (s, 1H), 7.28 – 7.25 (m, 1H), 7.03 – 6.99 (m, 1H), 5.34 (t, J = 4.4 Hz, 2H), 3.50 – 3.46 (m, 2H), 3.15 – 3.12 (m, 2H), 3.07 (s, 6H).

Example 8: (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(ethyl-d5)-1-(methyl-d3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide
and Example 9: (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(ethyl-d5)-1-(methyl-d3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00226] **Step A:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (1.3 g, 2.79 mmol) in DMF (20 mL) was added NaH (0.22 g, 5.58 mmol, 60% in mineral oil) at 0 °C. The mixture was stirred for 10 min. Then 2-bromo-1,1,1,2,2-pentadeuterioethane (0.64 g, 5.58 mmol) was added and the mixture was stirred for 6 hours. The mixture was quenched with H₂O and 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 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(pentadeuterioethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (1 g, 2.01 mmol, 72 %) as a brown solid. LCMS: ESI m/z 499.1 [M + H]⁺.

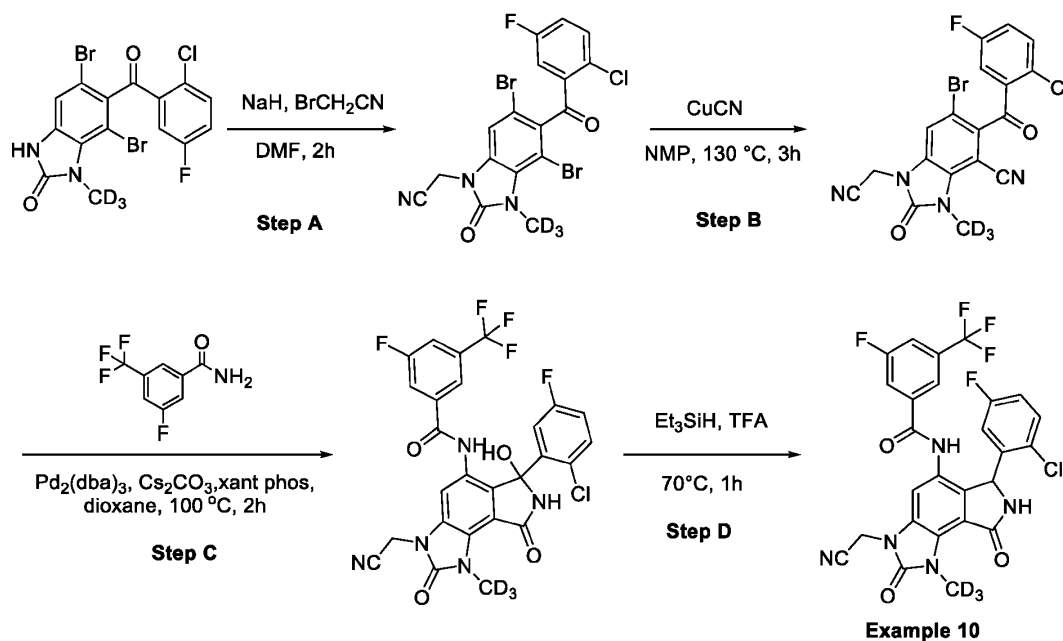
[00227] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(pentadeuterioethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (1 g, 2 mmol) in NMP (15 mL) was added CuCN (0.18 g, 2 mmol). The mixture was stirred at 130 °C under N₂ for 5 hours. The cooled mixture was poured into water and 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 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-1-(pentadeuterioethyl)-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (360 mg, 0.810 mmol, 29 %) as a brown solid. LCMS: ESI m/z 446.1 [M + H]⁺.

[00228] **Step C:** To a solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-1-(pentadeuterioethyl)-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (180 mg, 0.405 mmol) and 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (101 mg, 0.486 mmol) in dioxane (8 mL) was added XANT PHOS (46.8 mg, 0.081 mmol), Cs₂CO₃ (264 mg, 0.810 mmol) and Pd₂(dba)₃ (37.1 mg, 0.040 mmol). The mixture was stirred at 100 °C for 2 hours under N₂. The cooled mixture was concentrated under vacuum and the residue was purified by silica gel chromatography (3 g column) using 0 - 30% EtOAc/hexane to afford N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-3-(pentadeuterioethyl)-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (80 mg, 0.068 mmol, 17%) as a brown solid. LCMS: ESI m/z 589 [M + H]⁺.

[00229] **Step D:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-3-(pentadeuterioethyl)-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (80 mg, 0.136 mmol) in TFA (2 mL) was added Et₃SiH (0.5 mL). The mixture was stirred at 60 °C for 1 hour. The mixture was concentrated. The residue was poured into NaHCO₃, extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated in vacuum to give a residue, which was purified by prep-TLC (PE/EA=1: 1) to give a crude. It was separated by prep-SFC method 4 to give (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(ethyl-d₅)-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-

hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (2.3 mg, 0.004 mmol, 2.97%) as a white solid. LCMS: ESI m/z 573.3 $[M + H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.29 (s, 1H), 9.14 (s, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.81 – 7.66 (m, 2H), 7.36 (s, 1H), 7.28 (dd, $J = 8.8, 5.2$ Hz, 1H), 7.14 – 7.02 (m, 1H), 6.64 (brs, 1H), 6.01 (brs, 1H). And (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(ethyl- d_5)-1-(methyl- d_3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (2.0 mg, 0.004 mmol, 2.58%) as a white solid. LCMS: ESI m/z 573.3 $[M + H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.29 (s, 1H), 9.14 (s, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.81 – 7.66 (m, 2H), 7.36 (s, 1H), 7.28 (dd, $J = 8.8, 5.2$ Hz, 1H), 7.14 – 7.02 (m, 1H), 6.64 (brs, 1H), 6.01 (brs, 1H).

Example 10: N-(6-(2-chloro-5-fluorophenyl)-3-(cyanomethyl)-1-(methyl- d_3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00230] **Step A:** To a solution of 5,7-dibromo-6-(2-chloro-5-fluorobenzoyl)-1-(methyl- d_3)-1,3-dihydro-2H-benzo[d]imidazol-2-one (3.2 g, 6.8 mmol) in DMF (30 mL) was added NaH (0.55 g, 13.7 mmol, 60% in mineral) at 0 °C and the mixture was stirred for 10 min. Then bromoacetonitrile (1.65 g, 13.7 mmol) was added, and the mixture was stirred for 2 h. The mixture was quenched with H_2O , diluted with EA and washed with H_2O and brine. The organic layer was concentrated under vacuum. The residue was purified using silica gel column

chromatography eluting with 0-30% ethyl acetate in petroleum ether to afford the title compound 2-(4,6-dibromo-5-(2-chloro-5-fluorobenzoyl)-3-(methyl-d3)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)acetonitrile (2.5 g, 4.96 mmol, 72%) as a yellow solid. LCMS: ESI m/z 503 [M + H]⁺.

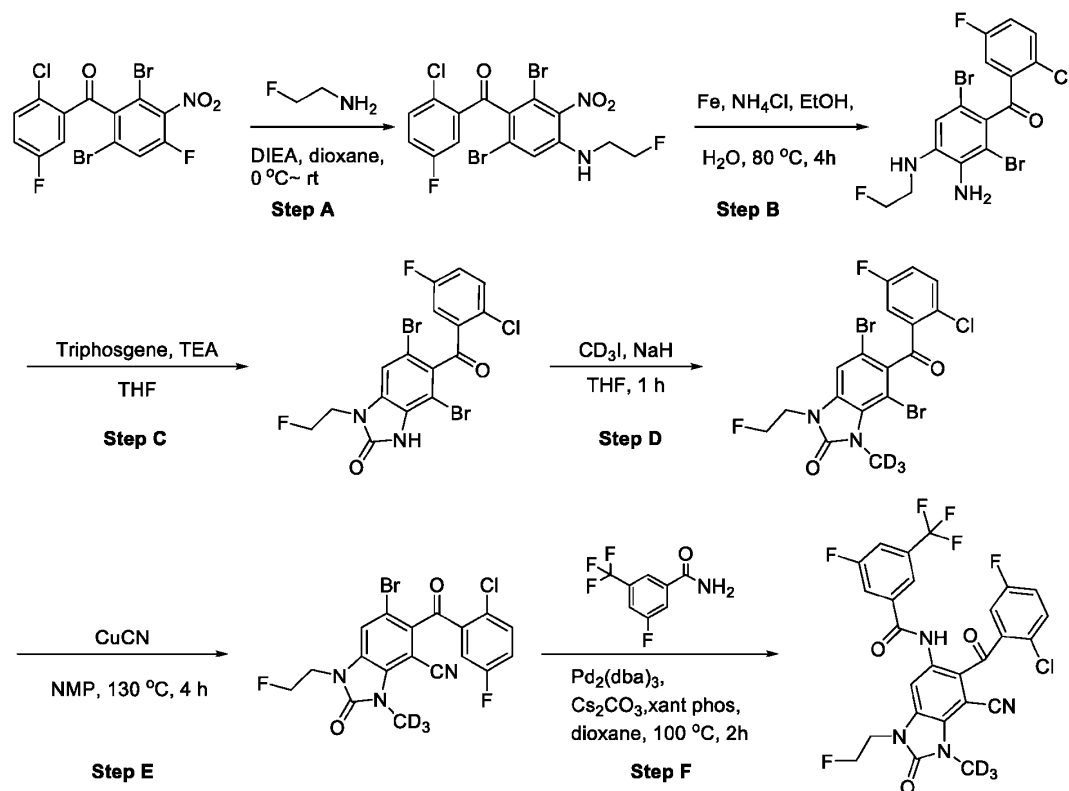
[00231] **Step B:** To a solution of 2-(4,6-dibromo-5-(2-chloro-5-fluorobenzoyl)-3-(methyl-d3)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)acetonitrile (1 g, 1.98 mmol) in NMP (15 mL) was added CuCN (0.16 g, 1.78 mmol). The mixture was stirred at 130 °C for 3 h. The mixture was diluted with EA and washed with H₂O and brine. The organic layer was concentrated under vacuum. The residue was purified using silica gel column chromatography eluting with 0-30% ethyl acetate in petroleum ether to afford the title compound 6-bromo-5-(2-chloro-5-fluorobenzoyl)-1-(cyanomethyl)-3-(methyl-d3)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (240 mg, 0.53 mmol, 27%) as a yellow solid. LCMS: ESI m/z 450 [M + H]⁺.

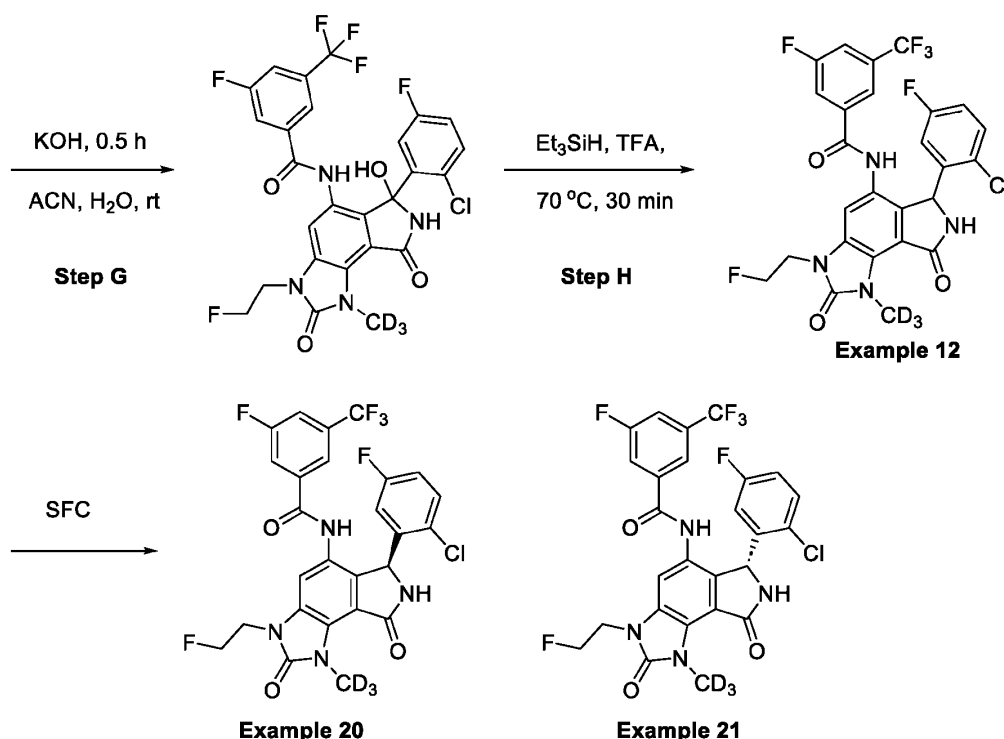
[00232] **Step C:** To a solution of 6-bromo-5-(2-chloro-5-fluorobenzoyl)-1-(cyanomethyl)-3-(methyl-d3)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (80 mg, 0.17 mmol) in dioxane (5 mL) was added 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (40.4 mg, 0.19 mmol), XANT PHOS (20.5 mg, 0.036 mmol), Cs₂CO₃ (116 mg, 0.36 mmol) and Pd₂(dba)₃ (16.3 mg, 0.018 mmol). The mixture was stirred at 100 °C for 4 h under N₂. The mixture was diluted with EA and washed with H₂O and brine. The organic layer was concentrated under vacuum. The residue was purified using silica gel column chromatography eluting with 0-50% ethyl acetate in petroleum ether to afford the title compound N-(6-(2-chloro-5-fluorophenyl)-3-(cyanomethyl)-6-hydroxy-1-(methyl-d3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (20 mg, 0.034 mmol, 19%) as a yellow solid. LCMS: ESI m/z 595 [M + H]⁺.

[00233] **Step D:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-3-(cyanomethyl)-6-hydroxy-1-(methyl-d3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (20 mg, 0.034 mmol) in TFA (2 mL) was added Et₃SiH (20 mg, 0.17 mmol). The mixture was stirred at 70 °C for 1 hour. The mixture was concentrated under vacuum. The residue was purified using pre-HPLC to afford the title compound N-(6-(2-chloro-5-fluorophenyl)-3-(cyanomethyl)-1-(methyl-d3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (2.2 mg, 0.004 mmol, 11%) as a white solid. LCMS: ESI m/z 579 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.39 (s, 1H), 9.22 (s,

1H), 7.94 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.70 (s, 1H), 7.52 (s, 1H), 7.31 – 7.24 (m, 1H), 7.14 – 7.04 (m, 1H), 6.65 (brs, 1H), 6.03 (brs, 1H), 5.21 (s, 2H).

Example 12: N-[6-(2-chloro-5-fluorophenyl)-3-(2-fluoroethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e] isoindol-5-yl]-5-fluoro-3-(trifluoromethyl) benzamide, **Example 20:** (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(2-fluoroethyl)-1-(methyl-d3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide and **Example 21:** (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(2-fluoroethyl)-1-(methyl-d3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide





[00234] **Step A** To a solution of (2-chloro-5-fluorophenyl) (2,6-dibromo-4-fluoro-3-nitrophenyl) methanone (3 g, 6.58 mmol) in dioxane (30 mL) was added 2-fluoroethan-1-amine (0.50 g, 7.91 mmol) and DIEA (1.70 g, 13.2 mmol) at 0 °C. After stirred at rt overnight under N₂ atmosphere, the mixture was poured into water (50 mL) and extracted with EtOAc (50 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-chloro-5-fluorophenyl) {2,6-dibromo-4-[(2-fluoroethyl) amino]-3-nitrophenyl} methanone (1.6 g, 3.21 mmol, 48 %) as a white solid. LCMS: ESI m/z 499 [M + H]⁺.

[00235] **Step B** To a solution of (2-chloro-5-fluorophenyl) {2,6-dibromo-4-[(2-fluoroethyl) amino]-3-nitrophenyl} methanone (1.6 g, 3.21 mmol) in EtOH (15 mL)/H₂O (5 mL) was added NH₄Cl (0.52 g, 9.63 mmol) and Fe (1.79 g, 32.1 mmol) at rt. After stirred at 80 °C for 3h under N₂ atmosphere, the mixture was filtered, concentrated. The residue was diluted with water (50 mL) and extracted with EtOAc (50 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 {3-amino-2,6-dibromo-4-[(2-

fluoroethyl) amino] phenyl} (2-chloro-5-fluorophenyl) methanone (420 mg, 0.896 mmol, 28%) as a white solid. LCMS: ESI m/z 468 [M + H]⁺.

[00236] **Step C** To a solution of {3-amino-2,6-dibromo-4-[(2-fluoroethyl) amino] phenyl} (2-chloro-5-fluorophenyl) methanone (400 mg, 0.854 mmol) in tetrahydrofuran (8 mL) was added Triphosgene (380 mg, 1.28 mmol) and TEA (0.2 mL, 1.71 mmol) at 0 °C. After stirred at rt for 2h under N₂ atmosphere, 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, 0-50 %, EtOAc in PE) to give 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2-fluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (280 mg, 0.566 mmol, 66 %) as a white solid. LCMS: ESI m/z 495 [M + H]⁺.

[00237] **Step D** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2-fluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (280 mg, 0.566 mmol) in THF (5 mL) was added NaH (41 mg, 1.70 mmol) at 0 °C. The reaction mixture was stirred at 0 °C under N₂ for 10 min. CD₃I (410 mg, 2.83 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature under N₂ for 1 hr. The reaction was complete detected by TLC. The cooled reaction mixture was dissolved in EA (50 mL), washed with H₂O (30 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 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2-fluoroethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (270 mg, 0.528 mmol, 93%) as a yellow solid. LCMS: ESI m/z 510/511/512 [M+H]⁺.

[00238] **Step E** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2-fluoroethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (270 mg, 0.528 mmol) in NMP (2 mL) was added CuCN (47 mg, 0.528 mmol). The reaction mixture was stirred at 130 °C under N₂ for 2 hr. The reaction was complete detected by LCMS. The cooled reaction mixture was dissolved with H₂O, extracted with EA (20 mL), washed (10 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 6-bromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2-fluoroethyl)-2-oxo-3-(trideuteriomethyl) benzo[d]imidazole-4-carbonitrile (240 mg, 0.524 mmol, 99 %) as a yellow solid. LCMS: ESI m/z 457/459 [M + H]⁺.

[00239] **Step F** To a stirred solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2-fluoroethyl)-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (150 mg, 0.328 mmol) in dioxane (5 mL) was added 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (101 mg, 0.492 mmol), Pd₂(dba)₃ (30 mg, 0.033 mmol), Cs₂CO₃ (213 mg, 0.655 mmol) and Xant-PHOS (38 mg, 0.066 mmol) at rt. After stirred at 100 °C for 2h, the mixture was poured into 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 residue was purified by chromatography (silica gel, 0-50%, EtOAc in PE) to give N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-(2-fluoroethyl)-2-oxo-1-(trideuteriomethyl) benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl) benzamide (50 mg, 0.086 mmol, 26%) as a yellow solid. LCMS: ESI m/z 583 [M+H]⁺

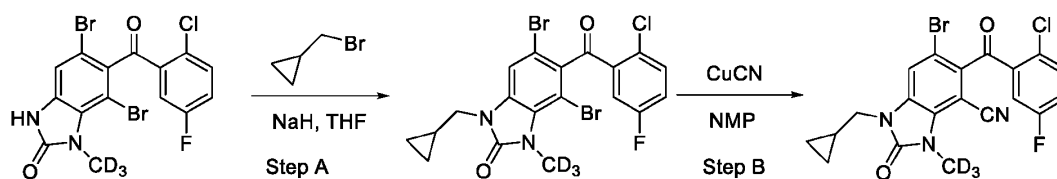
[00240] **Step G** To a stirred solution of N-{6-[(2-chloro-5-fluorophenyl) carbonyl]-7-cyano-3-(2-fluoroethyl)-2-oxo-1-(trideuteriomethyl) benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl) benzamide (50 mg, 0.086 mmol) in ACN (4 mL) and H₂O (1 mL) was added potassium hydroxide (48 mg, 0.856 mmol) at rt. After stirred at rt for 0.5h, the mixture was poured into water (20 mL) and extracted with EtOAc (10 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. To afford the title compound crude N-[6-(2-chloro-5-fluorophenyl)-3-(2-fluoroethyl)-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e] isoindol-5-yl]-5-fluoro-3-(trifluoromethyl) benzamide (50 mg, 0.083 mmol, 97%) as a white solid. LCMS: ESI m/z 584 [M+H]⁺

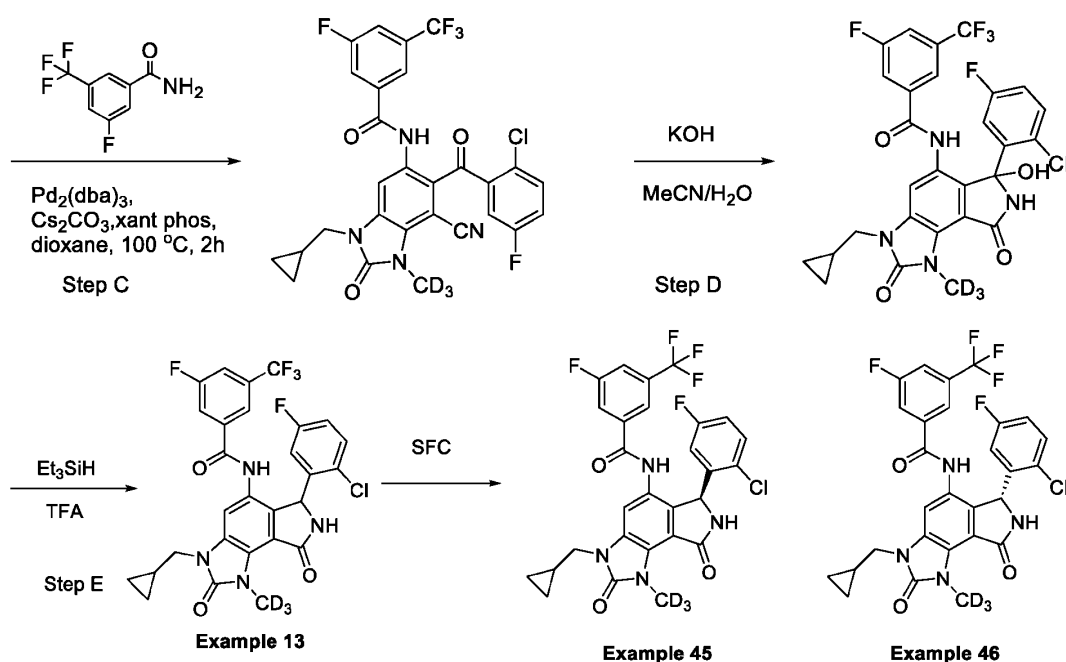
[00241] **Step H** To a stirred solution of N-[6-(2-chloro-5-fluorophenyl)-3-(2-fluoroethyl)-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e] isoindol-5-yl]-5-fluoro-3-(trifluoromethyl) benzamide (50 mg, 0.083 mmol) in TFA (1 mL) and Et₃SiH (1 mL) at rt. After stirred at 70 °C for 0.5 h, 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-[6-(2-chloro-5-fluorophenyl)-3-(2-fluoroethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e] isoindol-5-yl]-5-fluoro-3-(trifluoromethyl) benzamide (10 mg, 0.017 mmol, 20 %) as a white solid. LCMS: ESI m/z 586.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.32 (s, 1H), 9.16 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.75 – 7.70

(m, 2H), 7.38 (s, 1H), 7.28 (dd, $J = 8.0, 4.0$ Hz, 1H), 7.08 (dd, $J = 8.4, 3.2$ Hz, 1H), 6.62 (brs, 1H), 6.00 (brs, 1H), 4.76 (t, $J = 4$ Hz, 1H), 4.64 (t, $J = 4$ Hz, 1H), 4.28 – 4.18 (m, 2H).

[00242] N-[6-(2-chloro-5-fluorophenyl)-3-(2-fluoroethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl) benzamide (100 mg) was then subjected to chiral prep-SFC separation method 5 to give (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(2-fluoroethyl)-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (43 mg, 0.073 mmol, 43%) as a white solid LCMS: ESI m/z 586.2 $[M + H]^+$. ¹H NMR (400 MHz, DMSO-d₆) δ 10.31 (s, 1H), 9.16 (s, 1H), 7.93 (d, $J = 8.0$ Hz, 1H), 7.75 – 7.70 (m, 2H), 7.38 (s, 1H), 7.28 (dd, $J = 8.0, 4.0$ Hz, 1H), 7.08 (dd, $J = 8.4, 3.2$ Hz, 1H), 6.65 (brs, 1H), 6.00 (s, 1H), 4.76 (t, $J = 4.0$ Hz, 1H), 4.64 (t, $J = 4.0$ Hz, 1H), 4.28 – 4.18 (m, 2H). And (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(2-fluoroethyl)-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (35.1 mg, 0.060 mmol, 35%) as a white solid. LCMS: ESI m/z 586.2 $[M + H]^+$. ¹H NMR (400 MHz, DMSO-d₆) δ 10.31 (s, 1H), 9.15 (s, 1H), 7.93 (d, $J = 8.0$ Hz, 1H), 7.85 – 7.61 (m, 2H), 7.38 (s, 1H), 7.28 (dd, $J = 8.0, 4.0$ Hz, 1H), 7.14 – 7.03 (m, 1H), 6.65 (brs, 1H), 6.01 (s, 1H), 4.76 (t, $J = 4.0$ Hz, 1H), 4.64 (t, $J = 4.0$ Hz, 1H), 4.28 – 4.18 (m, 2H).

Example 13: N-[6-(2-chloro-5-fluorophenyl)-3-(cyclopropylmethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide, **Example 45:** N-[(6S)-6-(2-chloro-5-fluorophenyl)-3-(cyclopropylmethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide and **Example 46:** N-[(6R)-6-(2-chloro-5-fluorophenyl)-3-(cyclopropylmethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide





[00243] **Step A:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (2 g, 4.30 mmol) in DMF (30 mL) was added NaH (0.34 g, 8.59 mmol) at 0 °C. The mixture was stirred at rt for 10 min. Then (bromomethyl)cyclopropane (0.87 g, 6.44 mmol) was added and the mixture was stirred at 20 °C for 12 hours. The mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated in vacuum to give the residue. The residue was purified by a silica gel column chromatography eluted with EtOAc in PE (gradient: 0~20%) to give 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(cyclopropylmethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (780 mg, 1.50 mmol, 35 %) as a yellow solid. LCMS: ESI m/z 520.1 [M + H]⁺.

[00244] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(cyclopropylmethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (770 mg, 1.48 mmol) in NMP (10 mL) was added CuCN (133 mg, 1.48 mmol). The reaction mixture was stirred at 130 °C for 2 hours. The cooled mixture was poured into water and 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 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(cyclopropylmethyl)-2-oxo-3-

(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (230 mg, 0.494 mmol, 33 %) as a brown solid. LCMS: ESI m/z 467.2 [M + H]⁺.

[00245] **Step C:** To a solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(cyclopropylmethyl)-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (210 mg, 0.451 mmol) and 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (112 mg, 0.541 mmol) in dioxane (10 mL) was added Cs₂CO₃ (294 mg, 0.902 mmol), Xant-PHOS (52.2 mg, 0.090 mmol) and Pd₂(dba)₃ (41.3 mg, 0.045 mmol). The mixture was stirred at 100 °C under N₂ for 2 hours. The cooled reaction mixture was diluted with water, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to give N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-(cyclopropylmethyl)-2-oxo-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (260 mg, 0.439 mmol, 97 %) as a brown solid. LCMS: ESI m/z 592.3 [M + H]⁺.

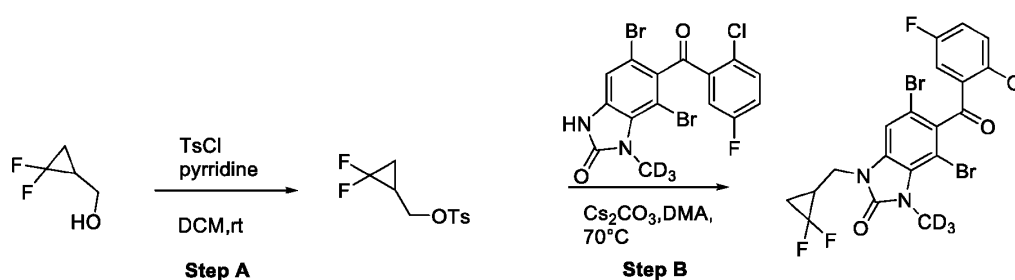
[00246] **Step D:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-(cyclopropylmethyl)-2-oxo-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (220 mg, 0.372 mmol) in CH₃CN (10 mL) and H₂O (2.5 mL) was added KOH (41.7 mg, 0.743 mmol). The mixture was stirred at 20 °C for 1 hour. The reaction mixture was diluted with water, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to give N-[6-(2-chloro-5-fluorophenyl)-3-(cyclopropylmethyl)-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (220 mg, 0.361 mmol, 97%) as a brown solid. LCMS: ESI m/z 608.3 [M - H]⁻.

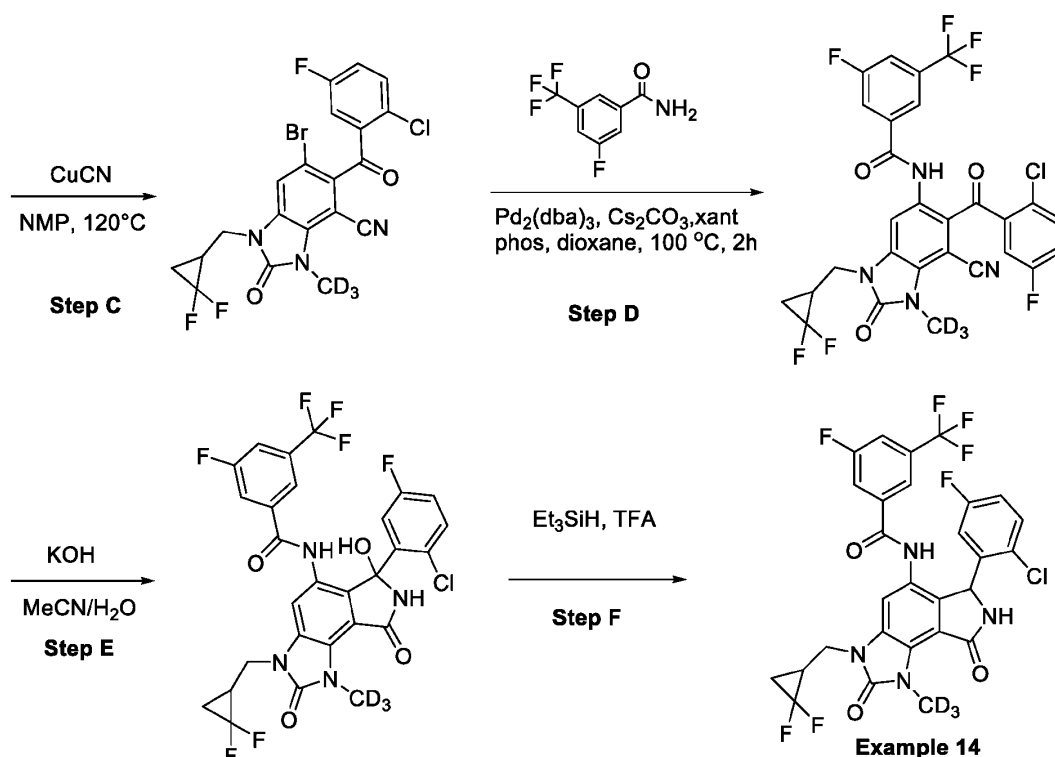
[00247] **Step E:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-3-(cyclopropylmethyl)-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (250 mg, 0.410 mmol) in TFA (10 mL) was added Et₃SiH (2 mL). The reaction mixture was stirred at 70 °C for 1 hour. The cooled mixture was concentrated and the residue was purified by silica gel chromatography (2 g column) using 0 - 60% EtOAc/hexane to afford a yellow crude, which was purified by prep-HPLC to give N-[6-(2-chloro-5-fluorophenyl)-3-(cyclopropylmethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (22.6 mg, 0.038 mmol, 9%) as a white solid. LCMS: ESI m/z 594.4 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.28 (s, 1H), 9.14 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.76 – 7.72 (m, 2H), 7.41 (s, 1H), 7.27 (dd, J =

8.8, 5.2 Hz, 1H), 7.10 – 7.08 (m, 1H), 6.66 (brs, 1H), 6.02 (brs, 1H), 3.79 (d, J = 7.2 Hz, 2H), 1.25 – 1.16 (m, 1H), 0.51 – 0.45 (m, 2H), 0.44 – 0.37 (m, 2H).

[00248] N-[6-(2-chloro-5-fluorophenyl)-3-(cyclopropylmethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (90 mg) was then separated in the chiral prep-SFC (method 12) to give N-[(6S)-6-(2-chloro-5-fluorophenyl)-3-(cyclopropylmethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (17.2 mg, 0.029 mmol, 19 %) as a white solid. LCMS: ESI m/z 594.2 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.28 (s, 1H), 9.13 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.76 – 7.72 (m, 2H), 7.42 (s, 1H), 7.27 (dd, J = 8.8, 5.2 Hz, 1H), 7.10 – 7.08 (m, 1H), 6.63 (brs, 1H), 6.02 (brs, 1H), 3.79 (d, J = 7.2 Hz, 2H), 1.25 – 1.16 (m, 1H), 0.52 – 0.45 (m, 2H), 0.44 – 0.38 (m, 2H). And N-[(6R)-6-(2-chloro-5-fluorophenyl)-3-(cyclopropylmethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (19.9 mg, 0.034 mmol, 22 %) as a white solid. LCMS: ESI m/z 594.2 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.28 (s, 1H), 9.13 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.76 – 7.72 (m, 2H), 7.42 (s, 1H), 7.27 (dd, J = 8.8, 5.2 Hz, 1H), 7.10 – 7.08 (m, 1H), 6.66 (s, 1H), 6.01 (s, 1H), 3.79 (d, J = 7.2 Hz, 2H), 1.25 – 1.16 (m, 1H), 0.52 – 0.45 (m, 2H), 0.44 – 0.38 (m, 2H).

Example 14: N-(6-(2-chloro-5-fluorophenyl)-3-((2,2-difluorocyclopropyl)methyl)-1-(methyl-d3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide





[00249] **Step A:** To a solution of (2,2-difluorocyclopropyl)methanol (500 mg, 4.626 mmol) in DCM (6 mL) was added pyridine (0.8 mL, 9.25 mmol) and TsCl (1.3 g, 6.939 mmol). The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with H_2O , extracted with EA. The organic phase was washed with brine, dried by Na_2SO_4 , filtered and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 15%] to afford the title compound (2,2-difluorocyclopropyl)methyl 4-methylbenzenesulfonate (800 mg, 3.050 mmol, 65%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.81 (d, $J = 8.0$ Hz, 2H), 7.50 (d, $J = 8.0$ Hz, 2H), 4.33 – 4.17 (m, 1H), 4.00 (ddd, $J = 12.0, 8.0, 4.0$ Hz, 1H), 2.19 – 2.04 (m, 1H), 1.69 (tdd, $J = 12.0, 8.0, 4.0$ Hz, 1H), 1.54 – 1.35 (m, 1H).

[00250] **Step B:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (400 mg, 0.859 mmol) in DMA (6 mL) was added Cs_2CO_3 (280 mg, 0.859 mmol) and (1,1-difluorocycloprop-2-yl)methyl 4-methylbenzenesulfonate (225 mg, 0.859 mmol). The reaction mixture was stirred at 70°C under N_2 for 3h. The cooled reaction mixture was diluted with H_2O , 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: 10%] to give 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(2,2-difluorocyclopropyl)methyl]-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (180 mg, 0.324 mmol, 37%) as a white solid. LCMS: ESI m/z 556 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.79 (s, 1H), 7.73 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.63 – 7.56 (m, 1H), 7.52 – 7.45 (m, 1H), 4.16 – 4.08 (m, 1H), 4.02 – 3.95 (m, 1H), 2.32 – 2.21 (m, 1H), 1.66 (ddd, *J* = 12.0, 8.0, 4.0 Hz, 1H), 1.46 (ddd, *J* = 12.0, 8.0, 4.0 Hz, 1H).

[00251] **Step C:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(2,2-difluorocyclopropyl)methyl]-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (150 mg, 0.270 mmol) in NMP (5 mL) was added CuCN (48 mg, 0.540 mmol). The cooled reaction mixture was stirred at 120 °C under N₂ 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: 15%] to afford 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(2,2-difluorocyclopropyl)methyl]-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (70 mg, 0.140 mmol, 52%) as a white solid. LCMS: ESI m/z 503 [M+H]⁺

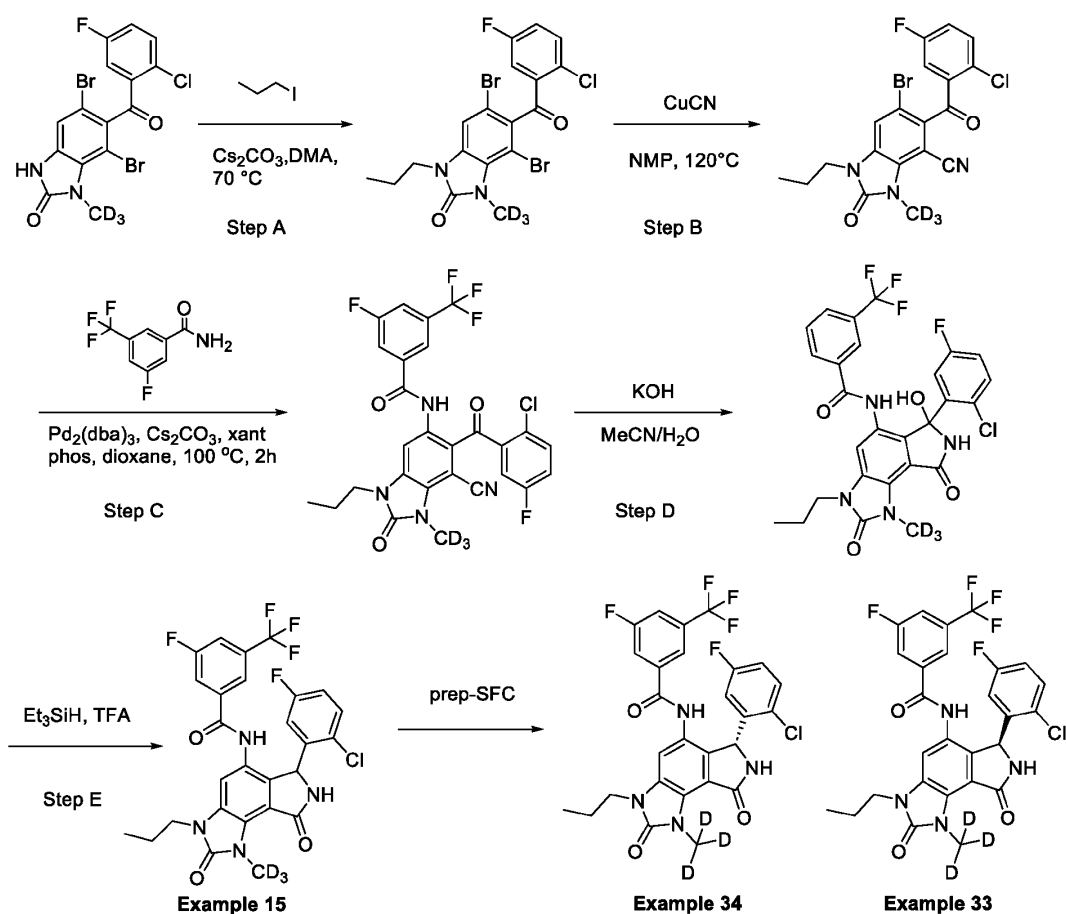
[00252] **Step D:** To a solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(2,2-difluorocyclopropyl)methyl]-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (70 mg, 0.140 mmol) in dioxane (10 mL) was added Cs₂CO₃ (90 mg, 0.279 mmol), 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (28 mg, 0.140 mmol), Xant-phos (16 mg, 0.028 mmol) and Pd₂(dba)₃ (12 mg, 0.014 mmol). The reaction mixture was stirred at 100 °C under N₂ 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: 15%] to afford the title compound N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-[(2,2-difluorocyclopropyl)methyl]-2-oxo-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (60 mg, 0.096 mmol, 68%) as a white solid. LCMS: ESI m/z 628 [M+H]⁺

[00253] **Step E:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-[(2,2-difluorocyclopropyl)methyl]-2-oxo-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (60 mg, 0.096 mmol) in MeCN/H₂O (5 mL) was added potassium

hydroxide (26 mg, 0.478 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 to afford the title compound N-[6-(2-chloro-5-fluorophenyl)-3-[(2,2-difluorocyclopropyl)methyl]-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (50 mg, 0.077 mmol, 81%) as a white solid. LCMS: ESI m/z 645 [M+H]⁺

[00254] **Step F:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-3-[(2,2-difluorocyclopropyl)methyl]-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (60 mg, 0.093 mmol) in TFA (5 mL) was added Et₃SiH (21 mg, 0.186 mmol). The reaction mixture was stirred at 70 °C for 1h. 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 afford N-[6-(2-chloro-5-fluorophenyl)-3-[(2,2-difluorocyclopropyl)methyl]-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (12.5 mg, 0.020 mmol, 21%) as a white solid. LCMS: ESI m/z 630 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.30 (d, *J* = 4.0 Hz, 1H), 9.16 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 12.0 Hz, 2H), 7.43 (s, 1H), 7.28 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.09 (s, 1H), 6.65 (s, 1H), 6.02 (s, 1H), 4.20 – 3.91 (m, 2H), 2.32 – 2.09 (m, 1H), 1.73 – 1.61 (m, 1H), 1.47 (s, 1H).

Example 15: N-(6-(2-chloro-5-fluorophenyl)-1-(methyl-d₃)-2,8-dioxo-3-propyl-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide, **Example 33:** (S)-N-(6-(2-chloro-5-fluorophenyl)-1-(methyl-d₃)-2,8-dioxo-3-propyl-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide and **Example 34:** (R)-N-(6-(2-chloro-5-fluorophenyl)-1-(methyl-d₃)-2,8-dioxo-3-propyl-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00255] **Step A:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (500 mg, 1.074 mmol) in DMA (6 mL) was added Cs_2CO_3 (1.04 g, 3.222 mmol), and 1-iodopropane (0.157 mL, 1.611 mmol). The reaction mixture was stirred at 70 °C for 3h. The reaction mixture was diluted with H_2O , extracted with EA. The organic phase was washed with brine, dried by Na_2SO_4 , filtered and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 10%] to afford the title compound 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-propyl-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (200 mg, 0.394 mmol, 37%) as a white solid. LCMS: ESI m/z 508 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.75 – 7.70 (m, 2H), 7.63 – 7.55 (m, 1H), 7.47 (dd, $J = 8.0, 4.0$ Hz, 1H), 3.85 (t, $J = 8.0$ Hz, 2H), 1.69 – 1.63 (m, 2H), 0.89 (t, $J = 8.0$ Hz, 3H).

[00256] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-propyl-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (200 mg, 0.394 mmol) in NMP (5 mL) was added CuCN (14 mg, 0.158 mmol). The reaction mixture was stirred at 120 °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: 15%] to afford the title compound 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-1-propyl-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (120 mg, 0.264 mmol, 67%) as a white solid. LCMS: ESI m/z 455 [M+H]⁺

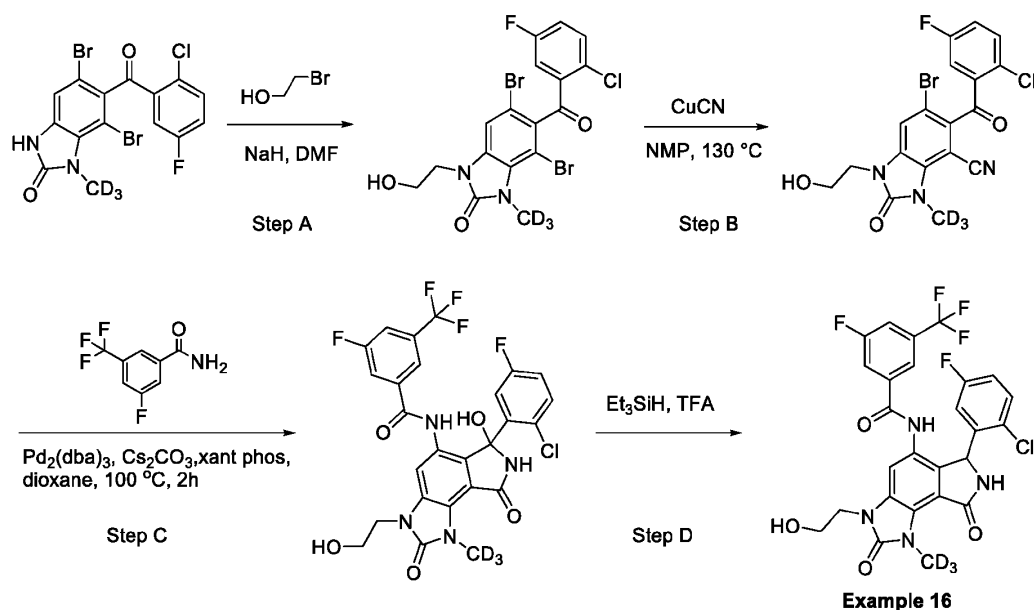
[00257] **Step C:** To a solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-1-propyl-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (120 mg, 0.264 mmol) in dioxane (5 mL) was added Cs₂CO₃ (172 mg, 0.529 mmol), 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (54 mg, 0.264 mmol), Xant-phos (30.61 mg, 0.053 mmol) and Pd₂(dba)₃ (24 mg, 0.026 mmol). The reaction mixture was stirred at 100 °C under N₂ 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: 15%] to afford the title compound N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-2-oxo-3-propyl-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (90 mg, 0.155 mmol, 58%) as a white solid. LCMS: ESI m/z 580 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.58 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.53 (s, 1H), 7.42 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.30 – 7.16 (m, 2H), 3.87 (t, *J* = 8.0 Hz, 2H), 1.71 – 1.66 (m, 2H), 0.90 (t, *J* = 8.0 Hz, 3H).

[00258] **Step D:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-2-oxo-3-propyl-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (90 mg, 0.155 mmol) in MeCN/H₂O (5 mL) was added potassium hydroxide (43 mg, 0.776 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: 30%] to afford the title compound N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-3-propyl-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-

3-(trifluoromethyl)benzamide (70 mg, 0.117 mmol, 75%) as a white solid. LCMS: ESI m/z 598 [M+H]⁺

[00259] **Step E:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-3-propyl-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (70 mg, 0.117 mmol) in TFA (5 mL) was added Et₃SiH (40 mg, 0.351 mmol). The reaction mixture was stirred at 70 °C for 1h. 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 afford N-[6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-propyl-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (47.9 mg, 0.082 mmol, 70%) as a white solid. LCMS: ESI m/z 582 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.28 (s, 1H), 9.13 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.71 (s, 1H), 7.36 (s, 1H), 7.27 (dd, J = 8.0, 4.0 Hz, 1H), 7.10 – 7.07 (m, 1H), 6.65 (brs, 1H), 6.01 (brs, 1H), 3.89 – 3.80 (m, 2H), 1.71 – 1.65 (m, 2H), 0.89 (t, J = 8.0 Hz, 3H). N-[6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-propyl-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (45 mg, 0.079 mmol) was purified by chiral prep-SFC method 9 to afford the title compound (R)-N-(6-(2-chloro-5-fluorophenyl)-1-(methyl-d₃)-2,8-dioxo-3-propyl-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (12.9 mg, 0.022 mmol, 28 %) as a white solid LCMS: ESI m/z 606 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.28 (s, 1H), 9.13 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.77 – 7.70 (m, 2H), 7.37 (s, 1H), 7.27 (dd, J = 8.0, 4.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 6.66 (brs, 1H), 6.01 (brs, 1H), 3.87 – 3.82 (m, 2H), 1.71 – 1.65 (m, 2H), 0.89 (t, J = 8.0 Hz, 3H). And (S)-N-(6-(2-chloro-5-fluorophenyl)-1-(methyl-d₃)-2,8-dioxo-3-propyl-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (15.5 mg, 0.027 mmol, 33 %) as a white solid. LCMS: ESI m/z 606 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.28 (s, 1H), 9.13 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.77 – 7.70 (m, 2H), 7.37 (s, 1H), 7.27 (dd, J = 8.0, 4.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 6.66 (brs, 1H), 6.01 (brs, 1H), 3.87 – 3.82 (m, 2H), 1.71 – 1.65 (m, 2H), 0.89 (t, J = 8.0 Hz, 3H).

Example 16: N-[6-(2-chloro-5-fluorophenyl)-3-(2-hydroxyethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide



[00260] **Step A:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (1 g, 2.15 mmol) in DMF (15 mL) was added NaH (0.17 g, 4.30 mmol, 60% in mineral oil) at 0 °C. The mixture was stirred for 10 min. Then 2-bromoethanol (400 mg, 3.22 mmol) was added and the mixture was stirred at 70 °C for 3 hours. The cooled mixture was quenched with MeOH and poured into water, extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated in vacuum to give a residue, which was purified by a silica gel column chromatography eluted with EtOAc in PE (gradient: 0~60%) to give 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2-hydroxyethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (450 mg, 0.883 mmol, 41 %) as a brown solid. LCMS: ESI m/z 509.9 [M + H]⁺.

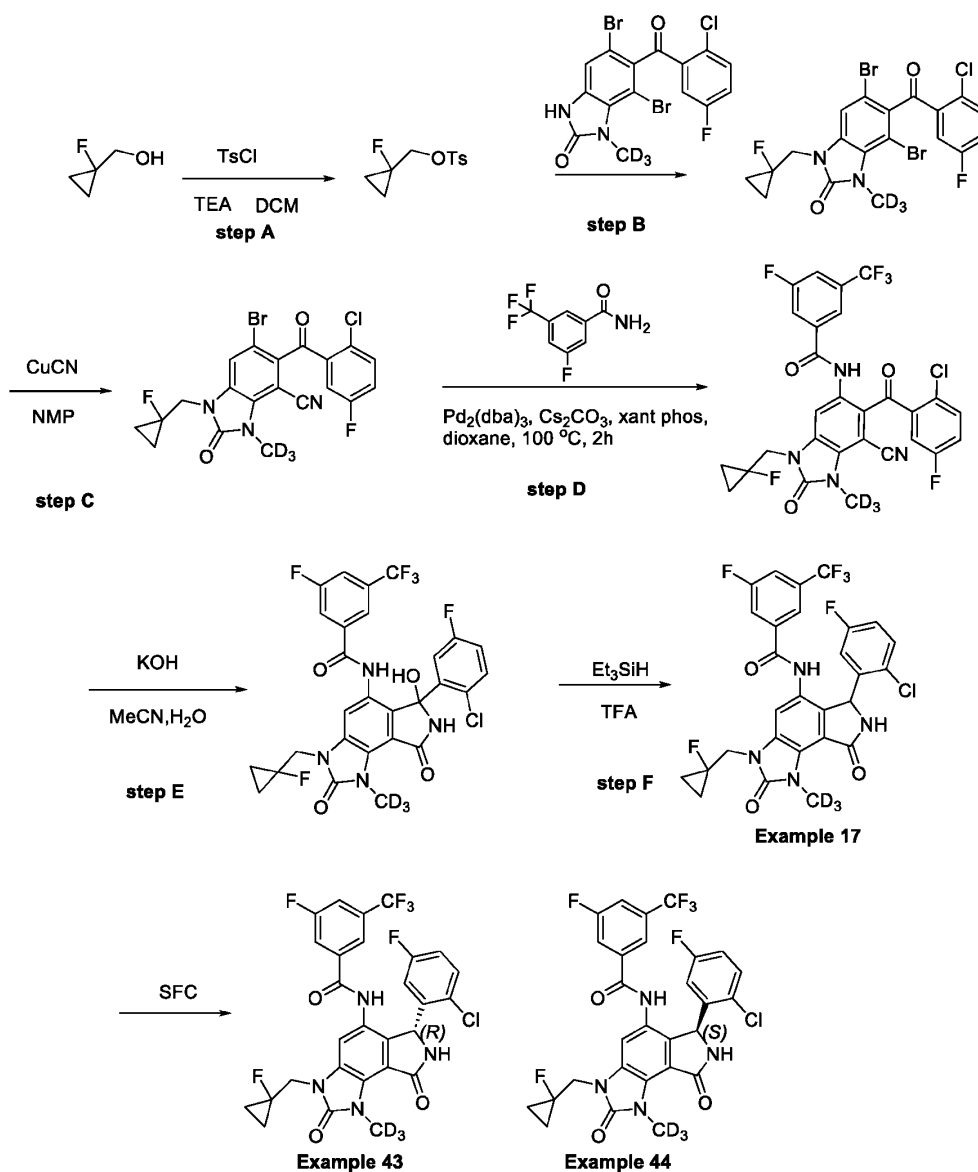
[00261] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2-hydroxyethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (430 mg, 0.844 mmol) in NMP (5 mL) was added CuCN (75.6 mg, 0.844 mmol). The mixture was stirred at 130 °C under N₂ for 2 hours. The cooled mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to afford a residue, which was purified by silica gel chromatography (10 g column) using 0 - 60% EtOAc/hexane to afford 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2-hydroxyethyl)-2-oxo-3-

(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (300 mg, 0.658 mmol, 78 %) as a brown solid. LCMS: ESI m/z 457.1 [M + H]⁺.

[00262] **Step C:** To a solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2-hydroxyethyl)-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (300 mg, 0.661 mmol) and 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (164 mg, 0.792 mmol) in dioxane (10 mL) was added XANT PHOS (38.2 mg, 0.0658 mmol), Cs₂CO₃ (430 mg, 1.32 mmol) and Pd₂(dba)₃ (60.5 mg, 0.0658 mmol). The mixture was stirred at 100 °C under N₂ for 2 hours. The cooled mixture was concentrated and the residue was purified using silica gel column chromatography eluted with MeOH in DCM (gradient: 10%) to afford N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-(2-hydroxyethyl)-2-oxo-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (50 mg, 0.086 mmol, 13 %) as a brown solid. LCMS: ESI m/z 600.3 [M + H]⁺.

[00263] **Step D:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-3-(2-hydroxyethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (30 mg, 0.050 mmol) in TFA (2 mL) was added Et₃SiH (0.5 mL). The mixture was stirred at 70 °C for 10 min. The cooled mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to afford a residue, which was purified by prep-HPLC to afford N-[6-(2-chloro-5-fluorophenyl)-3-(2-hydroxyethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (2.2 mg, 0.004 mmol, 7 %) as a white solid. LCMS: ESI m/z 584.3 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.30 (s, 1H), 9.13 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.79 – 7.67 (m, 2H), 7.34 (s, 1H), 7.28 (dd, J = 8.8, 5.2 Hz, 1H), 7.10 – 7.07 (m, 1H), 6.66 (brs, 1H), 6.00 (brs, 1H), 4.00 – 3.86 (m, 2H), 3.67 (t, J = 5.6 Hz, 2H).

Example 17: N-(6-(2-chloro-5-fluorophenyl)-3-((1-fluorocyclopropyl)methyl)-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide, **Example 43:** (R)-N-(6-(2-chloro-5-fluorophenyl)-3-((1-fluorocyclopropyl)methyl)-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide and **Example 44:** (S)-N-(6-(2-chloro-5-fluorophenyl)-3-((1-fluorocyclopropyl)methyl)-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00264] **Step A:** To a solution of (fluorocyclopropyl)methanol (600 mg, 6.67 mmol) and TEA (1.35 g, 13.32 mmol) in dry DCM (6 mL) was added 4-methylbenzenesulfonic acid (2.29 g, 13.32 mmol) at 0°C in portions. The mixture was stirred at room temperature overnight. The reaction was quenched with cold water and extracted with DCM. The combined organic layer was washed with brine, dried and concentrated. The residue was purified by FCC, eluting with

EA/PE(10%) to give (fluorocyclopropyl)methyl 4-methylbenzenesulfonate (980 mg, 4.01 mmol, 60%) as a yellow oil and used directly as a crude.

[00265] **Step B:** The mixture of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (934 mg, 2.0 mmol), (fluorocyclopropyl)methyl 4-methylbenzenesulfonate (980 mg, 4.0 mmol) and Cs_2CO_3 (1.96 g, 6.0 mmol) in DMA (23 mL) was stirred at 70 °C for 80 min. The cooled mixture was poured into cold water and extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by FCC eluting with EA/PE (20%) to give 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(fluorocyclopropyl)methyl]-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (520 mg, 0.77 mmol, 38%) as a white solid. LCMS: m/z 538 $[\text{M}+\text{H}]^+$.

[00266] **Step C:** To the mixture of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(fluorocyclopropyl)methyl]-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (400 mg, 0.74 mmol) in NMP (4 mL) was added CuCN (200 mg, 2.2 mmol). The mixture was stirred under N_2 at 120°C for 3 hours. The cooled mixture was diluted with EA and water. The mixture was filtered and the filtrate was extracted with EA. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by FCC eluting with EA/PE(20%) to give 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(fluorocyclopropyl)methyl]-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (70 mg, 0.145 mmol, 19%) as a white solid. LCMS: ESI m/z 483 $[\text{M} + \text{H}]^+$, 485 $[\text{M} + \text{H}]^+$.

[00267] **Step D:** The mixture of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-[(fluorocyclopropyl)methyl]-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (97 mg, 0.20 mmol), 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (45.7 mg, 0.22 mmol), $\text{Pd}_2(\text{dba})_3$ (18.4 mg, 0.02 mmol), Xantphos (23.2 mg, 0.04 mmol) and Cs_2CO_3 (130.7 mg, 0.40 mmol) in dioxane (5 mL) was stirred at 100 °C for 3 hours. The cooled mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was used directly in the next step.

[00268] **Step E:** To a mixture of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-[(fluorocyclopropyl)methyl]-2-oxo-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (134.8 mg, 0.22 mmol) in acetonitrile (10 mL) was added potassium hydroxide (124 mg, 2.21 mmol) in water (3 mL). The mixture was stirred at room temperature for

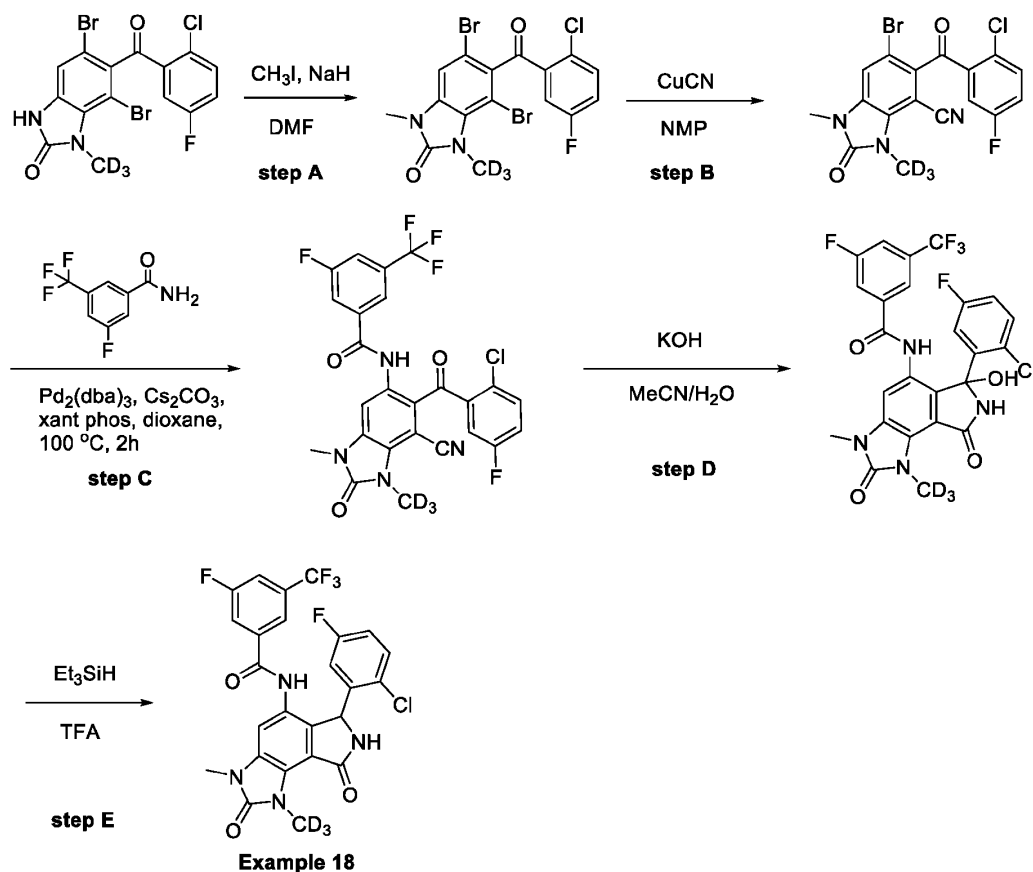
30 min. The mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by FCC, eluting with EA/PE (0-50%) to give N-[6-(2-chloro-5-fluorophenyl)-3-[(fluorocyclopropyl)methyl]-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (70 mg, 0.11 mmol, 50%) as a yellow solid. LCMS: m/z 626 [M-H]⁻.

[00269] **Step F:** The mixture of N-[6-(2-chloro-5-fluorophenyl)-3-[(fluorocyclopropyl)methyl]-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (60 mg, 0.096 mmol) in TFA (5 mL) and Et₃SiH (0.5 mL) was stirred at 50 °C for 30 min. The mixture was concentrated and purified by prep-HPLC to give N-[6-(2-chloro-5-fluorophenyl)-3-[(fluorocyclopropyl)methyl]-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (35 mg, 0.06 mmol, 60%) as a white solid. LCMS: m/z 612 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.31 (s, 1H), 9.15 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.37 (s, 1H), 7.28 (dd, J = 8.8, 5.2 Hz, 1H), 7.10 – 7.08 (m, 1H), 6.66 (brs, 1H), 6.01 (brs, 1H), 4.46 – 4.21 (m, 2H), 1.11 – 1.02 (m, 2H), 1.03 – 0.95 (m, 2H).

[00270] N-[6-(2-chloro-5-fluorophenyl)-3-[(fluorocyclopropyl)methyl]-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (30 mg) was subjected to chiral prep-SFC separation (method 11) to give: (R)-N-(6-(2-chloro-5-fluorophenyl)-3-((1-fluorocyclopropyl)methyl)-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (10.9 mg, 17.8mmol, 33%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 10.32 (s, 1H), 9.15 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.70 (s, 1H), 7.37 (s, 1H), 7.28 (dd, J = 8.8, 5.2 Hz, 1H), 7.10 – 7.08 (m, 1H), 6.63 (brs, 1H), 6.00 (brs, 1H), 4.46 – 4.21 (m, 2H), 1.11 – 1.03 (m, 2H), 1.03 – 0.95 (m, 2H). LCMS: ESI m/z 612 [M + H]⁺. And (S)-N-(6-(2-chloro-5-fluorophenyl)-3-((1-fluorocyclopropyl)methyl)-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (10.7 mg, 17.5 mmol, 32%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 10.32 (s, 1H), 9.15 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.70 (s, 1H), 7.37 (s, 1H), 7.28 (dd, J = 8.8, 5.2 Hz,

1H), 7.10 – 7.08 (m, 1H), 6.58 (brs, 1H), 5.97 (brs, 1H), 4.46 – 4.21 (m, 2H), 1.11 – 1.03 (m, 2H), 1.03 – 0.96 (m, 2H). LCMS: ESI m/z 612 [M + H]⁺.

Example 18: N-(6-(2-chloro-5-fluorophenyl)-3-methyl-1-(methyl-d3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00271] **Step A:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (700 mg, 1.50 mmol) in N,N-dimethylmethanamide (20 mL) was added NaH (120 mg, 3.00 mmol, 60% in mineral oil) at 0°C . The mixture was stirred at 0°C for 5 min. Iodomethane (0.244 mL, 3.007 mmol) was added. The mixture was stirred at room temperature for 4 hours. The mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by FCC, eluting with EA/PE (0-20%) to give 4,6-

dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-methyl-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (220 mg, 0.46 mmol, 31%) as a yellow solid. LCMS: m/z 480 [M+H]⁺.

[00272] **Step B:** To the mixture of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-methyl-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (220 mg, 0.46 mmol) in NMP (10 mL) was added CuCN (82 mg, 0.92 mmol). The mixture was stirred under N₂ at 130 °C for 2 hours. The cooled mixture was diluted with EA and water. The mixture was filtered and the filtrate was extracted with EA. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by FCC eluting with EA/PE (0-20%) to give 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-methyl-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (38 mg, 0.09 mmol, 19%) as a white solid. LCMS: m/z 425 [M+H]⁺.

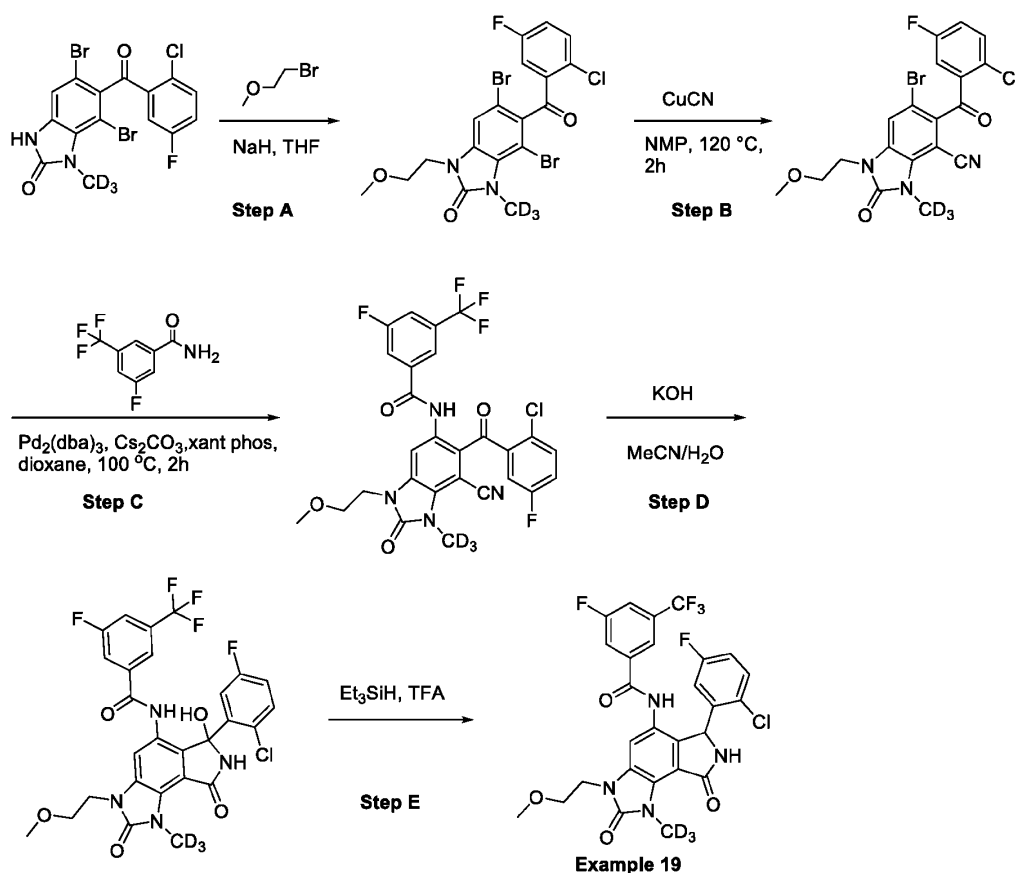
[00273] **Step C:** The mixture of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-methyl-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (38 mg, 0.09 mmol), 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (28 mg, 0.13 mmol), Pd₂(dba)₃ (8 mg, 0.01 mmol), Xantphos (10 mg, 0.018 mmol) and Cs₂CO₃ (58 mg, 0.18 mmol) in dioxane (5 mL) was stirred at 100 °C under N₂ for 3 hours. The cooled mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was used directly in the next step. LCMS: m/z 552 [M+H]⁺.

[00274] **Step D:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-methyl-2-oxo-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (65 mg, 0.12 mmol) in acetonitrile (5 mL) was added potassium hydroxide (33 mg, 0.59 mmol) in H₂O (2 mL). The mixture was stirred at room temperature for 20 min. The mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by FCC, eluting with EA/PE (0-70) to give N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-3-methyl-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (30 mg, 0.053 mmol, 45%) as a white solid.

[00275] **Step E:** To a mixture of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-3-methyl-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (33 mg, 0.058 mmol) in 2,2,2-trifluoroacetaldehyde (2 mL) was added Et₃SiH (0.2 mL). The mixture was stirred at 50 °C for 40 min. The mixture was purified by

prep-HPLC to give N-[6-(2-chloro-5-fluorophenyl)-3-methyl-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (8 mg, 0.014 mmol, 25%) as a white solid. LCMS: m/z 554 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.29 (s, 1H), 9.14 (s, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.77 – 7.67 (m, 2H), 7.33 – 7.21 (m, 2H), 7.10 – 7.07 (m, 1H), 6.53 (brs, 1H), 6.02 (brs, 1H), 3.39 (s, 3H).

Example 19: N-(6-(2-chloro-5-fluorophenyl)-3-(2-methoxyethyl)-1-(methyl- d_3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00276] **Step A:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (1.0 g, 2.15 mmol) in DMF (10 mL) was added NaH (172 mg, 4.30 mmol, 60% purity in mineral oil) at 0 °C. The mixture was stirred for 10 min, then 2-bromo-1-methoxyethane (0.4 mL, 4.30 mmol) was added. The mixture was stirred at 50 °C for 18h. 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: 0-30%) afford 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2-methoxyethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (520 mg, 0.99 mmol, 46%) as an yellow solid. LCMS: ESI m/z 524 [M + H]⁺.

[00277] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2-methoxyethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (520 mg, 0.99 mmol) in NMP (10 mL) was added CuCN (94 mg, 1.04 mmol). The reaction mixture was stirred at 120 °C under N₂ for 3h. The cooled reaction mixture was diluted with EA, filtered through a pad of celite. The filtrate was extracted with EtOAc (10 mL*3). The organic phase was washed with brine for 3 times, dried over Na₂SO₄ and concentrated. Then the crude was purified by prep-HPLC to afford 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2-methoxyethyl)-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (120 mg, 0.26 mmol, 26%) as a yellow solid. LCMS: ESI m/z 469/471 [M + H]⁺.

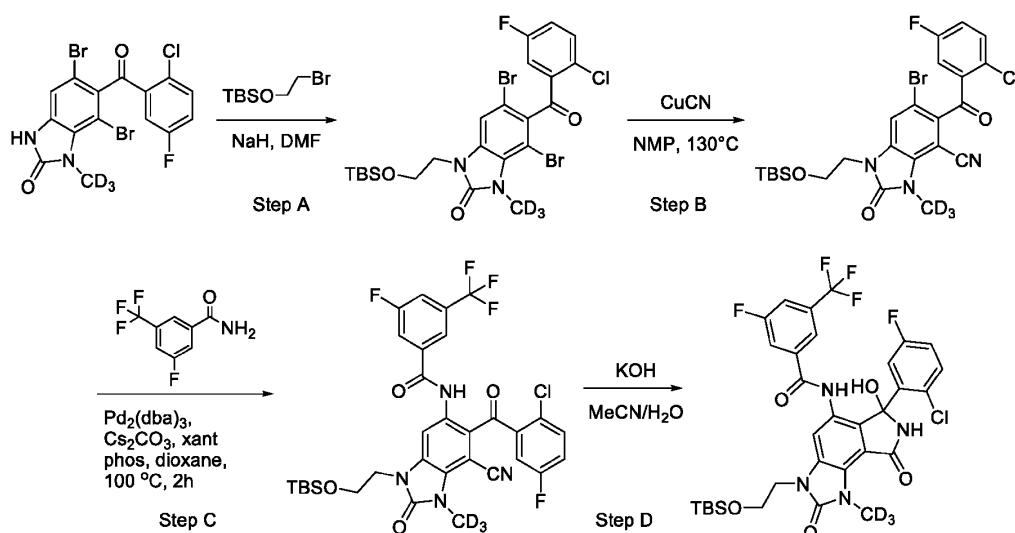
[00278] **Step C:** To a solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2-methoxyethyl)-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (120 mg, 0.26 mmol) in 1,4-dioxane (5 mL) was added 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (79 mg, 0.38 mmol), Pd₂(dba)₃ (37 mg, 0.04 mmol), Xantphos (47 mg, 0.08 mmol), Cs₂CO₃ (166.48 mg, 0.511 mmol). The reaction was stirred at 100 °C under N₂ for 2h. The reaction mixture was concentrated. The residue was purified by silica gel chromatograph (PE/EA =3/1) to afford N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-(2-methoxyethyl)-2-oxo-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (120 mg, 0.20 mmol, 79%) as a yellow solid. LCMS: ESI m/z 596 [M + H]⁺.

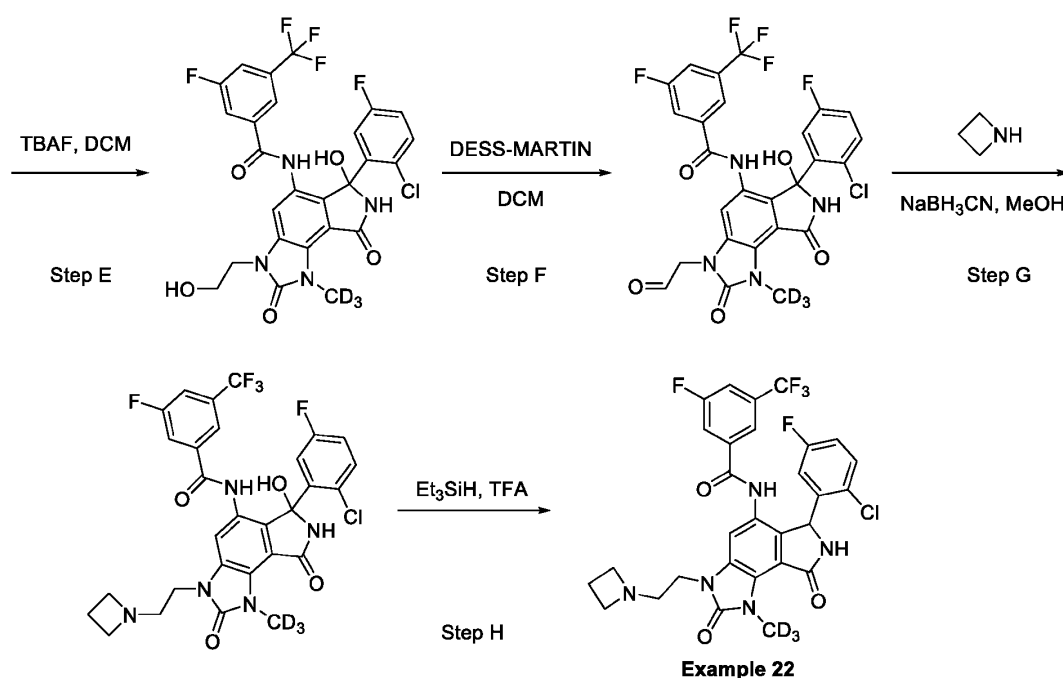
[00279] **Step D:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-(2-methoxyethyl)-2-oxo-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (120 mg, 0.20 mmol) in MeCN (5 mL) and H₂O (1 mL) were added KOH (23 mg, 0.40 mmol). The reaction was stirred at room temperature for 2 hr. LCMS showed the reaction was completed. 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-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-3-(2-

methoxyethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (110 mg, 0.18 mmol, 89%) as a yellow solid. LCMS: ESI m/z 614 $[M + H]^+$.

[00280] **Step E:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-3-(2-methoxyethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (110 mg, 0.18 mmol) in TFA (2 mL) were added triethylsilane (1 mL). The reaction was stirred at 70 °C for 20 min. LCMS showed the reaction was completed. The cooled reaction mixture was concentrated and purified by prep-HPLC to afford N-[6-(2-chloro-5-fluorophenyl)-3-(2-methoxyethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (49.5 mg, 0.08 mmol, 42%) as a white solid. LCMS: ESI m/z 598 $[M + H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.29 (s, 1H), 9.13 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 9.6 Hz, 1H), 7.71 (s, 1H), 7.35 (s, 1H), 7.28 (dd, J = 8.8, 5.2 Hz, 1H), 7.10 – 7.07 (m, 1H), 6.65 (brs, 1H), 5.98 (brs, 1H), 4.13 – 3.97 (m, 2H), 3.62 (t, J = 5.2 Hz, 2H), 3.23 (s, 3H).

Example 22: N-{3-[2-(azetidin-1-yl)ethyl]-6-(2-chloro-5-fluorophenyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide





[00281] **Step A:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (2 g, 4.30 mmol) in DMF (30 mL) was added NaH (0.34 g, 8.59 mmol, 60% in mineral oil) at 0 °C. The mixture was stirred at 0 °C for 10 min. Then 1-bromo-4,4,5,5-tetramethyl-3-oxa-4-silahexane (1.54 g, 6.44 mmol) was added and the mixture was stirred at 70 °C for 5 hours. The mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to afford a residue, which was purified by silica gel chromatography (10 g column) using 0 - 30% EtOAc/hexane to afford 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(4,4,5,5-tetramethyl-3-oxa-4-silahex-1-yl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (630 mg, 1.01 mmol, 23%) as a yellow solid. LCMS: ESI m/z 624.0 [M + H]⁺.

[00282] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(4,4,5,5-tetramethyl-3-oxa-4-silahex-1-yl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (610 mg, 0.978 mmol) in NMP (10 mL) was added CuCN (105 mg, 1.17 mmol). The mixture was stirred at 130 °C under N₂ for 3 hours. The cooled mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to afford a residue, which was purified by silica gel chromatography

(10 g column) using 0 - 30% EtOAc/hexane to afford 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-1-(4,4,5,5-tetramethyl-3-oxa-4-silahex-1-yl)-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (220 mg, 0.386 mmol, 39%) as a brown solid. LCMS: ESI m/z 571.1 $[M + H]^+$.

[00283] **Step C:** To a solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-1-(4,4,5,5-tetramethyl-3-oxa-4-silahex-1-yl)-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (200 mg, 0.351 mmol) and 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (87.2 mg, 0.421 mmol) in dioxane (10 mL) was added XANT PHOS (40.6 mg, 0.070 mmol) and $Pd_2(dba)_3$ (32.1 mg, 0.035 mmol). The mixture was stirred at 100 °C under N_2 for 2 hours. The cooled mixture was diluted with H_2O , extracted with EA. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated to afford N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-2-oxo-3-(4,4,5,5-tetramethyl-3-oxa-4-silahex-1-yl)-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (230 mg, 0.330 mmol, 94%) as a brown solid. It was used for the next step without purification. LCMS: ESI m/z 696.2 $[M + H]^+$.

[00284] **Step D:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-2-oxo-3-(4,4,5,5-tetramethyl-3-oxa-4-silahex-1-yl)-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (230 mg, 0.330 mmol) in CH_3CN (10 mL) and H_2O (2 mL) was added KOH (37.1 mg, 0.661 mmol). The mixture was stirred at 20 °C for 1 hour. TLC (PE/EA=1: 1) showed starting material was consumed and new spot was observed. The mixture was concentrated and the residue was purified using silica gel column chromatography eluted with EA in PE (gradient: 50%) to afford N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-3-(4,4,5,5-tetramethyl-3-oxa-4-silahex-1-yl)-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (127 mg, 0.178 mmol, 54%) as a brown solid. LCMS: ESI m/z 712 $[M - H]^-$.

[00285] **Step E:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-3-(4,4,5,5-tetramethyl-3-oxa-4-silahex-1-yl)-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (117 mg, 0.164 mmol) in THF (5 mL) was added TBAF (0.328 mL, 0.328 mmol). The mixture was stirred at 20 °C for 1 hour. The mixture was diluted with HCl (1M), extracted with EA. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated to afford a residue, which was purified by silica gel

chromatography (4 g column) using 0 - 70% EtOAc/hexane to afford N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-3-(2-hydroxyethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (90 mg, 0.150 mmol, 91%) as a yellow solid. LCMS: ESI m/z 600.3 [M + H]⁺.

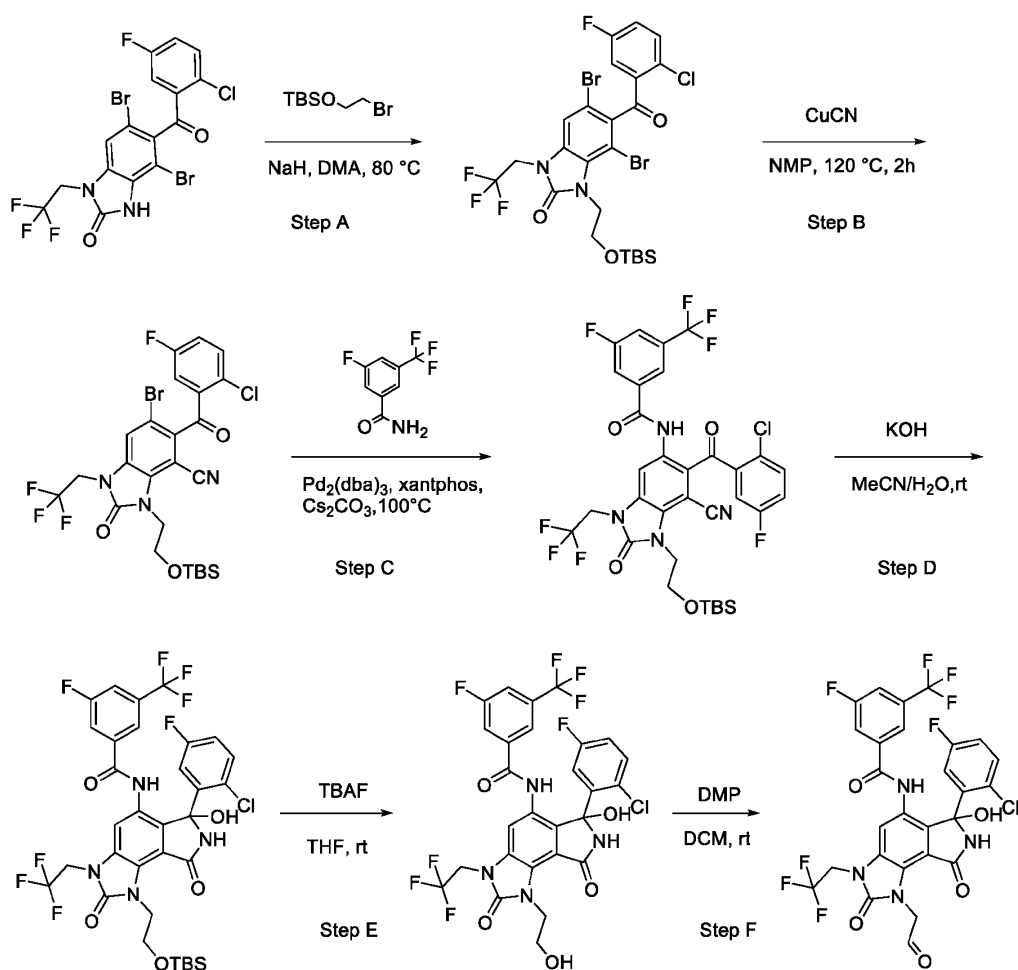
[00286] **Step F:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-3-(2-hydroxyethyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (30 mg, 0.050 mmol) in DCM (5 mL) was added DESS-MARTIN (63.6 mg, 0.150 mmol). The mixture was stirred at 20 °C for 1 hour. The mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to afford N-[6-(2-chloro-5-fluorophenyl)-3-(formylmethyl)-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (30 mg, 0.030 mmol, 60 %) as a white solid. LCMS: ESI m/z 596.2 [M + H]⁺.

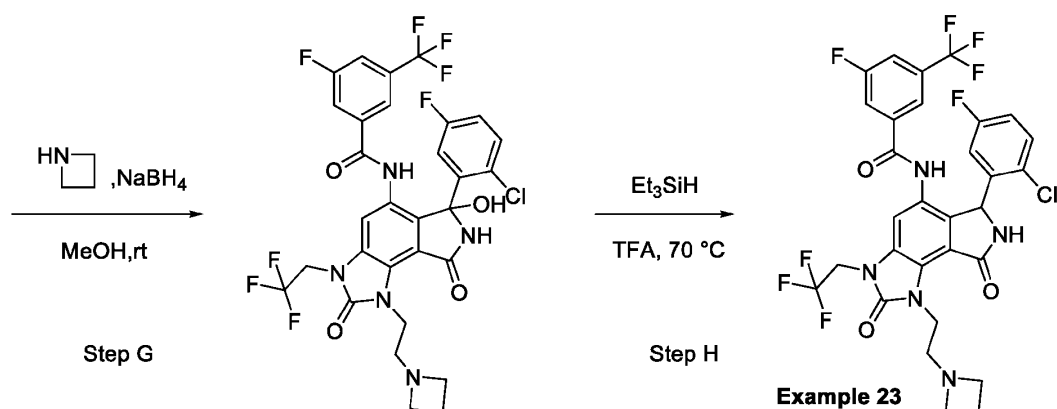
[00287] **Step G:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-3-(formylmethyl)-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (30 mg, 0.050 mmol) in MeOH (5 mL) was added azetidine (4.30 mg, 0.075 mmol). The mixture was stirred at 20 °C for 1 hour. Then sodium cyanoborohydride (9.46 mg, 0.151 mmol) was added and the mixture was stirred at 20 °C for 1 hour. The mixture was diluted with H₂O, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to afford a residue, which was purified by pre-TLC (DCM/MeOH=10:1) to give N-{3-[2-(azetidin-1-yl)ethyl]-6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (10 mg, 0.016 mmol, 31%) as a white solid. LCMS: ESI m/z 639.3 [M + H]⁺.

[00288] **Step H:** To a solution of N-{3-[2-(azetidin-1-yl)ethyl]-6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (10 mg, 0.016 mmol) in TFA (2 mL) was added Et₃SiH (0.5 mL, 0.008 mmol). The mixture was stirred at 70 °C for 30 min. The mixture was concentrated under vacuum to remove TFA and Et₃SiH. The residue was purified by pre-TLC (DCM/MeOH=10:1) to give a solid, which was purified by pre-HPLC to give N-{3-[2-(azetidin-1-yl)ethyl]-6-(2-chloro-5-fluorophenyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-

5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (2.3 mg, 0.004 mmol, 23%) as a white solid. LCMS: ESI m/z 623.4 $[M + H]^+$. 1H NMR (400 MHz, MeOD) δ 7.72 – 7.66 (m, 2H), 7.63 (d, J = 9.2 Hz, 1H), 7.37 (s, 1H), 7.24 (dd, J = 8.8, 5.2 Hz, 1H), 7.00 – 6.97 (m, 1H), 6.54 (brs, 1H), 6.23 (brs, 1H), 4.05 (td, J = 5.6, 2.4 Hz, 2H), 3.60 (t, J = 7.2 Hz, 4H), 3.09 (t, J = 5.6 Hz, 2H), 2.22 (p, J = 7.6 Hz, 2H).

Example 23: N-(1-(2-(azetidin-1-yl)ethyl)-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





[00289] **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 (3 g, 5.66 mmol) in DMA (35 mL) were added 1-bromo-4,4,5,5-tetramethyl-3-oxa-4-silahexane (4.06 g, 17 mmol) and NaH (0.27 g, 11.3 mmol, 60% in mineral oil). The reaction was stirred at 70 °C under N₂ for 6 hr. LCMS showed the reaction was completed. The reaction mixture was quenched H₂O at 0 °C, 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 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-(4,4,5,5-tetramethyl-3-oxa-4-silahex-1-yl)-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (3.5 g, 5.08 mmol, 90%) as a yellow solid. LCMS: 687/689 [M-H]⁻.

[00290] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-(4,4,5,5-tetramethyl-3-oxa-4-silahex-1-yl)-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (3.5 g, 5.08 mmol) in NMP (40 mL) were added CuCN (0.55 g, 6.1 mmol). The reaction was stirred at 130 °C under N₂ for 2 hr. LCMS showed the reaction was 30% DP. 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 DCM (gradient: 20-30%) to afford 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-3-(4,4,5,5-tetramethyl-3-oxa-4-silahex-1-yl)-1-(2,2,2-trifluoroethyl)benzo[d]imidazole-4-carbonitrile (500 mg, 0.787 mmol, 16%) as a yellow oil. LCMS: 634/635 [M-H]⁻.

[00291] **Step C:** To a solution of 6-bromo-3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-(2-chloro-5-fluorobenzoyl)-2-oxo-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (500 mg, 0.787 mmol) in dioxane (5 mL) were added 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (244 mg, 1.18 mmol), Pd₂(dba)₃ (72.1 mg, 0.079 mmol), xantphos (91.1 mg, 0.157 mmol) and Cs₂CO₃ (256 mg, 0.787 mmol). The reaction was stirred at 100 °C under N₂ for 2 hr. LCMS showed the reaction was completed. 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 petroleum ether (gradient: 15-20%) to afford the title compound N-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-(2-chloro-5-fluorobenzoyl)-7-cyano-2-oxo-3-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (240 mg, 0.315 mmol, 40%) as a yellow oil. LCMS: ESI m/z 761/763 [M+H]⁺.

[00292] **Step D:** To a solution of N-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-(2-chloro-5-fluorobenzoyl)-7-cyano-2-oxo-3-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (240 mg, 0.315 mmol) in H₂O (1 mL) and ACN (5 mL) were added KOH (35.4 mg, 0.631 mmol). The reaction was stirred at room temperature under N₂ for 1 hr. LCMS showed the reaction was completed. 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-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-(2-chloro-5-fluorophenyl)-6-hydroxy-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 (200 mg, 0.257 mmol, 81%) as a yellow solid. LCMS: ESI m/z 779/781 [M + H]⁺.

[00293] **Step E:** To a solution of N-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-(2-chloro-5-fluorophenyl)-6-hydroxy-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 (200 mg, 0.257 mmol) in THF (5 mL) were added TBAF (134 mg, 0.513 mmol). The reaction was stirred at rt under N₂ for 4 hr. LCMS showed the reaction was completed. 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-(6-(2-chloro-5-fluorophenyl)-6-

hydroxy-1-(2-hydroxyethyl)-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 (120 mg, 0.180 mmol, 70%) as a yellow solid. LCMS: ESI m/z 665/667 [M + H]⁺.

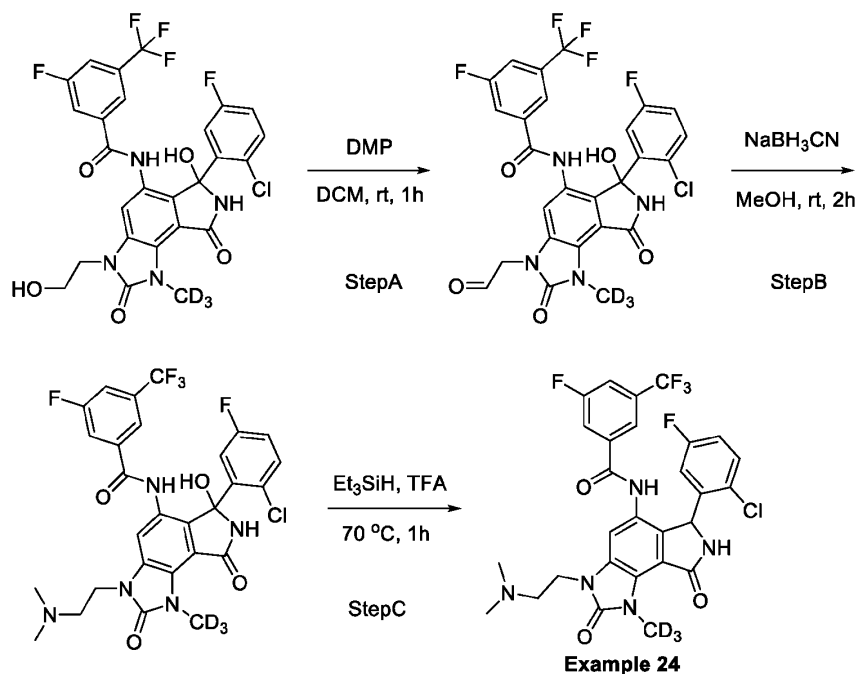
[00294] **Step F:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-(2-hydroxyethyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (40 mg, 0.06 mmol) in DCM (3 mL) were added DMP (76.6 mg, 0.180 mmol). The mixture was stirred at rt for 1 hr. LCMS showed the reaction was completed. 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: 40-50%) to afford N-(6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-1-(2-oxoethyl)-3-(2,2,2-trifluoroethyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (30 mg, 0.045 mmol, 75%) as a yellow solid. LCMS: ESI m/z 663/665 [M + H]⁺.

[00295] **Step G:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-1-(2-oxoethyl)-3-(2,2,2-trifluoroethyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (30 mg, 0.045 mmol) in MeOH (5 mL) were added azetidine (7.75 mg, 0.136 mmol), sodium cyanoborohydride (8.53 mg, 0.136 mmol). The reaction was stirred at rt under N₂ for 2 hr. LCMS showed the reaction was completed. 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: 50-60%) to afford N-(1-(2-(azetidin-1-yl)ethyl)-6-(2-chloro-5-fluorophenyl)-6-hydroxy-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 (13 mg, 0.018 mmol, 41%) as a yellow oil. LCMS: ESI m/z 704/706 [M + H]⁺.

[00296] **Step H:** To a solution of N-{1-[2-(azetidin-1-yl)ethyl]-6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (20 mg, 0.028 mmol) in TFA (3 mL) were added Et₃SiH (0.010 mL, 0.028 mmol). The reaction was stirred at 70 °C for 1 hr. LCMS showed the reaction was completed. 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 by prep-HPLC to afford N-{1-[2-(azetidin-1-yl)ethyl]-6-

(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(2,2,2-trifluoroethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (4.4 mg, 0.006 mmol, 23%) as a white solid. LCMS: ESI m/z 688/690 $[M + H]^+$. ^1H NMR(400 MHz, DMSO- d_6) δ 10.40 (s, 1H), 9.73 (s, 1H), 9.32 (s, 1H), 7.95 (d, $J = 7.6$ Hz, 1H), 7.80 – 7.67 (m, 2H), 7.55 (s, 1H), 7.28 (s, 1H), 7.10 (s, 1H), 6.64 (brs, 1H), 6.07 (brs, 1H), 5.04 – 4.77 (m, 2H), 4.68 – 4.61 (m, 2H), 4.18 – 4.12 (m, 4H), 3.72 – 3.66 (m, 2H), 2.44 – 2.19 (m, 2H).

Example 24: N-(6-(2-chloro-5-fluorophenyl)-3-(2-(dimethylamino)ethyl)-1-(methyl- d_3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



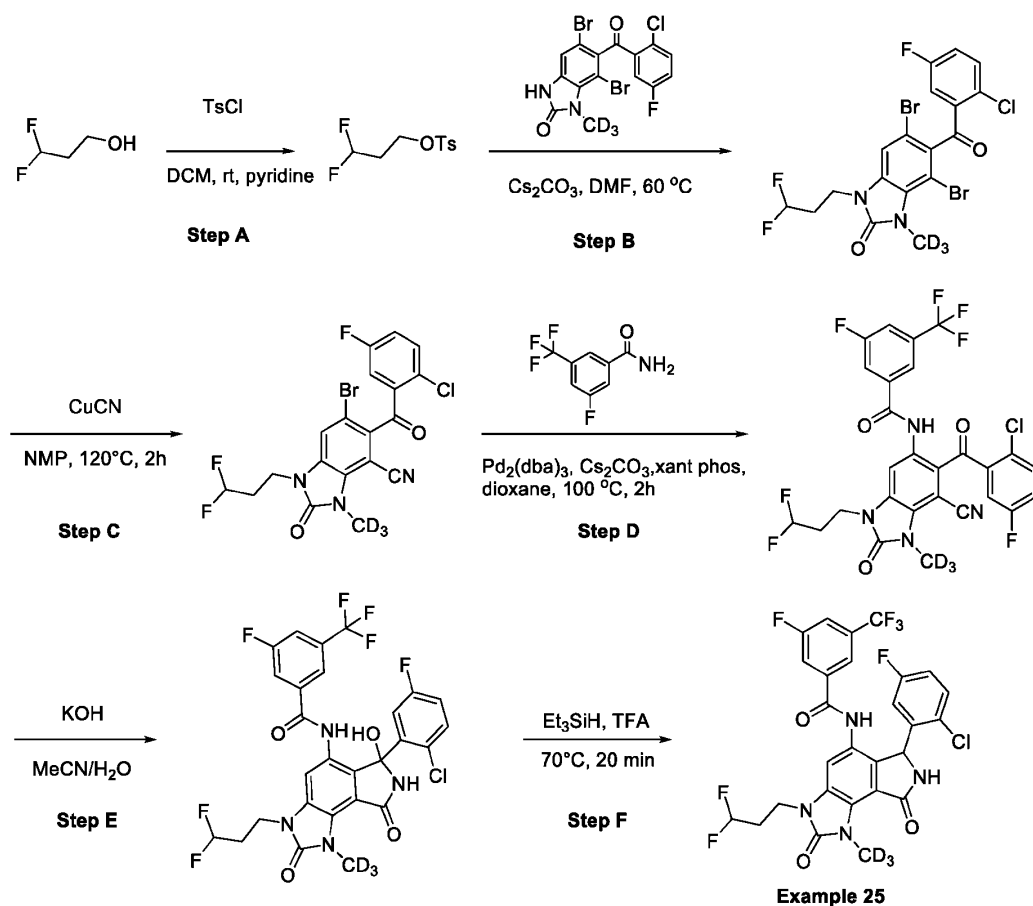
[00297] **Step A:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-6-hydroxy-3-(2-hydroxyethyl)-1-(methyl- d_3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (40 mg, 0.067 mmol) in DCM (3 mL) were added Dess-Martin periodinane (28.3 mg, 0.067 mmol). The mixture was stirred at room temperature for 1 hr. LCMS showed the reaction was completed. The reaction was diluted with DCM and H_2O . The organic layer was separated and concentrated in vacuo afford N-(6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-(methyl- d_3)-2,8-dioxo-3-(2-oxoethyl)-1,2,3,6,7,8-

hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (20 mg, 0.034 mmol, 50%) as a yellow solid. LCMS: 598/600 [M-H]⁻.

[00298] **Step B:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-(methyl-d3)-2,8-dioxo-3-(2-oxoethyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (20 mg, 0.034 mmol) in MeOH (3 mL) were added dimethylamine hydrochloride (5.46 mg, 0.067 mmol). The reaction mixture was stirred at room temperature for 1 hr, then sodium cyanoborohydride (6.32 mg, 0.101 mmol) was added. The reaction mixture was stirred at room temperature for 1 hr. LCMS showed the reaction was 50% DP. 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 by prep-TLC methanol in dichloroform gradient: (0-10%) to afford N-(6-(2-chloro-5-fluorophenyl)-3-(2-(dimethylamino)ethyl)-6-hydroxy-1-(methyl-d3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (10.5 mg, 0.017 mmol, 50%) as a yellow solid. LCMS: 627/629 [M-H]⁻.

[00299] **Step C:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-3-(2-(dimethylamino)ethyl)-6-hydroxy-1-(methyl-d3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (20 mg, 0.032 mmol) in TFA (3 mL) were added Et₃SiH (0.4 mL, 2.5 mmol). The reaction was stirred at 70 °C for 1 hr. LCMS showed the reaction was completed. 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 by prep-HPLC to afford N-(6-(2-chloro-5-fluorophenyl)-3-(2-(dimethylamino)ethyl)-1-(methyl-d3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (1.8 mg, 0.003 mmol, 9%) as a white solid. LCMS: ESI m/z 611/613 [M+H]⁺. ¹H NMR(400 MHz, MeOD-d₄) δ 7.74 – 7.70 (m, 2H), 7.65 (d, J = 8.8 Hz, 1H), 7.48 (s, 1H), 7.24 (dd, J = 8.8, 5.0 Hz, 1H), 7.04 – 6.92 (m, 1H), 6.57 (brs, 1H), 6.27 (brs, 1H), 4.42 – 4.38 (m, 2H), 3.62 – 3.58 (m, 2H), 3.05 (s, 6H).

Example 25: N-(6-(2-chloro-5-fluorophenyl)-3-(3,3-difluoropropyl)-1-(methyl-d3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00300] **Step A:** To a solution of 3,3-difluoropropan-1-ol (0.45 mL, 5.20 mmol) in DCM (5 mL) was added pyridine (0.84 mL, 10.41 mmol) and 4-methylbenzenesulfonyl chloride (1.19 g, 6.25 mmol) at 0 °C. The mixture was stirred at rt for 2h. The reaction mixture was quenched by H₂O, extracted with DCM (three times). The separated organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified using silica gel column chromatography eluted with EA in PE (gradient: 0-20%) afford 3,3-difluoropropyl 4-methylbenzenesulfonate (700 mg, 2.80 mmol, 54%) as a yellow oil. LCMS: ESI m/z 251 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 6.10 (tt, *J* = 56.0, 4.4 Hz, 1H), 4.14 (t, *J* = 6.2 Hz, 2H), 2.43 (s, 3H), 2.30 – 2.11 (m, 2H).

[00301] **Step B:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-(trideuteriomethyl)-2,3-dihydro-1H-benzodimidazol-2-one (900 mg, 1.93 mmol) in DMF (10 mL) was added Cs₂CO₃ (1.89 g, 5.80 mmol) at 0 °C. The mixture was stirred at 0 °C for 10min,

then 3,3-difluoropropyl 4-methylbenzenesulfonate (700 mg, 2.80 mmol) was added. The mixture was stirred at 60 °C for 18h. The reaction mixture was quenched by water, and the mixture was extracted with EtOAc (30 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: 0-30%) afford 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(3,3-difluoropropyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (800 mg, 1.47 mmol, 76%) as a yellow solid. LCMS: ESI m/z 544 [M + H]⁺.

[00302] **Step C:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(3,3-difluoropropyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (800 mg, 1.47 mmol) in NMP (10 mL) was added CuCN (138 mg, 1.55 mmol). The reaction mixture was stirred at 120 °C for 2h. The cooled reaction mixture was diluted with EA, filtered through a pad of celite. The filtrate was extracted with EtOAc (10 mL*3). The organic phase was washed with brine for 3 times, dried over Na₂SO₄ and concentrated. Then the crude was purified by prep-HPLC to afford 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(3,3-difluoropropyl)-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (80 mg, 0.16 mmol, 11%) as a yellow solid. LCMS: ESI m/z 489/491 [M + H]⁺.

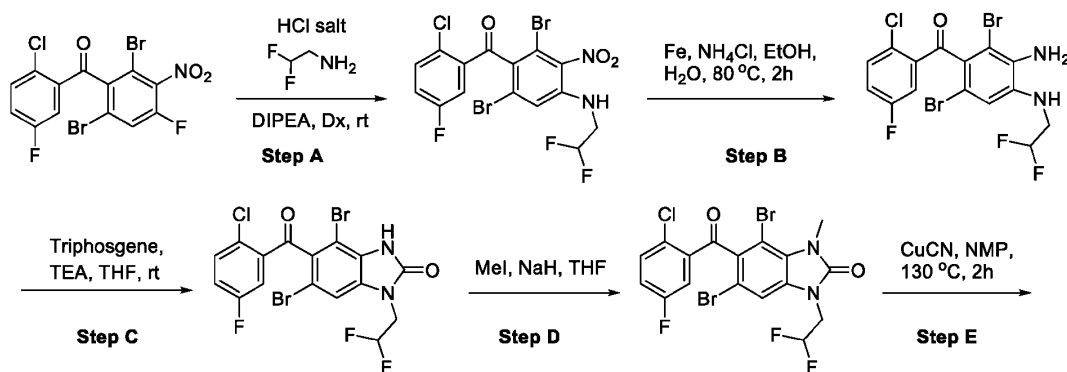
[00303] **Step D:** To a solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(3,3-difluoropropyl)-2-oxo-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (80 mg, 0.16 mmol) in 1,4-dioxane (5 mL) was added 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (51 mg, 0.25 mmol), Pd₂(dba)₃ (15 mg, 0.016 mmol), Xantphos (19 mg, 0.033 mmol), Cs₂CO₃ (106 mg, 0.33 mmol). The reaction was stirred at 100 °C under N₂ for 2h. The reaction mixture was concentrated, and chromatographed (PE/EA = 2/1) to afford N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-(3,3-difluoropropyl)-2-oxo-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (80 mg, 0.13 mmol, 80%) as a yellow solid. LCMS: ESI m/z 616 [M + H]⁺.

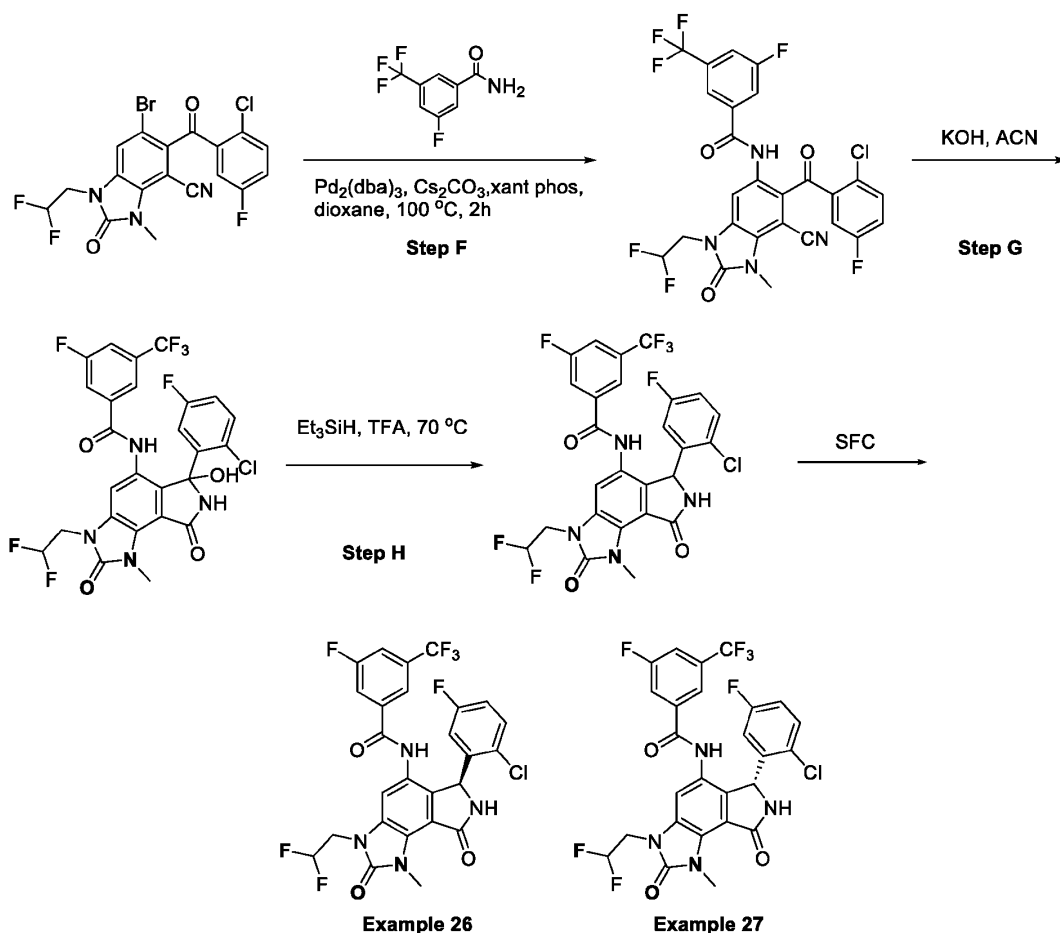
[00304] **Step E:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-(3,3-difluoropropyl)-2-oxo-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (80 mg, 0.13 mmol) in MeCN (5 mL) and H₂O (1 mL) were added potassium hydroxide (15 mg, 0.26 mmol). The reaction was stirred at room temperature for 2 hr. LCMS showed the reaction was completed. The reaction mixture was

diluted with water, extracted with EA. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The organic layer was separated and concentrated to afford N-[6-(2-chloro-5-fluorophenyl)-3-(3,3-difluoropropyl)-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (80 mg, 0.13 mmol, 97%) as a yellow solid. LCMS: ESI m/z 616 $[\text{M} - \text{OH}]^+$.

[00305] **Step F:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-3-(3,3-difluoropropyl)-6-hydroxy-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (70 mg, 0.11 mmol) in TFA (2 mL) was added triethylsilane (1 mL, 0.110 mmol). The reaction was stirred at 70 °C for 20 min. LCMS showed the reaction was completed. The reaction mixture was concentrated and purified by prep-HPLC to afford N-[6-(2-chloro-5-fluorophenyl)-3-(3,3-difluoropropyl)-2,8-dioxo-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (34.5 mg, 0.056 mmol, 51%) as a white solid. LCMS: ESI m/z 618 $[\text{M} + \text{H}]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 9.15 (s, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.77 – 7.66 (m, 2H), 7.38 (s, 1H), 7.28 (dd, $J = 8.8, 5.2$ Hz, 1H), 7.10 – 7.06 (m, 1H), 6.65 (s, 1H), 6.39 – 5.87 (m, 2H), 4.14 – 3.96 (m, 2H), 2.36 – 2.17 (m, 2H).

Example 26: N-[(6S)-6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide and
Example 27: N-[(6R)-6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide





[00306] **Step A.** To a stirred solution of (2-chloro-5-fluorophenyl)(2,6-dibromo-4-fluoro-3-nitrophenyl)methanone (4.5 g, 9.8 mmol) in dioxane (50 mL) was added 2,2-difluoroethan-1-amine (0.7 g, 8.7 mmol) and DIPEA (2.5 g, 19.7 mmol) at rt. After stirred at rt for 72h under N₂ atmosphere, the mixture was poured into ice-water (100 mL) and extracted with EtOAc (60 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- 15 %, EtOAc in PE) to give (2-chloro-5-fluorophenyl){2,6-dibromo-4-[(2,2-difluoroethyl)amino]-3-nitrophenyl}methanone (4.5 g, 8.7 mmol, 88 %) as a yellow solid. No LCMS.

[00307] **Step B.** To a stirred solution of (2-chloro-5-fluorophenyl){2,6-dibromo-4-[(2,2-difluoroethyl)amino]-3-nitrophenyl}methanone (4.5 g, 8.7 mmol) in EtOH (50 mL)/ H₂O (10 mL) was added Fe (4.8 g, 87.1 mmol) and NH₄Cl (0.9 g, 17.4 mmol) at rt. After stirred at 80 °C

for 2h under N₂ atmosphere, the mixture was poured into ice-water (200 mL) and extracted with EtOAc (100 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-25 %, EtOAc in PE) to give {3-amino-2,6-dibromo-4-[(2,2-difluoroethyl)amino]phenyl}(2-chloro-5-fluorophenyl)methanone (3.9 g, 8.1 mmol, 92 %) as a yellow solid. LCMS: ESI m/z 487 [M + H]⁺.

[00308] **Step C.** To a stirred solution of {3-amino-2,6-dibromo-4-[(2,2-difluoroethyl)amino]phenyl}(2-chloro-5-fluorophenyl)methanone (3.8 g, 7.811 mmol) in THF (40 mL) was added triphosgene (3.48 g, 11.716 mmol) slowly at 0 °C. After stirred at 0 °C for 2h under N₂ atmosphere, the mixture was poured into ice-water (80 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, 0-35 %, EtOAc in PE) to give 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (3.5 g, 6.8 mmol, 87 %) as a white solid. No LCMS.

[00309] **Step D.** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (3.5 g, 6.8 mmol) in THF (50 mL) were added NaH (900 mg, 22.6 mmol, 60% in mineral oil) at 0 °C. After stirred at 0 °C for 1h, CH₃I (2.4 g, 16.9 mmol) was added. The reaction mixture was stirred at rt overnight. The reaction mixture was diluted with H₂O, extracted with EA, washed with brine and concentrated. The residue was purified by chromatography (silica gel, 0-25 %, EtOAc in PE) to give 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-3-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (3.2 g, 6.1 mmol, 89 %) as a white solid and used directly for the next step.

[00310] **Step E.** To a stirred solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-3-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (3.2 g, 6.1 mmol) in NMP (35 mL) was added CuCN (710 mg, 7.9 mmol) at rt. After stirred at 130 °C for 2h, the cooled mixture was poured into brine (80 mL) and extracted with EtOAc (50 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, 0-50 %, EtOAc in PE) to give 6-amino-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-3-

methyl-2-oxobenzo[d]imidazole-4-carbonitrile (1 g, 2.4 mmol, 40 %) as a yellow solid. LCMS: m/z 474 [M+H]⁺.

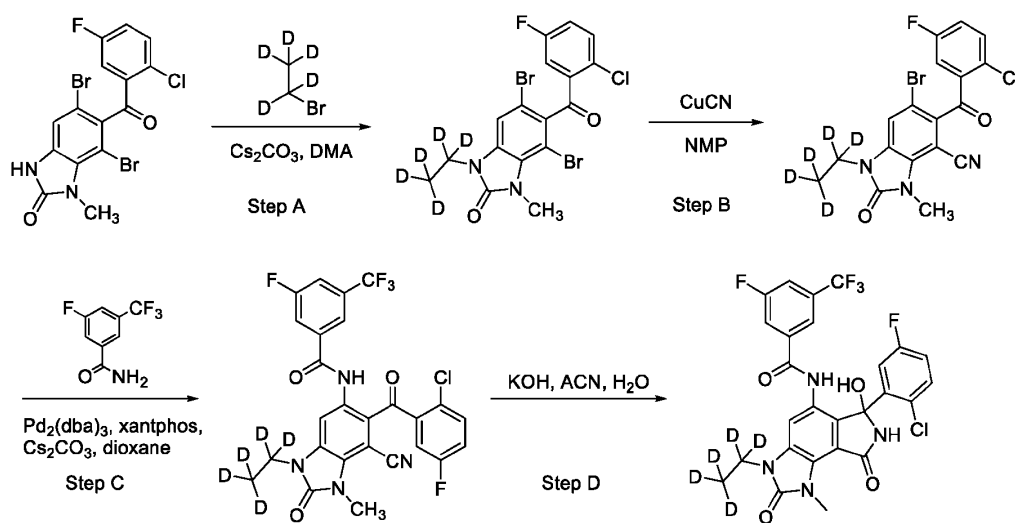
[00311] **Step F.** To a stirred solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-3-methyl-2-oxobenzo[d]imidazole-4-carbonitrile (1 g, 2.1 mmol) in dioxane (30 mL) was added 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (660 mg, 3.2 mmol), Pd₂(dba)₃ (190 mg, 0.21 mmol), XANT PHOS (240 mg, 0.42 mmol) and Cs₂CO₃ (1.7 g, 5.2 mmol) at rt. After stirred at 100 °C under N₂ for 3h, the mixture was poured into ice-water (80 mL) and extracted with EtOAc (30 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- 60%, EtOAc in PE) to give N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-(2,2-difluoroethyl)-1-methyl-2-oxobenzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (1 g, 1.6 mmol, 79 %) as a brown solid. LCMS: m/z 600 [M+H]⁺.

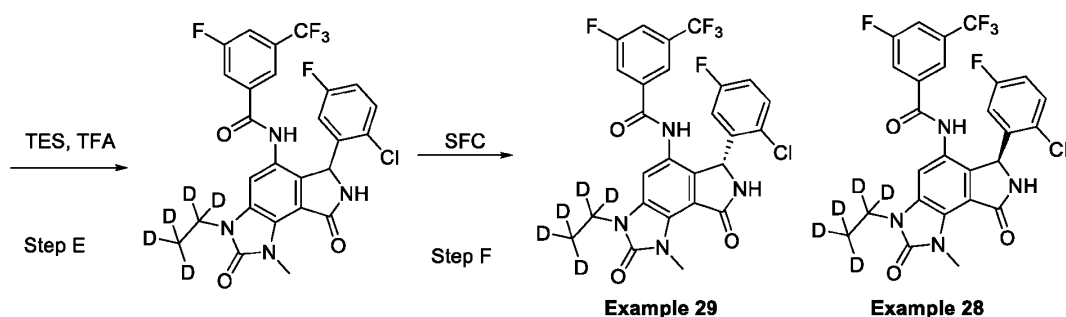
[00312] **Step G.** To a stirred solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-(2,2-difluoroethyl)-1-methyl-2-oxobenzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (1 g, 1.6 mmol) in ACN (12 mL)/ H₂O (4 mL) was added KOH (0.5 g, 8.3 mmol) slowly at rt. After stirred at rt for 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 to give crude N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-6-hydroxy-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (1 g, 1.6 mmol, 97 %) as a white solid. LCMS: m/z 617 [M+H]⁺.

[00313] **Step H.** To a stirred solution of N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-6-hydroxy-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (1 g, 1.6 mmol) in TFA (16 mL) was added Et₃SiH (4 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) to give N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (900 mg, 1.5 mmol, 92 %) as a white solid. LCMS: m/z 601 [M+H]⁺.

[00314] Which was purified by chiral prep-SFC method 6 to give N-[(6S)-6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (26 mg, 0.04 mmol, 26 %) ^1H NMR (400 MHz, DMSO- d_6) δ 10.34 (s, 1H), 9.18 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 9.2 Hz, 1H), 7.70 (s, 1H), 7.40 (s, 1H), 7.31 – 7.23 (m, 1H), 7.14 – 7.05 (m, 1H), 6.36 (t, J = 54.4 Hz, 1H), 6.01 (brs, 1H), 4.47 – 4.32 (m, 2H), 3.91 (s, 3H). And N-[(6R)-6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (26 mg, 0.04 mmol, 26 %) both as a white solid. LCMS: m/z 601 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 10.33 (s, 1H), 9.18 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 9.2 Hz, 1H), 7.70 (s, 1H), 7.40 (s, 1H), 7.32 – 7.24 (m, 1H), 7.13 – 7.04 (m, 1H), 6.36 (t, J = 54.8 Hz, 1H), 6.00 (brs, 1H), 4.47 – 4.31 (m, 2H), 3.91 (s, 3H).

Example 28: (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(ethyl- d_5)-1-methyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide and Example 29: (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(ethyl- d_5)-1-methyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide





[00315] **Step A:** To a solution of 5,7-dibromo-6-[(2-chloro-4-fluorophenyl)carbonyl]-1-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (1 g, 2.16 mmol) and 1-bromo-1,1,2,2,2-pentadeuterioethane (0.49 g, 4.32 mmol) in N,N-dimethylacetamide (15 mL) was added Cs_2CO_3 (2.11 g, 6.49 mmol). The mixture was stirred at 60 °C for 5h. The cooled reaction mixture was diluted with H_2O , extracted with EA. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column (eluted with (EA: PE=30%)) to give 4,6-dibromo-5-[(2-chloro-4-fluorophenyl)carbonyl]-3-methyl-1-(pentadeuterioethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (600 mg, 1.21 mmol, 56%) as a brown solid. LCMS: ESI m/z 496 $[\text{M} + \text{H}]^+$.

[00316] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-(pentadeuterioethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (600 mg, 1.21 mmol) in NMP (6 mL) was added CuCN (108 mg, 1.21 mmol), and the mixture was stirred at 130 °C under N_2 for 2h. The mixture was stirred at 60 °C for 5h. The cooled reaction mixture was diluted with H_2O , extracted with EA. The organic phase 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]-3-methyl-2-oxo-1-(pentadeuterioethyl)benzo[d]imidazole-4-carbonitrile (200 mg, 0.453 mmol, 37%) as a brown solid. LCMS: ESI m/z 441 $[\text{M} + \text{H}]^+$.

[00317] **Step C:** A solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-2-oxo-1-(pentadeuterioethyl)benzo[d]imidazole-4-carbonitrile (210 mg, 0.475 mmol), 5-fluoro-3-(trifluoromethyl)benzene-1-carboxamide (108 mg, 0.523 mmol), $\text{Pd}_2(\text{dba})_3$ (43.5 mg, 48 μmol), Xantphos (55.0 mg, 95 μmol), Cs_2CO_3 (465 mg, 1.43 mmol) in dioxane (11 mL) was stirred at 100 °C for 2h. The reaction mixture was concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with MeOH in DCM (gradient: 0%~10%) to

afford N-{6-[(1-chloro-4-fluorobenzen-2-yl)carbonyl]-7-cyano-1-methyl-2-oxo-3-(pentadeuterioethyl)benzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (198 mg, 0.349 mmol, 73%) as a brown solid. LCMS: ESI m/z 568 [M + H]⁺.

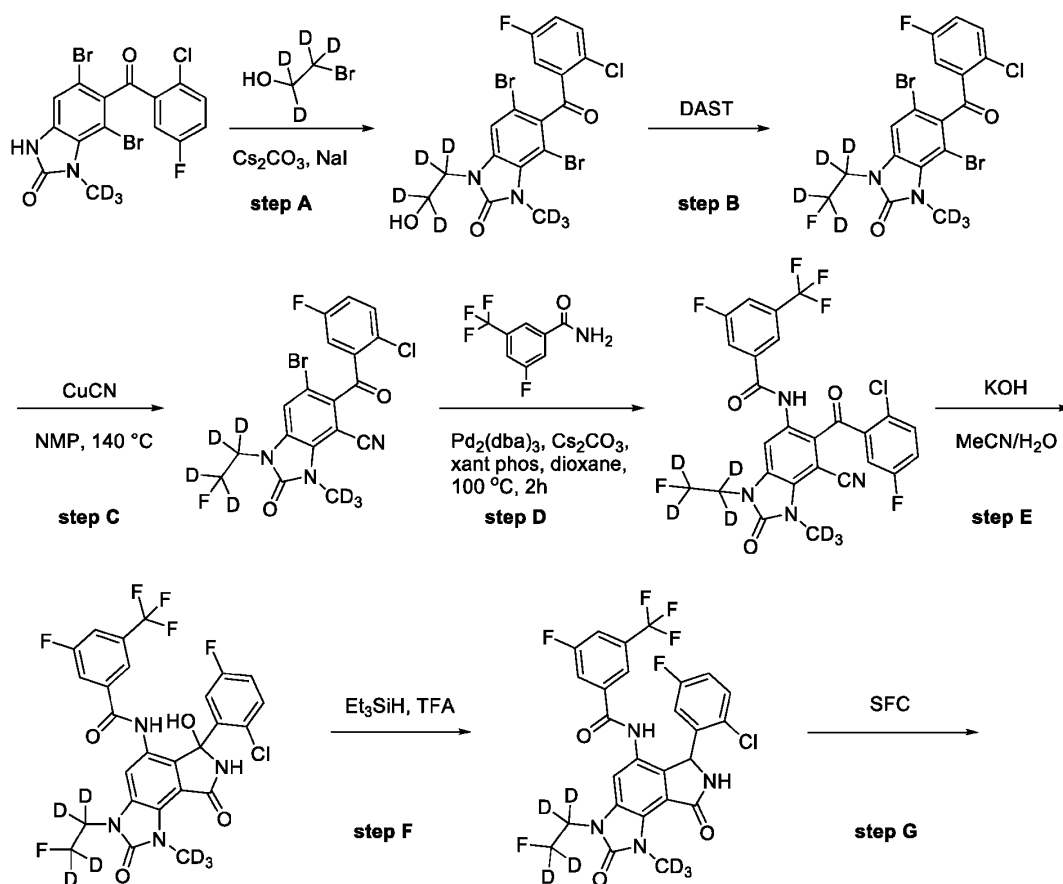
[00318] **Step D:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-1-methyl-2-oxo-3-(prop-2-yl)benzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (200 mg, 0.347 mmol) in ACN (2 mL) and H₂O (0.2 mL) was added KOH (98.8 mg, 1.76 mmol) at room temperature. The reaction mixture was stirred at rt for 30 min, then diluted with EA and H₂O. The combined organic phase was washed with brine (10 mL x 2), dried over Na₂SO₄ and concentrated to give N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-2,8-dioxo-3-(prop-2-yl)-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (150 mg, 0.252 mmol, 73%) as a brown solid. LCMS: ESI m/z 586 [M + H]⁺.

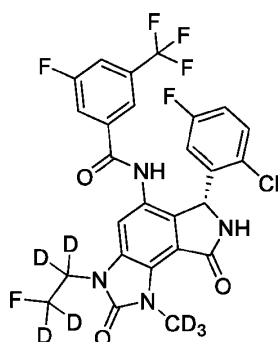
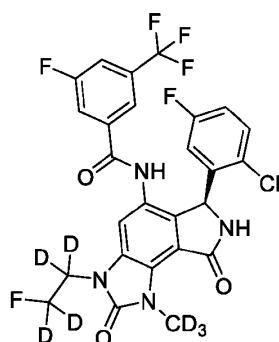
[00319] **Step E:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-2,8-dioxo-3-(prop-2-yl)-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (150 mg, 0.252 mmol) in TFA (2 mL) was added Et₃SiH (0.2 mL). The reaction mixture was stirred at 60 °C for 30 min. Then the reaction mixture was concentrated to give a residue. The residue was purified by pre-HPLC to give N-[6-(1-chloro-4-fluorobenzen-2-yl)-1-methyl-2,8-dioxo-3-(pentadeuterioethyl)-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (140 mg, 0.246 mmol, 96%) as a white solid. LCMS: ESI m/z 570 [M + H]⁺.

[00320] **Step F:** The N-(6-(2-chloro-5-fluorophenyl)-3-(ethyl-d₅)-1-methyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (120 mg) was separated by chiral prep-SFC method 7 to give N-[(6S)-6-(1-chloro-4-fluorobenzen-2-yl)-1-methyl-2,8-dioxo-3-(pentadeuterioethyl)-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (41 mg, 0.072 mmol, 34%, ee=99). LCMS: ESI m/z 570 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.29 (s, 1H), 9.13 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 9.2 Hz, 1H), 7.71 (s, 1H), 7.36 (s, 1H), 7.29 – 7.26 (m, 1H), 7.10 – 7.06 (m, 1H), 6.65 (brs, 1H), 6.01 (brs, 1H), 3.89 (s, 3H). And N-[(6R)-6-(1-chloro-4-fluorobenzen-2-yl)-1-methyl-2,8-dioxo-3-(pentadeuterioethyl)-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (38.5 mg, 0.068 mmol, 32%, ee=99). LCMS: ESI m/z 570 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.29 (s, 1H), 9.14 (s, 1H), 7.93 (d, J = 8.4 Hz,

1H), 7.75 (d, $J = 9.2$ Hz, 1H), 7.71 (s, 1H), 7.36 (s, 1H), 7.29 – 7.26 (m, 1H), 7.10 – 7.05 (m, 1H), 6.65 (brs, 1H), 6.01 (brs, 1H), 3.89 (s, 3H).

Example 30: (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(2-fluoroethyl-1,1,2,2-d₄)-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide and Example 31: (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(2-fluoroethyl-1,1,2,2-d₄)-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



**Example 31****Example 30**

[00321] **Step A:** The mixture of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (460 mg, 0.988 mmol), 2-bromo-1,1,2,2-tetradeuterioethan-1-ol (255 mg, 1.98 mmol), Cs₂CO₃ (870 mg, 2.67 mmol) and NaI (444 mg, 2.97 mmol) in DMF (10 mL) was stirred at 100 °C for 2h. The cooled mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by FCC, eluting with EA/PE (0-50%) to give 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(1,1,2,2-tetradeuterio-2-hydroxyethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (180 mg, 0.28 mmol, 28%). LCMS: ESI m/z 514 [M+H]⁺.

[00322] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(1,1,2,2-tetradeuterio-2-hydroxyethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (840 mg, 1.64 mmol) in DCM (40 mL) was added diethyl(trifluoro-λ4-sulfanyl)amine (527 mg, 3.27 mmol) at 0 °C. The mixture was stirred at room temperature overnight. The mixture was quenched with cold water and extracted with DCM. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by FCC, eluting with EA/PE (0-20%) to give 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(1,1,2,2-tetradeuterio-2-fluoroethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (640 mg, 1.24 mmol, 76%) as a yellow solid. LCMS: ESI m/z 516[M+H]⁺.

[00323] **Step C:** The mixture of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(1,1,2,2-tetradeuterio-2-fluoroethyl)-3-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (560 mg, 1.09 mmol) and cyanocopper(I) (292 mg, 3.26 mmol) in NMP (28 mL) was stirred at 140 °C for 2h. The cooled mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by

FCC, eluting with EA/PE(0-20%, 10% DCM) to give 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-1-(1,1,2,2-tetradeuterio-2-fluoroethyl)-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (170 mg, 0.37 mmol, 34%) as a pink solid. LCMS: ESI m/z 461[M+H]⁺.

[00324] **Step D:** The mixture of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-1-(1,1,2,2-tetradeuterio-2-fluoroethyl)-3-(trideuteriomethyl)benzo[d]imidazole-4-carbonitrile (170 mg, 0.37 mmol), 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (114 mg, 0.55 mmol), tris[(1E,4E)-1,5-diphenylpenta-1,4-dien-3-one] bis[palladium(0)] (34 mg, 0.037 mmol), Xantphos (43 mg, 0.074 mmol) and Cs₂CO₃ (240 mg, 0.74 mmol) in dioxane (20 mL) was stirred at 100 °C under N₂ for 2 hours. The cooled mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was used directly in the next step.

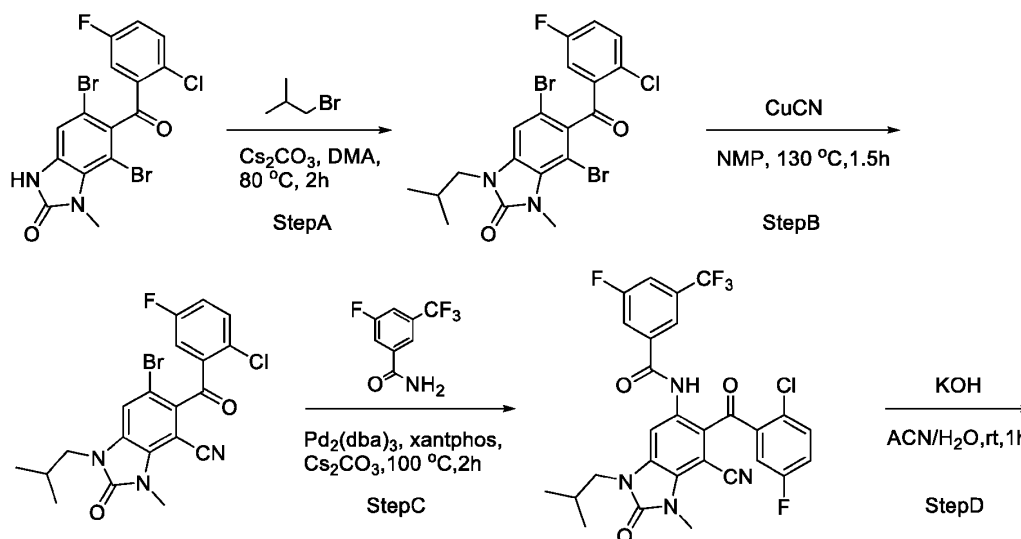
[00325] **Step E:** To the mixture of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-2-oxo-3-(1,1,2,2-tetradeuterio-2-fluoroethyl)-1-(trideuteriomethyl)benzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (200 mg, 0.34 mmol) in acetonitrile (20 mL) was added potassium hydroxide (191 mg, 3.40 mmol) in water (10 mL). The mixture was stirred at room temperature for 1 hour. The mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by FCC, eluting with EA/PE(0-80%) and then MeOH/DCM (10%) to give N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-3-(1,1,2,2-tetradeuterio-2-fluoroethyl)-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (200 mg, 0.33 mmol, 97%) as a yellow solid. LCMS: ESI m/z 606[M+H]⁺.

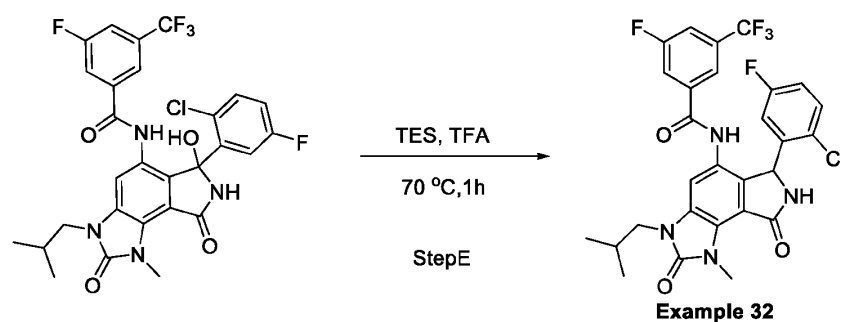
[00326] **Step F:** The mixture of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-2,8-dioxo-3-(1,1,2,2-tetradeuterio-2-fluoroethyl)-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (220 mg, 0.36 mmol) in 2,2,2-trifluoroacetaldehyde (5 mL) and triethylsilane (0.5 mL) was stirred at 50 °C for 30 min. The mixture was concentrated. The residue was purified by prep-HPLC to give N-[6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(1,1,2,2-tetradeuterio-2-fluoroethyl)-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (100 mg, 0.17 mmol, 47%) as a white solid. LCMS: ESI m/z 590.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.32 (s, 1H), 9.15 (s, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.70

(s, 1H), 7.38 (s, 1H), 7.28 (dd, $J = 8.8, 5.2$ Hz, 1H), 7.13 – 7.04 (m, 1H), 6.63 (s, 1H), 5.99 (s, 1H).

[00327] **Step G:** The N-[6-(2-chloro-5-fluorophenyl)-2,8-dioxo-3-(1,1,2,2-tetradeuterio-2-fluoroethyl)-1-(trideuteriomethyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (120 mg, 0.20 mmol) was purified by chiral prep-SFC method 8 to give (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(2-fluoroethyl-1,1,2,2-d₄)-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (47.8 mg, 0.08 mmol, 40%) as a white solid. LCMS: ESI m/z 590.3 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-d₆) δ 10.32 (s, 1H), 9.15 (s, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.74 (d, $J = 8.8$ Hz, 1H), 7.70 (s, 1H), 7.38 (s, 1H), 7.28 (dd, $J = 8.8, 5.2$ Hz, 1H), 7.13 – 7.04 (m, 1H), 6.64 (brs, 1H), 6.01 (brs, 1H). And (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(2-fluoroethyl-1,1,2,2-d₄)-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (51.6 mg, 0.087 mmol, 43%) as a white solid. LCMS: ESI m/z 590.3 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-d₆) δ 10.32 (s, 1H), 9.15 (s, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.74 (d, $J = 8.8$ Hz, 1H), 7.70 (s, 1H), 7.38 (s, 1H), 7.28 (dd, $J = 8.8, 5.2$ Hz, 1H), 7.13 – 7.04 (m, 1H), 6.64 (brs, 1H), 6.01 (brs, 1H).

Example 32: N-[6-(2-chloro-5-fluorophenyl)-1-methyl-3-(2-methylpropyl)-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide





[00328] **Step A:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (500 mg, 1.08 mmol) in DMA (8 mL) were added 1-bromo-2-methylpropane (0.177 mL, 1.62 mmol), Cs_2CO_3 (1056 mg, 3.24 mmol). The reaction was stirred at 80 °C under N_2 for 2 hr. LCMS showed the reaction was completed. The cooled reaction mixture was diluted water, extracted with EA. The organic phase 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: 15-25%) to afford the title compound 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-(2-methylpropyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (380 mg, 0.733 mmol, 68%) as a yellow solid. LCMS: ESI m/z 517/519 $[\text{M}-\text{H}]^-$.

[00329] **Step B:** To a solution of 4,6-dibromo-5-(2-chloro-5-fluorobenzoyl)-1-isobutyl-3-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (300 mg, 0.578 mmol) in NMP (5 mL) were added CuCN (67.4 mg, 0.752 mmol). The reaction was stirred at 120 °C under N_2 for 2 hr. LCMS showed the reaction was 30% DP. The cooled reaction mixture was diluted water, extracted with EA. The organic phase 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 dichloroform (gradient: 15-20%) to afford 6-bromo-5-(2-chloro-5-fluorobenzoyl)-1-isobutyl-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (80 mg, 30%) as a yellow solid. LCMS: 464/466 $[\text{M}-\text{H}]^-$.

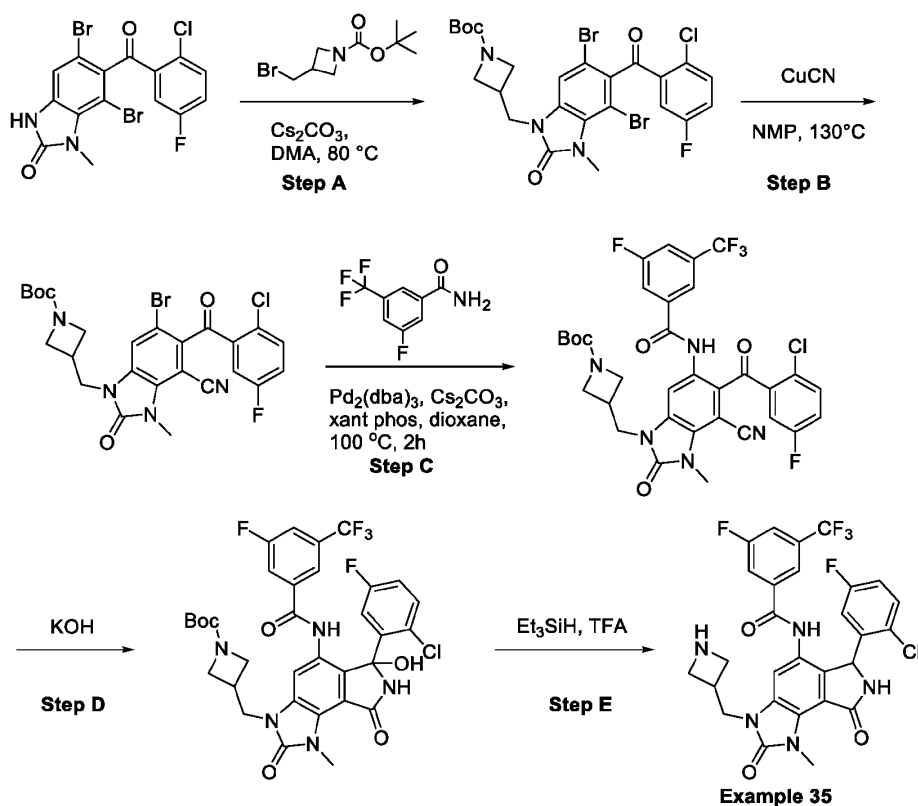
[00330] **Step C:** To a solution of 6-bromo-5-(2-chloro-5-fluorobenzoyl)-1-isobutyl-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (60 mg, 0.129 mmol) in dioxane (5 mL) were added 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (40.1 mg, 0.194 mmol), $\text{Pd}_2(\text{dba})_3$ (11.8 mg, 0.013 mmol), and XANT PHOS (14.9 mg, 0.026 mmol), Cs_2CO_3 (126 mg, 0.387 mmol). The reaction was stirred at 100 °C under N_2 for 2 hr. LCMS showed the

reaction was completed. 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 petroleum ether (gradient: 10-20%) to afford the title compound N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-1-methyl-3-(2-methylpropyl)-2-oxobenzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (45 mg, 0.076 mmol, 59%) as a yellow oil. LCMS: ESI m/z 591/593 [M+H]⁺.

[00331] **Step D:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-1-methyl-3-(2-methylpropyl)-2-oxobenzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (40 mg, 0.068 mmol) in H₂O (1 mL) and ACN (3 mL) were added KOH (7.60 mg, 0.135 mmol). The reaction was stirred at room temperature under N₂ for 1 hr. LCMS showed the reaction was completed. 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-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-3-(2-methylpropyl)-2,8-dioxo-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (35 mg, 0.057 mmol, 85%) as a yellow solid. LCMS: ESI m/z 609/611 [M + H]⁺.

[00332] **Step E:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-3-(2-methylpropyl)-2,8-dioxo-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (50 mg, 0.082 mmol) in TFA (3 mL) were added Et₃SiH (191 mg, 1.64 mmol). The reaction was stirred at 70 °C for 1 hr. LCMS showed the reaction was completed. 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 by prep-HPLC to afford N-[6-(2-chloro-5-fluorophenyl)-1-methyl-3-(2-methylpropyl)-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (18.4 mg, 0.031 mmol, 38%) as a white solid. LCMS: ESI m/z 593/595 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.26 (s, 1H), 9.14 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.80 – 7.65 (m, 2H), 7.35 (s, 1H), 7.27 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.08 (dd, *J* = 8.4, 3.2 Hz, 1H), 6.66 (brs, 1H), 6.00 (brs, 1H), 3.90 (s, 3H), 3.76 – 3.57 (m, 2H), 2.20 – 2.00 (m, 1H), 0.90 (dd, *J* = 6.8, 3.2 Hz, 6H).

Example 35: N-(3-(azetidin-3-ylmethyl)-6-(2-chloro-5-fluorophenyl)-1-methyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00333] **Step A:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (500 mg, 1.081 mmol) in DMA (4 mL) was added Cs_2CO_3 (1.05 g, 3.243 mmol) and 2-methylpropan-2-yl 3-(bromomethyl)azetidine-1-carboxylate (432 mg, 1.730 mmol). The reaction mixture was stirred at 80°C for 2h. The cooled reaction mixture was diluted with H_2O , extracted with EA. The organic phase was washed with brine, dried by Na_2SO_4 , filtered and concentrated. The residue was purified using silica gel column chromatography eluting with EA in PE [Gradient: 40%] to afford the title compound 2-methylpropan-2-yl 3-({4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-2-oxobenzo[d]imidazol-1-yl)methyl)azetidine-1-carboxylate (350 mg, 0.554 mmol, 51%) as a white solid. LCMS: ESI m/z 632/576 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.84 (s, 1H), 7.73 (dd, $J = 8.0, 4.0$ Hz, 1H), 7.65 – 7.55 (m, 1H), 7.46 (dd, $J = 8.0, 4.0$ Hz, 1H), 4.13 (d, $J = 8.0$ Hz, 2H), 3.87 (t, $J = 8.0$ Hz, 2H), 3.68 (s, 2H), 3.62 (s, 3H), 3.00 – 2.94 (m, 1H), 1.37 (s, 9H).

[00334] **Step B:** To a solution of 2-methylpropan-2-yl 3-({4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-2-oxobenzo[d]imidazol-1-yl}methyl)azetidine-1-carboxylate (350 mg, 0.554 mmol) in NMP (5 mL) was added CuCN (99 mg, 1.108 mmol). The reaction mixture was stirred at 130 °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 the title compound 2-methylpropan-2-yl 3-({6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-4-cyano-3-methyl-2-oxobenzo[d]imidazol-1-yl}methyl)azetidine-1-carboxylate (150 mg, 0.260 mmol, 47%) as a white solid. LCMS: ESI m/z 578/523 [M+H]⁺

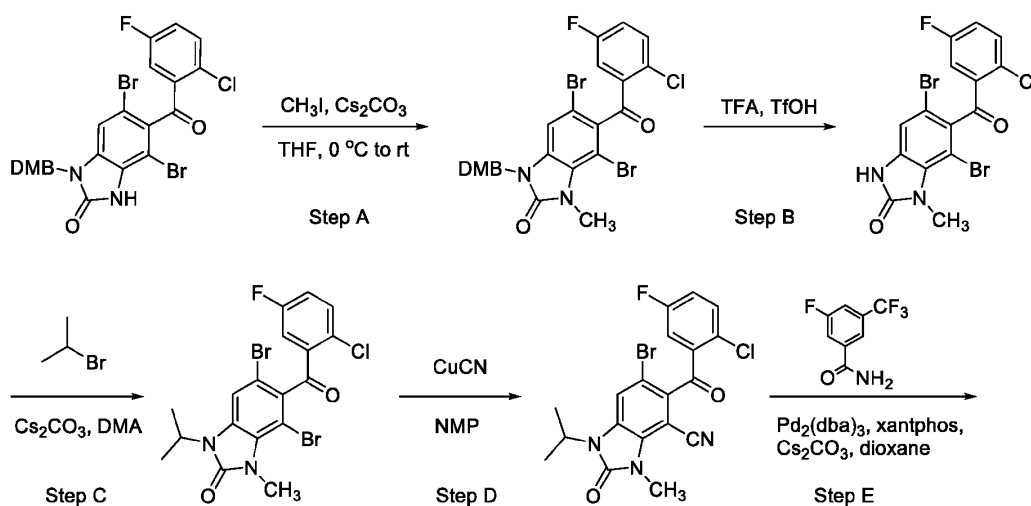
[00335] **Step C:** To a solution of 2-methylpropan-2-yl 3-({6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-4-cyano-3-methyl-2-oxobenzo[d]imidazol-1-yl}methyl)azetidine-1-carboxylate (150 mg, 0.260 mmol) in dioxane (4 mL) was added 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (80 mg, 0.389 mmol), Cs₂CO₃ (169 mg, 0.519 mmol), Xant-phos (15 mg, 0.026 mmol) and Pd₂(dba)₃ (47 mg, 0.519 mmol). The reaction mixture was stirred at 100 °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: 65%] to afford the title compound 2-methylpropan-2-yl 3-({5-[(2-chloro-5-fluorophenyl)carbonyl]-4-cyano-6-({[5-fluoro-3-(trifluoromethyl)phenyl]carbonyl}amino)-3-methyl-2-oxobenzo[d]imidazol-1-yl}methyl)azetidine-1-carboxylate (120 mg, 0.170 mmol, 65%) as a white solid. LCMS: ESI m/z 704/648 [M+H]⁺.

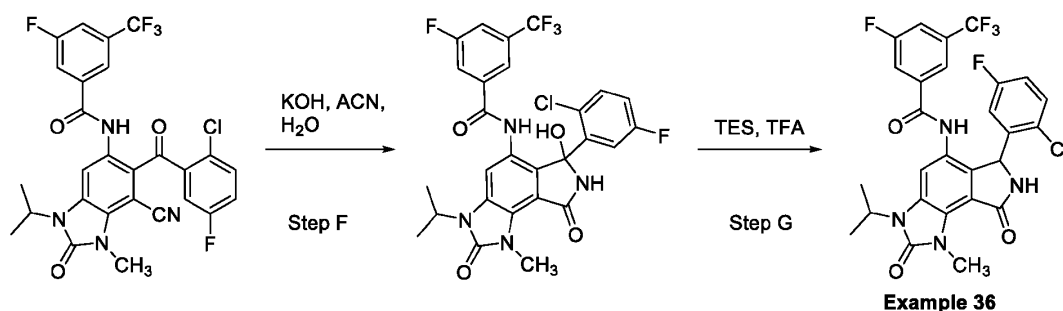
[00336] **Step D:** To a solution of 2-methylpropan-2-yl 3-({5-[(2-chloro-5-fluorophenyl)carbonyl]-4-cyano-6-({[5-fluoro-3-(trifluoromethyl)phenyl]carbonyl}amino)-3-methyl-2-oxobenzo[d]imidazol-1-yl}methyl)azetidine-1-carboxylate (120 mg, 0.199 mmol) in CH₃CN/H₂O (5 mL) was added potassium hydroxide (56 mg, 0.994 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: 60%] to afford the title compound 2-methylpropan-2-yl 3-({6-(2-chloro-5-fluorophenyl)-5-({[5-fluoro-3-(trifluoromethyl)phenyl]carbonyl}amino)-6-hydroxy-1-methyl-

2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-3-yl)methyl}azetidine-1-carboxylate (120 mg, 0.166 mmol, 83%) as a white solid. LCMS: ESI m/z 722/648/622 $[M+H]^+$

[00337] **Step E:** To a solution of 2-methylpropan-2-yl 3-{[6-(2-chloro-5-fluorophenyl)-5-({[5-fluoro-3-(trifluoromethyl)phenyl]carbonyl}amino)-6-hydroxy-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-3-yl)methyl}azetidine-1-carboxylate (100 mg, 0.138 mmol) in TFA (6 mL) was added Et_3SiH (32 mg, 0.277 mmol). The reaction mixture was stirred at 50 °C for 1 h. The reaction mixture was diluted with H_2O , extracted with EA. The organic phase was washed with brine, dried by Na_2SO_4 , filtered and concentrated. The residue was purified by prep-HPLC afford the title compound N-[3-(azetidin-3-ylmethyl)-6-(2-chloro-5-fluorophenyl)-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (28 mg, 0.046 mmol, 33%) as a white solid. LCMS: ESI m/z 606 $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.38 (brs, 1H), 9.16 (s, 1H), 8.37 (s, 1H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.76 – 7.73 (m, 2H), 7.46 (s, 1H), 7.28 (dd, $J = 8.0, 4.0$ Hz, 1H), 7.10 – 7.07 (m, 1H), 6.66 (brs, 1H), 6.01 (brs, 1H), 4.19 – 4.12 (m, 2H), 3.89 (s, 3H), 3.84 – 3.81 (m, 2H), 3.71 – 3.63 (m, 2H), 3.16 – 3.12 (m, 1H).

Example 36: N-(6-(2-chloro-5-fluorophenyl)-3-isopropyl-1-methyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide





[00338] **Step A:** To a solution of 4,6-dibromo-5-[(2-chloro-4-fluorophenyl)carbonyl]-1-[(2,4-dimethoxyphenyl)methyl]-2,3-dihydro-1H-benzo[d]imidazol-2-one (11 g, 18.4 mmol) in THF (3 mL) was added NaH (1.47 g, 36.7 mmol, 60% purity in mineral oil) at 0 °C. The mixture was stirred for 10 min, then iodomethane (5.22 g, 36.7 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 (50 mL*3). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated to afford 4,6-dibromo-5-[(2-chloro-4-fluorophenyl)carbonyl]-1-[(2,4-dimethoxyphenyl)methyl]-3-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (11 g, 18.0 mmol, 98%) as a brown solid. LCMS: ESI m/z 611 [M + H]⁺.

[00339] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-4-fluorophenyl)carbonyl]-1-[(2,4-dimethoxyphenyl)methyl]-3-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (11 g, 18.0 mmol) in TFA (110 mL) was added TfOH (11 mL). The mixture was stirred at 70°C for 16h. The mixture was concentrated. The residue was diluted with EA and aqueous NaHCO₃. The suspension was filtered and the filter cake was washed with H₂O (5 V* 3) and EA (5 V* 3). The solid was dry under vacuum to afford 5,7-dibromo-6-[(2-chloro-4-fluorophenyl)carbonyl]-1-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (7 g, 15.1 mmol, 84.3%) as a purple solid. LCMS: ESI m/z 461 [M + H]⁺.

[00340] **Step C:** To a solution of 5,7-dibromo-6-[(2-chloro-4-fluorophenyl)carbonyl]-1-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (500 mg, 1.08 mmol) and 2-bromopropane (266 mg, 2.16 mmol) in N,N-dimethylacetamide (5 mL) was added Cs₂CO₃ (1.05 g, 3.24 mmol). The mixture was stirred at 60 °C for 5h. The cooled 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 column (eluted with (EA: PE=30%) to give 4,6-dibromo-5-[(2-

chloro-4-fluorophenyl)carbonyl]-3-methyl-1-(prop-2-yl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (136 mg, 0.270 mmol, 25%) as a brown solid. LCMS: ESI m/z 505 $[M + H]^+$.

[00341] **Step D:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-(prop-2-yl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (136 mg, 0.270 mmol) in NMP (2 mL) was added CuCN (24.1 mg, 0.270 mmol). The reaction mixture was stirred at 120 °C under N₂ for 2h. The cooled 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 eluted with ethyl acetate in petroleum ether (gradient: 0%~20%) to afford 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-2-oxo-1-(prop-2-yl)benzo[d]imidazole-4-carbonitrile (55 mg, 0.122 mmol, 45%) as a brown solid. LCMS: ESI m/z 450 $[M + H]^+$.

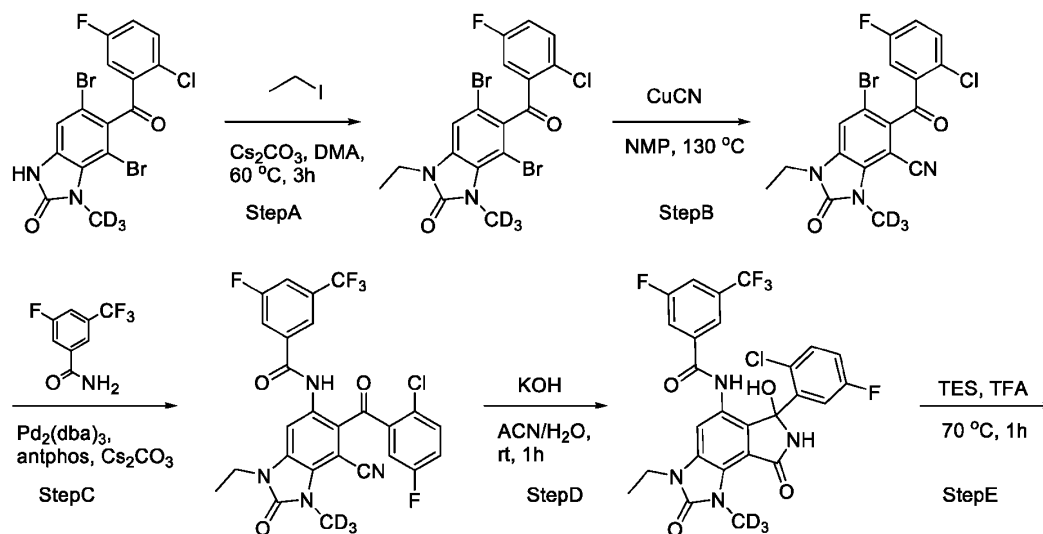
[00342] **Step E:** A solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-3-(trideuteriomethyl)-1-(2,2,2-trifluoroethyl)benzo[d]imidazole-4-carbonitrile (55 mg, 0.111 mmol), 5-fluoro-3-(trifluoromethyl)benzene-1-carboxamide (27.8 mg, 0.134 mmol), Pd₂(dba)₃ (11.2 mg, 12 μmol), Xantphos (14.1 mg, 24 μmol), Cs₂CO₃ (119 mg, 0.366 mmol) in dioxane (5 mL) was stirred at 100 °C under N₂ for 2h. The cooled reaction mixture was concentrated. The residue was purified using silica gel column chromatography eluted with MeOH in DCM (gradient: 0%~10%) to afford N-{6-[(1-chloro-4-fluorobenzen-2-yl)carbonyl]-7-cyano-1-methyl-2-oxo-3-(prop-2-yl)benzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (50 mg, 0.087 mmol, 71%) as a brown solid. LCMS: ESI m/z 577 $[M + H]^+$.

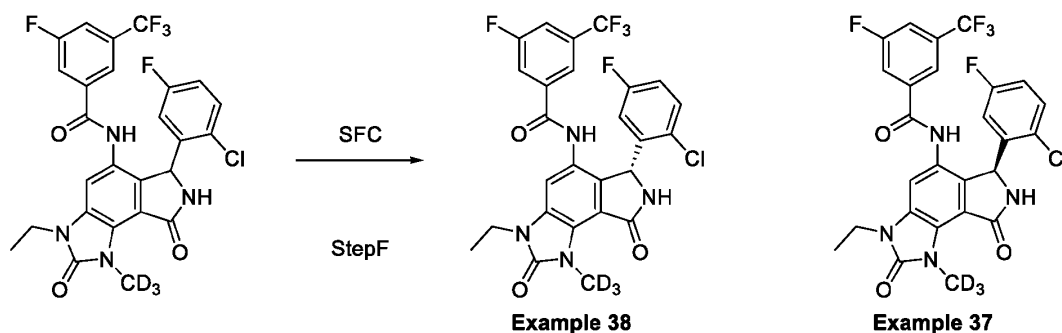
[00343] **Step F:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-1-methyl-2-oxo-3-(prop-2-yl)benzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (50 mg, 87 μmol) in ACN (2 mL) and H₂O (0.2 mL) was added KOH (24.3 mg, 0.433 mmol). The reaction mixture was stirred at rt for 30min. The mixture was diluted with water (10 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 N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-2,8-dioxo-3-(prop-2-yl)-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (50 mg, 84 μmol, 97%) as a brown solid. LCMS: ESI m/z 595 $[M + H]^+$.

[00344] **Step G:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-2,8-dioxo-3-(prop-2-yl)-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-

(trifluoromethyl)benzamide (50 mg, 84 μ mol) in TFA (2 mL) was added Et₃SiH (0.2 mL). The reaction mixture was stirred at 60 °C for 30 min. Then the reaction mixture was concentrated to give a residue. The residue was purified by pre-HPLC to give N-[6-(1-chloro-4-fluorobenzen-2-yl)-1-methyl-2,8-dioxo-3-(prop-2-yl)-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (18.4 mg, 0.032 mmol, 38%) as a white solid. LCMS: ESI m/z 579 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.26 (s, 1H), 9.12 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 9.2 Hz, 1H), 7.71 (s, 1H), 7.43 (s, 1H), 7.28 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.10 – 7.07 (m, 1H), 6.65 (brs, 1H), 5.99 (brs, 1H), 4.80 – 4.52 (m, 1H), 3.88 (s, 3H), 1.49 – 1.46 (m, 6H).

Example 37: (S)-N-(6-(2-chloro-5-fluorophenyl)-3-ethyl-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide and Example 38: (R)-N-(6-(2-chloro-5-fluorophenyl)-3-ethyl-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide





[00345] **Step A:** To a solution of 5,7-dibromo-6-(2-chloro-5-fluorobenzoyl)-1-(methyl-d3)-1,3-dihydro-2H-benzo[d]imidazol-2-one (500 mg, 1.080 mmol) in DMA (8 mL) were added iodoethane (252 mg, 1.62 mmol), Cs_2CO_3 (1.05 g, 3.24 mmol). The reaction was stirred at 80 °C under N_2 for 2.5 hr in a sealed system. LCMS showed the reaction was completed. The cooled reaction mixture was diluted water, extracted with EA. The organic phase 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: 15-25%) to afford the title compound 4,6-dibromo-5-(2-chloro-5-fluorobenzoyl)-1-ethyl-3-(methyl-d3)-1,3-dihydro-2H-benzo[d]imidazol-2-one (350 mg, 0.713 mmol, 66%) as a yellow solid. LCMS: 492/494 $[\text{M}-\text{H}]^-$.

[00346] **Step B:** To a solution of 4,6-dibromo-5-(2-chloro-5-fluorobenzoyl)-1-ethyl-3-(methyl-d3)-1,3-dihydro-2H-benzo[d]imidazol-2-one (330 mg, 0.672 mmol) in NMP (5 mL) were added CuCN (78.3 mg, 0.874 mmol). The reaction was stirred at 130 °C under N_2 for 2 hr. LCMS showed the reaction was 60% DP. The cooled reaction mixture was diluted water, extracted with EA. The organic phase 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 dichloroform (gradient: 10-20%) to afford 6-bromo-5-(2-chloro-5-fluorobenzoyl)-1-ethyl-3-(methyl-d3)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (160 mg, 0.365 mmol, 54 %) as a yellow solid. LCMS: 439/441 $[\text{M}-\text{H}]^-$.

[00347] **Step C:** To a solution of 6-bromo-5-(2-chloro-5-fluorobenzoyl)-1-ethyl-3-(methyl-d3)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (150 mg, 0.342 mmol) in dioxane (10 mL) were added 3-fluoro-5-(trifluoromethyl)benzamide (106 mg, 0.514 mmol), $\text{Pd}_2(\text{dba})_3$ (31.4 mg, 0.034 mmol), and XANT PHOS (39.7 mg, 0.068 mmol), Cs_2CO_3 (334 mg, 1.02 mmol). The reaction was stirred at 100 °C under N_2 for 2 hr. LCMS showed the reaction was

completed. 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 petroleum ether (gradient: 10-20%) to afford the title compound N-(6-(2-chloro-5-fluorobenzoyl)-7-cyano-3-ethyl-1-(methyl-d₃)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (140 mg, 0.248 mmol, 72%) as a yellow oil. LCMS: ESI m/z 566/568 [M+H]⁺.

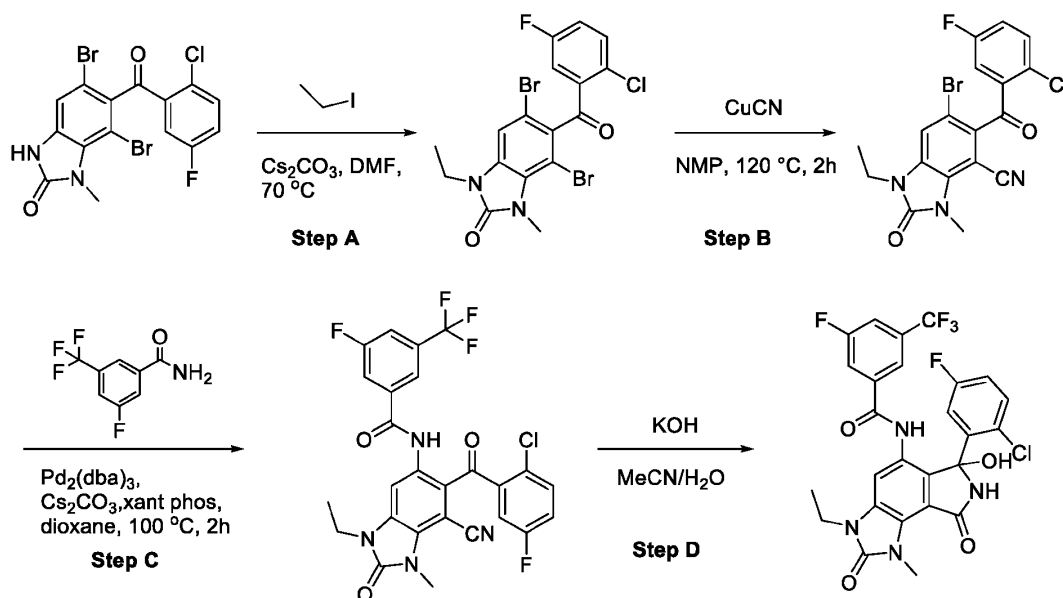
[00348] **Step D:** To a solution of N-(6-(2-chloro-5-fluorobenzoyl)-7-cyano-3-ethyl-1-(methyl-d₃)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (100 mg, 0.177 mmol) in ACN (5 mL) and H₂O (1.5 mL) were added KOH (19.9 mg, 0.354 mmol). The reaction was stirred at room temperature under N₂ for 1 hr. LCMS showed the reaction was completed. 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-(6-(2-chloro-5-fluorophenyl)-3-ethyl-6-hydroxy-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (80 mg, 0.137 mmol, 78%) as a yellow solid. LCMS: ESI m/z 584/586 [M + H]⁺.

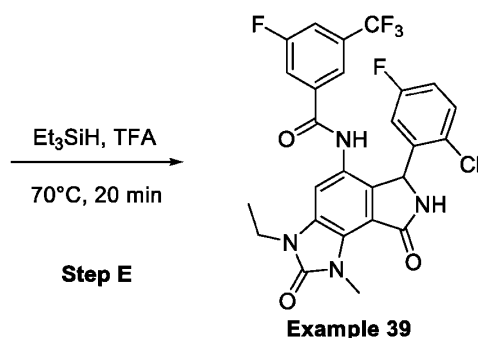
[00349] **Step E:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-3-ethyl-6-hydroxy-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (15 mg, 0.026 mmol) in TFA (3 mL) were added Et₃SiH (30 mg, 0.257 mmol). The reaction was stirred at 70 °C for 1 hr. LCMS showed the reaction was completed. 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: 40-50%) to afford N-(6-(2-chloro-5-fluorophenyl)-3-ethyl-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (4 mg, 0.007 mmol, 27%) as a white solid. LCMS: ESI m/z 568/570 [M + H]⁺.

[00350] **Step F:** A solution of N-(6-(2-chloro-5-fluorophenyl)-3-ethyl-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (55 mg, 0.097 mmol) was purified with chiral prep-SFC method 10 to afford (R)-N-(6-(2-chloro-5-fluorophenyl)-3-ethyl-1-(methyl-d₃)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-

e]isindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (13.8 mg, 0.024 mmol, 18%) as a white solid. LCMS: ESI m/z 568 $[M + H]^+$. 1H NMR (400 MHz, MeOD- d_4) δ 7.70 – 7.60 (m, 2H), 7.63 (d, J = 8.8 Hz, 1H), 7.35 (s, 1H), 7.24 (dd, J = 8.8, 5.0 Hz, 1H), 6.98 (dd, 1H), 6.59 (brs, 1H), 6.20 (brs, 1H), 4.07 – 3.95 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H). And (S)-N-(6-(2-chloro-5-fluorophenyl)-3-ethyl-1-(methyl- d_3)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-*e*]isindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (17 mg, 0.030 mmol, 22%) as a white solid. LCMS: ESI m/z 568 $[M + H]^+$. 1H NMR (400 MHz, MeOD- d_4) δ 7.70 – 7.60 (m, 2H), 7.63 (d, J = 8.8 Hz, 1H), 7.35 (s, 1H), 7.24 (dd, J = 8.8, 5.0 Hz, 1H), 6.98 (dd, 1H), 6.59 (brs, 1H), 6.20 (brs, 1H), 4.07 – 3.95 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H).

Example 39: N-(6-(2-chloro-5-fluorophenyl)-3-ethyl-1-methyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-*e*]isindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide





[00351] **Step A:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (500 mg, 1.08 mmol) in DMF (8 mL) was added Cs_2CO_3 (1.06 g, 3.24 mmol) at 0 °C. The mixture was stirred for 10 min, then iodoethane (0.13 mL, 1.62 mmol) was added. The mixture was stirred at 70 °C for 2h. The cooled reaction mixture was quenched by water, and the mixture was extracted with EtOAc (20 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: 0-30%) afford 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-ethyl-3-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (280 mg, 0.57 mmol, 53%) as a yellow solid. LCMS: ESI m/z 491 $[\text{M} + \text{H}]^+$.

[00352] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-ethyl-3-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (280 mg, 0.57 mmol) in NMP (5 mL) was added CuCN (54 mg, 0.60 mmol). The reaction mixture was stirred at 120 °C under N_2 for 2h. The cooled reaction mixture was diluted with EA, filtered through a pad of celite. The filtrate was extracted with EtOAc (10 mL*3). The organic phase was washed with brine for 5 times, dried over Na_2SO_4 and concentrated. Then the crude was purified by prep-HPLC to afford 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-ethyl-3-methyl-2-oxobenzo[d]imidazole-4-carbonitrile (80 mg, 0.18 mmol, 32%) as a yellow solid. LCMS: ESI m/z 436/438 $[\text{M} + \text{H}]^+$.

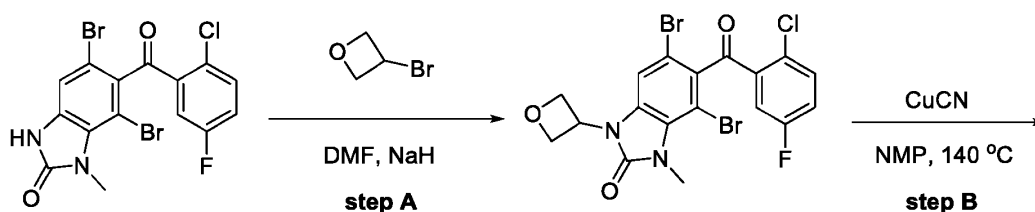
[00353] **Step C:** To a solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-ethyl-3-methyl-2-oxobenzo[d]imidazole-4-carbonitrile (80 mg, 0.18 mmol) in 1,4-dioxane (5 mL) was added 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (57 mg, 0.26 mmol), $\text{Pd}_2(\text{dba})_3$ (17 mg, 0.02 mmol), Xantphos (21 mg, 0.04 mmol), Cs_2CO_3 (120 mg, 0.37 mmol). The reaction was stirred at 100 °C under N_2 for 2h. The reaction mixture was concentrated, and chromatographed (PE/EA = 3/1) to afford N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-

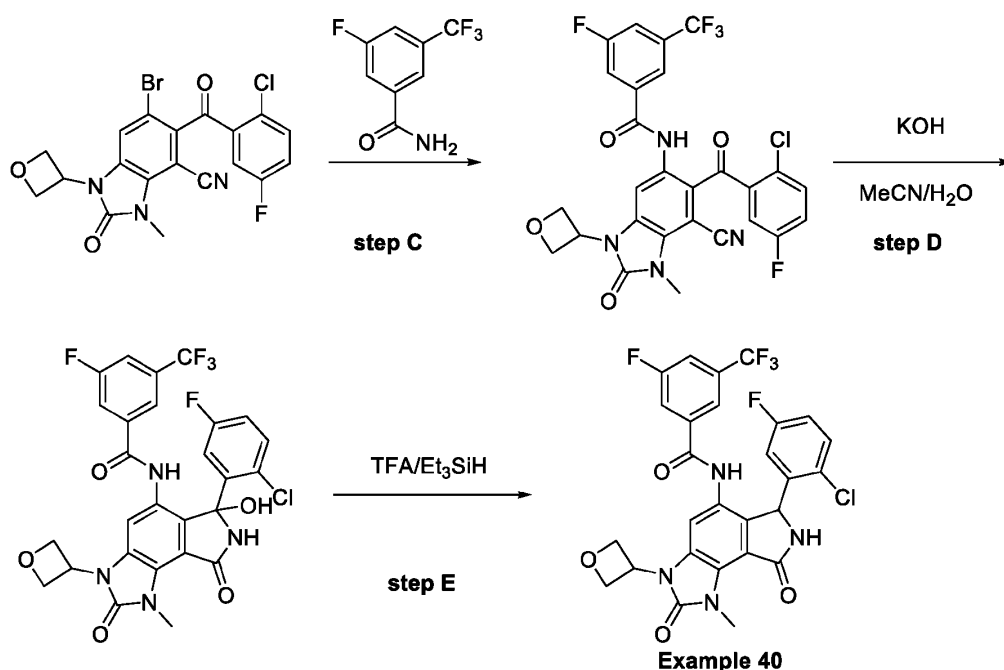
cyano-3-ethyl-1-methyl-2-oxobenzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (90 mg, 0.16 mmol, 87%) as a yellow solid. LCMS: ESI m/z 563 $[M + H]^+$.

[00354] **Step D:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-ethyl-1-methyl-2-oxobenzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (90 mg, 0.16 mmol) in MeCN (5 mL) and H₂O (1 mL) were added potassium hydroxide (18 mg, 0.32 mmol). The reaction was stirred at room temperature for 2 hr. LCMS showed the reaction was completed. 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-[6-(2-chloro-5-fluorophenyl)-3-ethyl-6-hydroxy-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (90 mg, 0.16 mmol, 97%) as a yellow solid. LCMS: ESI m/z 563 $[M - OH]^+$.

[00355] **Step E:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-3-ethyl-6-hydroxy-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (90 mg, 0.16 mmol) in TFA (2 mL) was added triethylsilane (1 mL). The reaction was stirred at 70 °C for 20 min. LCMS showed the reaction was completed. The cooled reaction mixture was concentrated and purified by prep-HPLC to afford N-(6-(2-chloro-5-fluorophenyl)-3-ethyl-1-methyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (56.7 mg, 0.10 mmol, 65%) as a white solid. LCMS: ESI m/z 565 $[M + H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.29 (s, 1H), 9.14 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.79 – 7.67 (m, 2H), 7.36 (s, 1H), 7.28 (dd, J = 8.8, 5.2 Hz, 1H), 7.14 – 7.01 (m, 1H), 6.64 (s, 1H), 6.02 (s, 1H), 3.98 – 3.90 (m, 2H), 3.89 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H).

Example 40: N-(6-(2-chloro-5-fluorophenyl)-1-methyl-3-(oxetan-3-yl)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide





[00356] **Step A:** To the mixture of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (700 mg, 1.51 mmol) and Cs_2CO_3 (986 mg, 3.03 mmol) in *N,N*-dimethylmethanamide (15 mL) was added 3-iodooxetane (557 mg, 3.03 mmol). The mixture was stirred at 100°C for 24 hours. The cooled mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude was purified by FCC, eluting with EA/PE (0-20%) to give 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-(oxetan-3-yl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (240 mg, 0.37 mmol, 24%) as a yellow solid. LCMS: m/z 519 $[\text{M}+\text{H}]^+$.

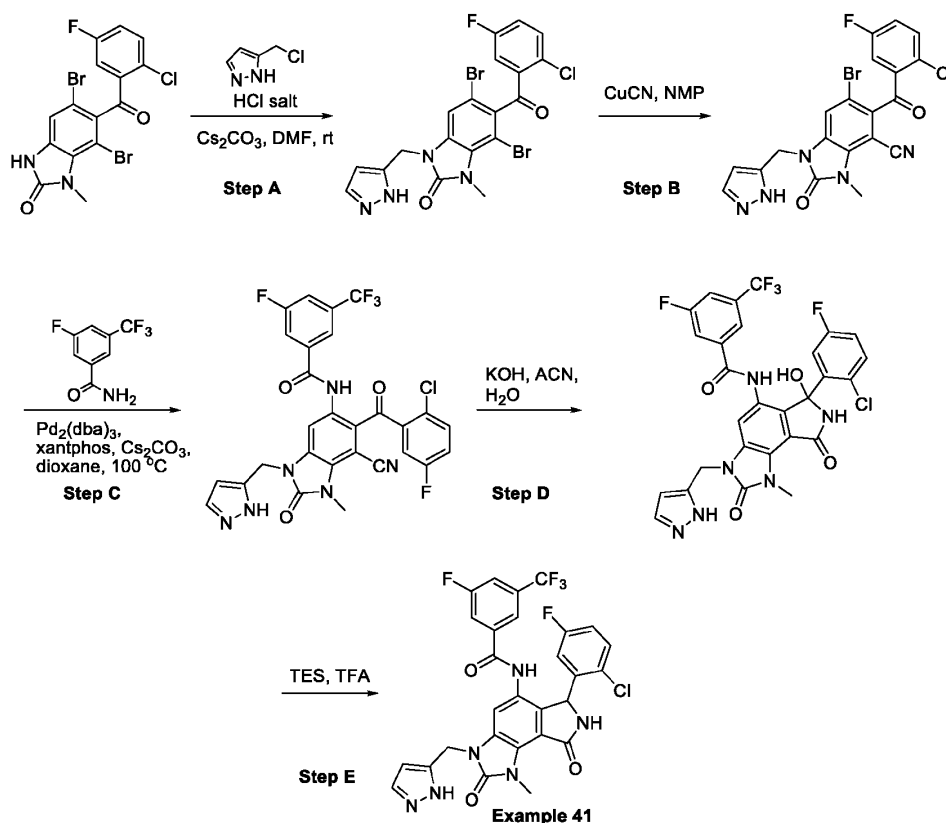
[00357] **Step B:** The mixture of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-(oxetan-3-yl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (220 mg, 0.42 mmol) and CuCN (114 mg, 1.27 mmol) in NMP (10 mL) was stirred at 140°C for 70 min. The cooled mixture was diluted with water and EA. The mixture was filtered and separated. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC (EA/PE=4: 5) to give 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-(oxetan-3-yl)-2-oxobenzo[d]imidazole-4-carbonitrile (53 mg, 0.114 mmol, 27%) as a yellow solid. LCMS: m/z 466 $[\text{M}+\text{H}]^+$.

[00358] **Step C:** The mixture of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-(oxetan-3-yl)-2-oxobenzo[d]imidazole-4-carbonitrile (53 mg, 0.114 mmol), 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (35 mg, 0.17 mmol), tris[(1E,4E)-1,5-diphenylpenta-1,4-dien-3-one] bis[palladium(0)] (10.44 mg, 0.011 mmol), Xantphos (13 mg, 0.023 mmol) and Cs₂CO₃ (74 mg, 0.23 mmol) in dioxane (5 mL) was stirred 100 °C for 2h. The mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by prep-TLC (EA/PE 4:5 twice) to give N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-1-methyl-3-(oxetan-3-yl)-2-oxobenzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (40 mg, 0.068 mmol, 59%) as a yellow solid. LCMS: m/z 591 [M+H]⁺.

[00359] **Step D:** To the mixture of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-1-methyl-3-(oxetan-3-yl)-2-oxobenzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (40 mg, 0.068 mmol) in acetonitrile (10 mL) and H₂O (2 mL) was added potassium hydroxide (38 mg, 0.68 mmol). The mixture was stirred at room temperature for 30min. The mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated to give N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-3-(oxetan-3-yl)-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (40 mg, 0.066 mmol, 97%) as a yellow solid.

[00360] **Step E:** The mixture of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-3-(oxetan-3-yl)-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (40 mg, 0.066 mmol) in TFA (5 mL) and Et₃SiH (0.5 mL) was stirred at 50 °C for 8-10min. The mixture was poured into a cold NaHCO₃ solution to adjust pH to 8. The mixture was extracted with EA and concentrated. The residue was purified by prep-HPLC to give N-[6-(2-chloro-5-fluorophenyl)-1-methyl-3-(oxetan-3-yl)-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (13.1 mg, 0.022 mmol, 34%) as a white solid. LCMS: m/z 593 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.37 (s, 1H), 9.18 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.68 (s, 1H), 7.60 (s, 1H), 7.29 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.09 (td, *J* = 8.4, 2.8 Hz, 1H), 6.63 (s, 1H), 6.05 (s, 1H), 5.66 – 5.50 (m, 1H), 5.08 (td, *J* = 6.4, 3.6 Hz, 2H), 4.96 (dd, *J* = 13.6, 6.8 Hz, 2H), 3.89 (s, 3H).

Example 41: N-[6-(2-chloro-5-fluorophenyl)-3-(2H-pyrazol-3-ylmethyl)-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide



[00361] **Step A:** To a stirred solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (500 mg, 1.08 mmol) in DMF (12 mL) was added 5-(chloromethyl)-1H-pyrazole (164 mg, 1.4 mmol) and Cs_2CO_3 (704 mg, 2.16 mmol) at rt. After stirred at rt for 2h, the cooled mixture was poured into brine (30 mL) and extracted with EtOAc (20 mL*3). The combined organic phase was washed with brine, dried with Na_2SO_4 , filtered and concentrated until there was no more drops. The residue was purified by chromatography (silica gel, 0-10 %, MeOH in DCM) to give 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2H-pyrazol-3-ylmethyl)-3-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (480 mg, 0.88 mmol, 82 %) as a yellow solid. LCMS: m/z 543 $[\text{M}+\text{H}]^+$.

[00362] **Step B:** To a stirred solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2H-pyrazol-3-ylmethyl)-3-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (480 mg, 0.88 mmol) in NMP (15 mL) was added CuCN (107 mg, 1.2 mmol) at rt. After stirred at 130 °C under N_2 for 2h, the cooled mixture was poured into brine (80 mL) and extracted with EtOAc (50

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, 0-10 %, MeOH in DCM) to give 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2H-pyrazol-3-ylmethyl)-3-methyl-2-oxobenzo[d]imidazole-4-carbonitrile (100 mg, 0.2 mmol, 22%) as a yellow solid. LCMS: m/z 489 [M+H]⁺.

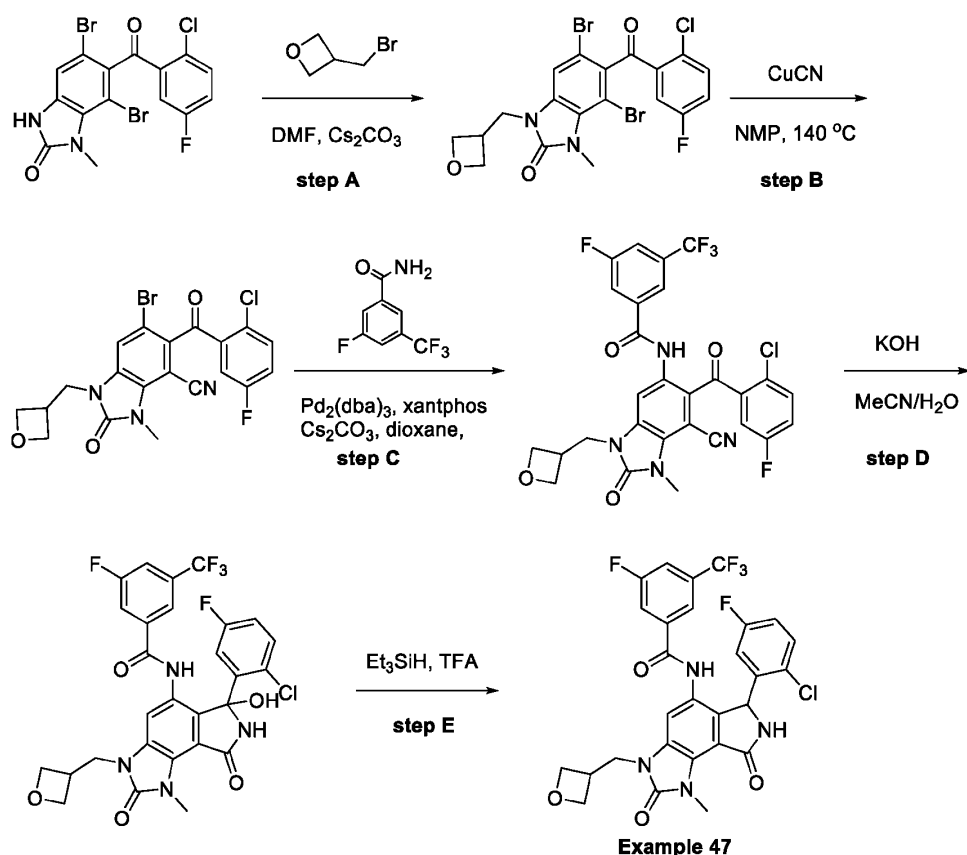
[00363] **Step C:** To a stirred solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2H-pyrazol-3-ylmethyl)-3-methyl-2-oxobenzo[d]imidazole-4-carbonitrile (100 mg, 0.2 mmol) in dioxane (8 mL) was added 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (63 mg, 0.31 mmol), Pd₂(dba)₃ (18 mg, 0.02 mmol), XANT PHOS (24 mg, 0.04 mmol) and Cs₂CO₃ (166 mg, 0.51 mmol) at rt. After stirred at 100 °C under N₂ for 2h, the mixture was poured into ice-water (12 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- 10%, MeOH in DCM) to give N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-(2H-pyrazol-3-ylmethyl)-1-methyl-2-oxobenzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (30 mg, 0.04 mmol, 19 %) as a brown solid. LCMS: m/z 615 [M+H]⁺.

[00364] **Step D:** To a stirred solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-3-(2H-pyrazol-3-ylmethyl)-1-methyl-2-oxobenzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (30 mg, 0.05 mmol) in ACN (4 mL)/ H₂O (1 mL) was added KOH (27 mg, 0.49 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 to give crude N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-3-(2H-pyrazol-3-ylmethyl)-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (25 mg, 0.04 mmol, 81%) as a white solid. LCMS: m/z 633 [M+H]⁺.

[00365] **Step E:** To a stirred solution of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-3-(2H-pyrazol-3-ylmethyl)-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (25 mg, 0.04 mmol) in TFA (2 mL) was added Et₃SiH (0.5 mL) at rt. After stirred at 70 °C for 1h, the cooled mixture was concentrated. The residue was purified by prep-HPLC (C18, 40 ~ 90 % MeCN in H₂O with 0.1 % TFA) to give N-[6-(2-chloro-5-

fluorophenyl)-3-(2H-pyrazol-3-ylmethyl)-1-methyl-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (3 mg, 0.005 mmol, 12 %) as a white solid. LCMS: m/z 617 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.29 (s, 1H), 9.14 (s, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 7.72 (d, $J = 9.2$ Hz, 1H), 7.67 (s, 1H), 7.63 (d, $J = 2.0$ Hz, 1H), 7.30 – 7.21 (m, 2H), 7.11 – 7.05 (m, 1H), 6.61 (brs, 1H), 6.18 (d, $J = 2.0$ Hz, 1H), 5.96 (brs, 1H), 5.13 – 5.01 (m, 2H), 3.92 (s, 3H).

Example 47: N-(6-(2-chloro-5-fluorophenyl)-1-methyl-3-(oxetan-3-ylmethyl)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00366] **Step A:** The mixture of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (600 mg, 1.30 mmol), 3-(bromomethyl)oxetane (294 mg, 1.95 mmol) and cesium carbonate (845 mg, 2.60 mmol) in N,N-dimethylmethanamide (15 mL) was stirred at 70 °C for 2 hours. The cooled mixture was diluted with water and

extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by FCC, eluting with EA/PE (0-70%) to give 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-(oxetan-3-ylmethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (248 mg, 0.47 mmol, 36%) as a yellow solid. LCMS: m/z 533 [M+H]⁺.

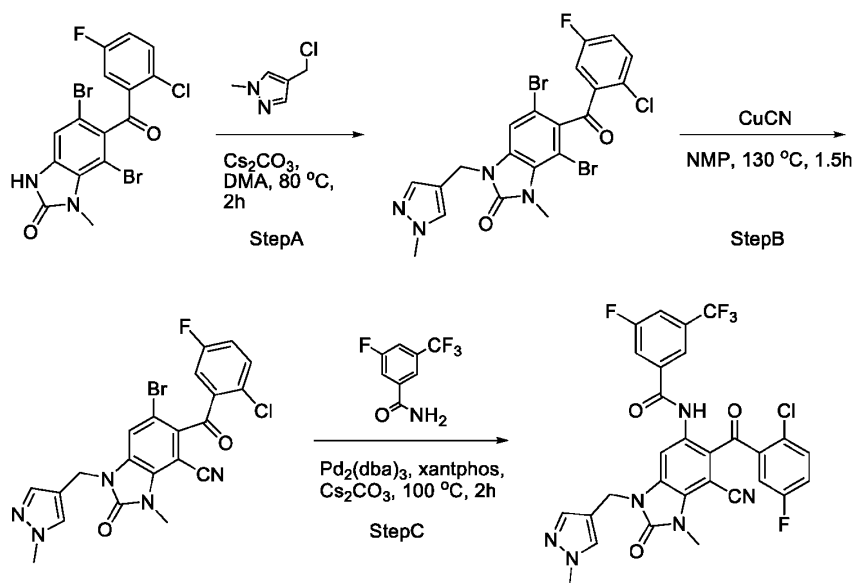
[00367] **Step B:** The mixture of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-(oxetan-3-ylmethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (248 mg, 0.47 mmol) and CuCN (125 mg, 1.40 mmol) in NMP (5 mL) was stirred at 140 °C for 70 min. The cooled mixture was diluted with water and EA. The mixture was filtered and the filtrate was extracted with EA. The combined organic layer was washed with brine twice, dried over Na₂SO₄ and concentrated. The residue was purified by prep-TLC (acetone: PE=1: 2) to give 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-(oxetan-3-ylmethyl)-2-oxobenzo[d]imidazole-4-carbonitrile (60 mg, 0.13 mmol, 27%) as a yellow solid.

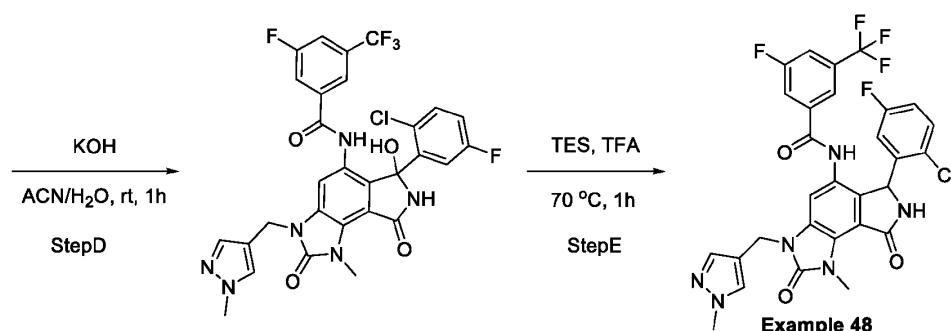
[00368] **Step C:** The mixture of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-(oxetan-3-ylmethyl)-2-oxobenzo[d]imidazole-4-carbonitrile (73 mg, 0.152 mmol), 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (47 mg, 0.23 mmol), tris[(1E,4E)-1,5-diphenylpenta-1,4-dien-3-one] bis[palladium(0)] (14 mg, 0.015 mmol), Xantphos (18 mg, 0.03 mmol) and Cs₂CO₃ (99 mg, 0.31 mmol) in dioxane (10 mL) was stirred at 110 °C under N₂ for 2h. The cooled mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by prep-TLC (EA/PE=5:4, twice) to give N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-1-methyl-3-(oxetan-3-ylmethyl)-2-oxobenzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (49 mg, 0.08 mmol, 53%) as a yellow solid. LCMS: m/z 605 [M+H]⁺.

[00369] **Step D:** To the mixture of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-1-methyl-3-(oxetan-3-ylmethyl)-2-oxobenzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl)benzamide (50 mg, 0.08 mmol) in H₂O (1 mL) and MeCN (5 mL) was added KOH (46 mg, 0.83 mmol). The mixture was stirred at room temperature for 30 min. The mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was used directly in the next step. LCMS: m/z 623 [M+H]⁺.

[00370] **Step E:** The mixture of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-3-(oxetan-3-ylmethyl)-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (15 mg, 0.024 mmol) in TFA (3 mL) and Et₃SiH (0.3 mL) was stirred at 50 °C for 8 min. The mixture was added dropwise into a cold solution of NaHCO₃ in water. The mixture was extracted with EA. The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give N-[6-(2-chloro-5-fluorophenyl)-1-methyl-3-(oxetan-3-ylmethyl)-2,8-dioxo-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-5-fluoro-3-(trifluoromethyl)benzamide (1.0 mg, 0.002 mmol, 7%) as a white solid. LCMS: m/z 607 [M+H]⁺. ¹H NMR (400 MHz, MeOD-d₄) δ 7.93 (s, 1H), 7.77 – 7.61 (m, 4H), 7.28 (dd, *J* = 8.8, 5.0 Hz, 1H), 7.05 – 6.99 (m, 1H), 6.44 (s, 1H), 5.16 – 5.12 (m, 1H), 4.96 – 4.87 (m, 1H), 4.56 – 4.47 (m, 1H), 4.34 (s, 3H), 4.29 – 4.22 (m, 1H), 3.87 – 3.80 (m, 2H), 2.82 (s, 1H).

Example 48: N-[6-(2-chloro-5-fluorophenyl)-1-methyl-3-[(1-methylpyrazol-4-yl)methyl]-2,8-dioxo-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide





[00371] **Step A:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (500 mg, 1.08 mmol) in DMA (10 mL) were added 4-(chloromethyl)-1-methylpyrazole (211 mg, 1.62 mmol), Cs_2CO_3 (1.01 g, 3.24 mmol). The reaction was stirred at 80 °C under N_2 for 2 hr. The cooled reaction mixture was diluted water, extracted with EA. The organic phase 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: 45-55%) to afford the title compound 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-[(1-methylpyrazol-4-yl)methyl]-2,3-dihydro-1H-benzo[d]imidazol-2-one (400 mg, 0.719 mmol, 66%) as a yellow solid. LCMS: 555/557 $[\text{M}-\text{H}]^-$.

[00372] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-[(1-methylpyrazol-4-yl)methyl]-2,3-dihydro-1H-benzo[d]imidazol-2-one (400 mg, 0.719 mmol) in NMP (5 mL) were added CuCN (96.5 mg, 1.08 mmol). The reaction was stirred at 130 °C under N_2 for 1.5hr. LCMS showed the reaction was 40% DP. The cooled reaction mixture was diluted water, extracted with EA. The organic phase 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 DCM (gradient: 20-30%) to afford 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-[(1-methylpyrazol-4-yl)methyl]-2-oxobenzo[d]imidazole-4-carbonitrile (100 mg, 0.199 mmol, 28%) as a yellow solid. LCMS: 502/504 $[\text{M}-\text{H}]^-$.

[00373] **Step C:** To a solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-1-[(1-methylpyrazol-4-yl)methyl]-2-oxobenzo[d]imidazole-4-carbonitrile (80 mg, 0.159 mmol) in dioxane (5 mL) were added 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (49.4 mg, 0.239 mmol), $\text{Pd}_2(\text{dba})_3$ (14.5 mg, 0.016 mmol), and xantphos (18.4 mg, 0.032 mmol), Cs_2CO_3 (130 mg, 0.398 mmol). The reaction was stirred at 100 °C under N_2 for 2 hr.

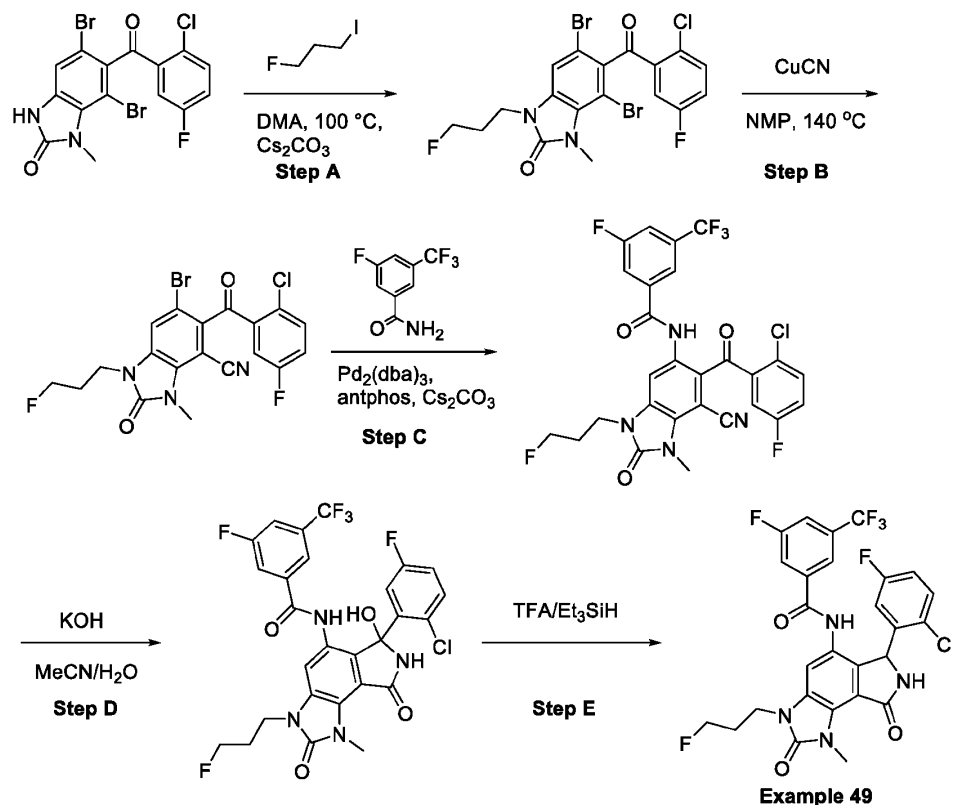
LCMS showed the reaction was completed. The cooled reaction mixture was diluted water, extracted with EA. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified using silica gel column chromatography eluted with ethyl acetate in petroleum ether (gradient: 10-20%) to afford the title compound N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-1-methyl-3-[(1-methylpyrazol-4-yl)methyl]-2-oxobenzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (80 mg, 0.127 mmol, 80%) as a yellow solid. LCMS: ESI m/z 629/631 [M+H]⁺.

[00374] **Step D:** To a solution of N-{6-[(2-chloro-5-fluorophenyl)carbonyl]-7-cyano-1-methyl-3-[(1-methylpyrazol-4-yl)methyl]-2-oxobenzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl)benzamide (80 mg, 0.127 mmol) in H₂O (1 mL) and ACN (3 mL) were added KOH (7.14 mg, 0.127 mmol). The reaction was stirred at room temperature under N₂ for 1 hr. LCMS showed the reaction was completed. 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-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-3-[(1-methylpyrazol-4-yl)methyl]-2,8-dioxo-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (40 mg, 0.062 mmol, 49%) as a yellow solid. LCMS: ESI m/z 647/649 [M + H]⁺.

[00375] **Step E:** To a solution of N-[6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-3-[(1-methylpyrazol-4-yl)methyl]-2,8-dioxo-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (50 mg, 0.077 mmol) in TFA (3 mL) were added Et₃SiH (8.99 mg, 0.077 mmol). The reaction was stirred at 70 °C for 1 hr. LCMS showed the reaction was completed. 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 by prep-HPLC to afford N-[6-(2-chloro-5-fluorophenyl)-1-methyl-3-[(1-methylpyrazol-4-yl)methyl]-2,8-dioxo-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (27.6 mg, 0.044 mmol, 57%) as a white solid. LCMS: ESI m/z 631/633 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.27 (s, 1H), 9.13 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 9.2 Hz, 1H), 7.71 – 7.69 (m, 2H), 7.44 (s, 1H), 7.36 (s, 1H), 7.26 (dd, J = 8.8, 5.2 Hz, 1H), 7.13 – 7.03 (m, 1H), 6.61 (brs, 1H), 5.97 (brs, 1H), 4.94 (s, 2H), 3.90 (s, 3H), 3.75 (s, 3H).

Example 49: N-(6-(2-chloro-5-fluorophenyl)-3-(3-fluoropropyl)-1-methyl-2,8-dioxo-

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



[00376] **Step A:** To a stirred solution of 5,7-dibromo-6-(2-chloro-5-fluorobenzoyl)-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (500 mg, 1.081 mmol) in DMA (3 mL) was added 1-fluoro-3-iodopropane (366 mg, 1.95 mmol) and Cs_2CO_3 (1057 mg, 3.24 mmol) at rt. After stirred at 100 °C for 1h, the mixture was poured into water (40 mL) and extracted with EtOAc (20 mL*3). 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 4,6-dibromo-5-(2-chloro-5-fluorobenzoyl)-1-(3-fluoropropyl)-3-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (230 mg, 0.440 mmol, 40 %) as a white solid. LCMS: m/z 521 $[\text{M}+\text{H}]^+$.

[00377] **Step B:** To a stirred solution of 4,6-dibromo-5-(2-chloro-5-fluorobenzoyl)-1-(3-fluoropropyl)-3-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (230 mg, 0.44 mmol) in NMP (6 mL) was added CuCN (59 mg, 0.66 mmol) at rt. After stirred at 130 °C for 1.5

h, the mixture was poured into 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 residue was purified by chromatography (silica gel, 0-30%, EtOAc in PE) to give 6-bromo-5-(2-chloro-5-fluorobenzoyl)-1-(3-fluoropropyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (80 mg, 0.171 mmol, 39%) as a white solid. LCMS: m/z 468 [M+H]⁺.

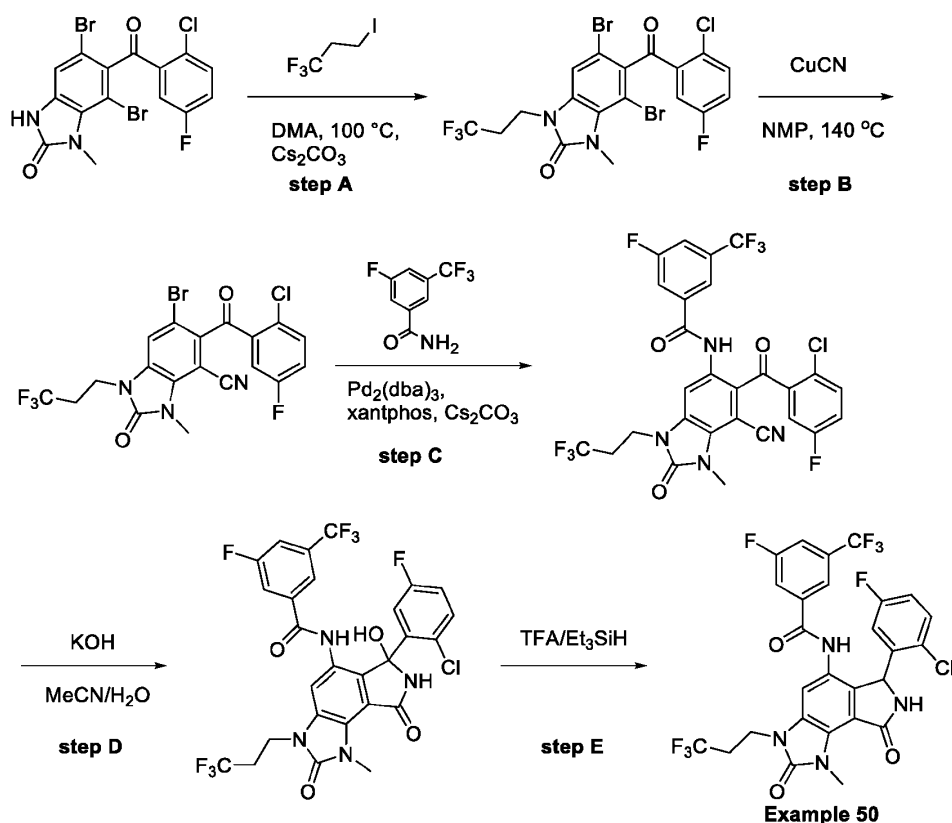
[00378] **Step C:** To a solution of 6-bromo-5-(2-chloro-5-fluorobenzoyl)-1-(3-fluoropropyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (50 mg, 0.107 mmol) in dioxane (3 mL) was added 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (33.15 mg, 0.160 mmol), Xantphos (12.35 mg, 0.021 mmol), Cs₂CO₃ (70 mg, 0.213 mmol) and Pd₂(dba)₃ (9.77 mg, 0.011 mmol). The reaction mixture was stirred at 100 °C under N₂ for 2 h. 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 0-10% methanol in dichloroform to afford the title compound N-(6-(2-chloro-5-fluorobenzoyl)-7-cyano-3-(3-fluoropropyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (60 mg, 0.101 mmol, 95%) as a yellow solid. LCMS: ESI m/z 595 [M + H]⁺.

[00379] **Step D:** To a solution of N-(6-(2-chloro-5-fluorobenzoyl)-7-cyano-3-(3-fluoropropyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (60 mg, 0.101 mmol) in ACN (5 mL) and H₂O (1 mL) was added KOH (28.3 mg, 0.504 mmol), and the mixture was stirred at 25 °C for 1 h. The mixture was diluted with EA and washed with H₂O and brine. The organic layer was concentrated under vacuum. The residue was purified using silica gel column chromatography eluting with 0-10% methanol in dichloroform to afford the title compound N-(6-(2-chloro-5-fluorophenyl)-3-(3-fluoropropyl)-6-hydroxy-1-methyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (50 mg, 0.082 mmol, 81%) as a white solid. LCMS: ESI m/z 613 [M + H]⁺.

[00380] **Step E:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-3-(3-fluoropropyl)-6-hydroxy-1-methyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (50 mg, 0.082 mmol) in TFA (2 mL) was added Et₃SiH (47 mg, 0.408 mmol), and the mixture was stirred at 50 °C for 1 h. The cooled mixture was concentrated

under vacuum. The residue was purified using pre-HPLC to afford N-(6-(2-chloro-5-fluorophenyl)-3-(3-fluoropropyl)-1-methyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (8.6 mg, 0.014 mmol, 18%) as a white solid. LCMS: ESI m/z 597 $[M + H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.30 (s, 1H), 9.14 (s, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.74 (d, $J = 8.8$ Hz, 1H), 7.71 (s, 1H), 7.35 (s, 1H), 7.28 (dd, $J = 8.8, 5.2$ Hz, 1H), 7.10 – 7.07 (m, 1H), 6.61 (brs, 1H), 6.02 (brs, 1H), 4.57 (t, $J = 5.8$ Hz, 1H), 4.46 (t, $J = 5.8$ Hz, 1H), 4.05 – 3.94 (m, 2H), 3.89 (s, 3H), 2.11 – 1.98 (m, 2H).

Example 50: N-[6-(2-chloro-5-fluorophenyl)-1-methyl-2,8-dioxo-3-(3,3,3-trifluoropropyl)-7,8-dihydro-6H-imidazo[4,5-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)cyclohexa-2,4-diene-1-carboxamide



[00381] **Step A:** To a solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl)carbonyl]-1-(trideuteriomethyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (100 mg, 0.215 mmol) in DMA (3 mL) was added 1,1,1-trifluoro-4-iodobutane (102 mg, 0.430 mmol), Cs_2CO_3 (210 mg, 0.644

mmol). The reaction mixture was stirred at 100 °C under N₂ for 2h. TLC showed the reaction was completed. The cooled mixture was poured in water (10 mL), extracted with EtOAc (10 mL*2). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo and purified by p-TLC (SiO₂, PE: EtOAc=5: 1) to give 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-(trideuteriomethyl)-1-(4,4,4-trifluorobutyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (35 mg, 25%) as yellow oil.

[00382] ¹H NMR (400 MHz, DMSO-d₆) δ 7.80 (s, 1H), 7.74 (dd, *J* = 8.8, 4.9 Hz, 1H), 7.65 – 7.57 (m, 1H), 7.52 – 7.43 (m, 1H), 4.18 (t, *J* = 6.8 Hz, 2H), 3.63 (s, 3H), 2.84 – 2.69 (m, 2H).

[00383] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-(trideuteriomethyl)-1-(4,4,4-trifluorobutyl)-2,3-dihydro-1H-benzo[d]imidazol-2-one (150 mg, 0.261 mmol) in NMP (2 mL) was added CuCN (46.6 mg, 0.521 mmol). The reaction mixture was stirred at 130 °C under N₂ for 2h. LCMS showed the reaction is half transformed. The mixture was poured in water (5 mL), extracted with EtOAc (5 mL*2). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo and purified by prep-HPLC (TFA) to give 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-2-oxo-3-(trideuteriomethyl)-1-(4,4,4-trifluorobutyl)benzo[d]imidazole-4-carbonitrile (50 mg, 0.086 mmol, 33%) as yellow oil. LCMS: ESI *m/z* 504/506 [*M* + *H*]⁺.

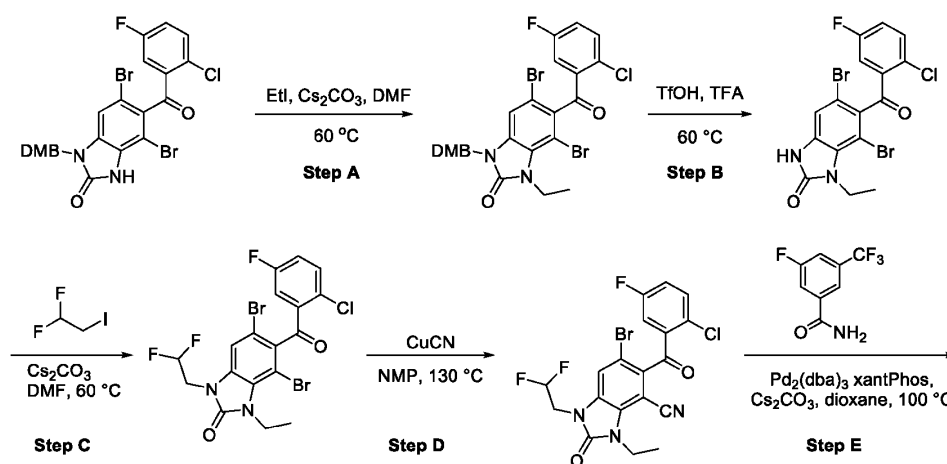
[00384] **Step C:** To a solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-3-methyl-2-oxo-1-(3,3,3-trifluoropropyl)benzo[d]imidazole-4-carbonitrile (25 mg, 0.050 mmol) in dioxane (1 mL) was added 3-fluoro-5-(trifluoromethyl)benzamide (13.8 mg, 0.063 mmol), xantphos (5.73 mg, 0.010 mmol), Cs₂CO₃ (48.42 mg, 0.149 mmol) and Pd₂(dba)₃ (4.54 mg, 0.005 mmol). The reaction mixture was stirred at 110 °C under N₂ for 2h. LCMS showed the reaction was completed. The mixture was poured in water (5 mL), extracted with EtOAc (5 mL*2). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo and purified by p-TLC (SiO₂, PE: EtOAc=2: 1) to give N-(6-(2-chloro-5-fluorobenzoyl)-7-cyano-1-methyl-2-oxo-3-(3,3,3-trifluoropropyl)-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (25 mg, 0.032 mmol, 64%) as yellow oil. LCMS: ESI *m/z* 631 [*M* + *H*]⁺.

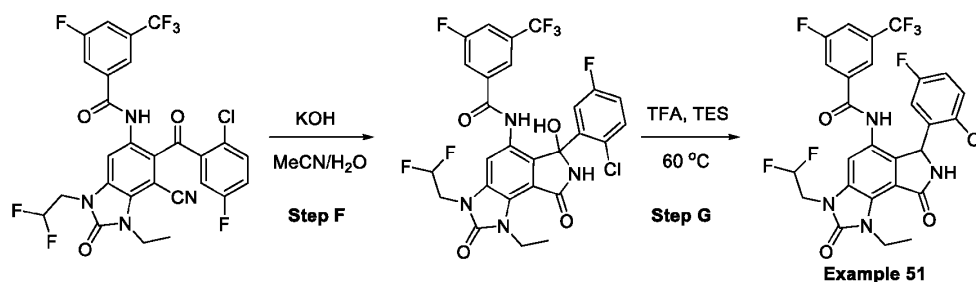
[00385] **Step D:** To a solution of N-(6-(2-chloro-5-fluorobenzoyl)-7-cyano-1-methyl-2-oxo-3-(3,3,3-trifluoropropyl)-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (25 mg, 0.040 mmol) in MeCN (2 mL) and H₂O (0.5 mL) was

added KOH (6.67 mg, 0.119 mmol). The reaction mixture was stirred at rt for 30 min. LCMS showed the reaction was completed. The mixture was poured in water (5 mL), extracted with EtOAc (5 mL*2). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo to give N-(6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-2,8-dioxo-3-(3,3,3-trifluoropropyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (15 mg, 47%) as yellow oil. LCMS: ESI m/z 649 [M+H]⁺.

[00386] **Step E:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-6-hydroxy-1-methyl-2,8-dioxo-3-(3,3,3-trifluoropropyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (15 mg, 0.023 mmol) in TFA (2 mL) was added triethylsilane (0.5 mL, 0.023 mmol). The reaction mixture was stirred at 70 °C for 15 min. LCMS showed the reaction was completed. The mixture was concentrated in vacuo and purified by prep-HPLC (TFA) to give N-(6-(2-chloro-5-fluorophenyl)-1-methyl-2,8-dioxo-3-(3,3,3-trifluoropropyl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (2.8 mg, 18%) as white solid. LCMS: ESI m/z 633 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.31 (s, 1H), 9.17 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.82 – 7.66 (m, 2H), 7.43 (s, 1H), 7.29 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.10 – 7.08 (m, 1H), 6.63 (brs, 1H), 6.00 (brs, 1H), 4.25 – 4.08 (m, 2H), 3.90 (s, 3H), 2.77 – 2.74 (m, 2H).

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





[00387] **Step A:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-[(2,4-dimethoxyphenyl) methyl]-2,3-dihydro-1H-benzo[d]imidazol-2-one (2 g, 3.34 mmol) in DMF (20 mL) was added iodoethane (1.04 g, 6.68 mmol) and Cs_2CO_3 (1.09 g, 3.34 mmol) at rt. After stirred at 60 °C for 2 h. The reaction was monitored by TLC. The cooled mixture was poured into water and extracted with EtOAc. The combined organic phase was washed with brine, dried with Na_2SO_4 , filtered and concentrated. The residue was purified by silica gel chromatography using 0 - 50% EtOAc/hexane to afford 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-[(2,4-dimethoxyphenyl) methyl]-3-ethyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (1.5 g, 2.39 mmol, 71%) as a yellow solid. LCMS: ESI m/z 626 $[\text{M} + \text{H}]^+$.

[00388] **Step B:** To a solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-[(2,4-dimethoxyphenyl) methyl]-3-ethyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (1.1 g, 1.755 mmol) in TFA (30 mL) was added TfOH (60 mg, 0.352 mmol). The mixture was stirred at 60 °C for 2 hours. The cooled mixture was concentrated under vacuum to remove TFA. The residue was poured into saturated NaHCO_3 and EA. The following mixture was filtrated to give 5,7-dibromo-6-[(2-chloro-5-fluorophenyl) carbonyl]-1-ethyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (800 mg, 1.679 mmol, 95%) as a purple solid. LCMS: ESI m/z 476 $[\text{M} + \text{H}]^+$.

[00389] **Step C:** To a stirred solution of 5,7-dibromo-6-[(2-chloro-5-fluorophenyl) carbonyl]-1-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (100 mg, 0.216 mmol) in DMA (20 mL) was added 1-fluoro-3-iodopropane (73.2 mg, 0.389 mmol) and Cs_2CO_3 (1846 mg, 5.66 mmol) at rt. After stirred at 70 °C for 3h, the cooled mixture was poured into water (40 mL) and extracted with EtOAc (30 mL*3). 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 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-

(2,2-difluoroethyl)-3-ethyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (600 mg, 1.110 mmol, 58%) as a white solid. LCMS: m/z 539 [M+H]⁺.

[00390] **Step D:** To a stirred solution of 4,6-dibromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2,2-difluoroethyl)-3-ethyl-2,3-dihydro-1H-benzo[d]imidazol-2-one (600 mg, 1.110 mmol) in NMP (6 mL) was added NMP (6 mL) at rt. After stirred at 130 °C for 2 h, the mixture was poured into 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 residue was purified by chromatography (silica gel, 0-30%, EtOAc in PE) to give 6-bromo-5-[(2-chloro-5-fluorophenyl) carbonyl]-1-(2,2-difluoroethyl)-3-ethyl-2-oxobenzo[d]imidazole-4-carbonitrile (200 mg, 0.411 mmol, 37.0%) as a white solid. LCMS: m/z 486 [M+H]⁺

[00391] **Step E:** To a stirred solution of 6-bromo-5-[(2-chloro-5-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-3-ethyl-2-oxobenzo[d]imidazole-4-carbonitrile (150 mg, 0.308 mmol) in dioxane (5 mL) was added 3-fluoro-5-(trifluoromethyl)benzene-1-carboxamide (96 mg, 0.462 mmol), Pd₂(dba)₃ (28 mg, 0.031 mmol), Cs₂CO₃ (201 mg, 0.616 mmol) and Xant-PHOS (36 mg, 0.062 mmol) at rt. After stirred at 100 °C under N₂ for 2h, the mixture was poured into 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 residue was purified by chromatography (silica gel, 0-50%, EtOAc in PE) to give N-{6-[(2-chloro-5-fluorophenyl) carbonyl]-7-cyano-3-(2,2-difluoroethyl)-1-ethyl-2-oxobenzo[d]imidazol-5-yl}-5-fluoro-3-(trifluoromethyl) benzamide (150 mg, 0.245 mmol, 79%) as a brown oil. LCMS: m/z 614 [M+H]⁺.

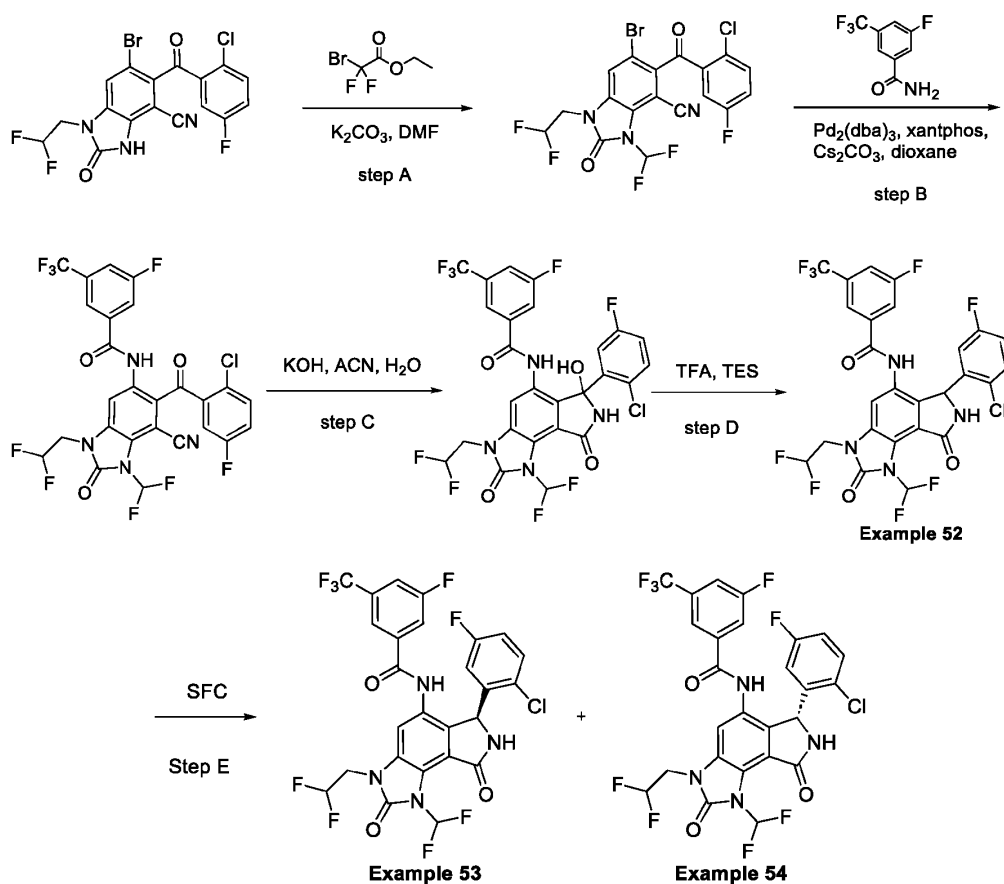
[00392] **Step F:** To a stirred solution of N-{6-[(2-chloro-5-fluorophenyl) carbonyl]-7-cyano-3-(2,2-difluoroethyl)-1-ethyl-2-oxobenzo[d]imidazol-5-yl}-3-fluoro-5-(trifluoromethyl) benzamide (200 mg, 0.326 mmol) in ACN (5 mL) and H₂O (1 mL) was added potassium hydroxide (91 mg, 1.632 mmol) at rt. After stirred at rt for 1h, the mixture was poured into 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 residue was purified by chromatography (silica gel, 0-10%, DCM in MeOH) to give N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-ethyl-6-hydroxy-2,8-dioxo-7,8-dihydro-6H-imidazo[5,4-e] isoindol-5-yl]-3-fluoro-5-(trifluoromethyl) benzamide (110 mg, 0.174 mmol, 53%) as a white oil. LCMS: m/z 631 [M+H]⁺.

[00393] **Step G:** To a stirred solution of N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-ethyl-6-hydroxy-2,8-dioxo-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (100 mg, 0.159 mmol) in TFA (3 mL) was added Et₃SiH (92.1 mg, 0.793 mmol) at rt. After stirred at 60 °C for 1h, 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 prep-HPLC (C18, 40 ~ 90 % MeCN in H₂O with 0.1 % TFA) to give N-[6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-ethyl-2,8-dioxo-7,8-dihydro-6H-imidazo[5,4-e]isoindol-5-yl]-3-fluoro-5-(trifluoromethyl)benzamide (18.5 mg, 0.030 mmol, 18%) as a white solid. LCMS: m/z 615 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.35 (s, 1H), 9.18 (s, 1H), 7.96 – 7.88 (m, 1H), 7.80 – 7.68 (m, 2H), 7.42 (s, 1H), 7.2 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.17 – 7.01 (m, 1H), 6.77 – 6.22 (m, 2H), 6.02 (brs, 1H), 4.65 – 4.48 (m, 2H), 4.47 – 4.14 (m, 2H), 1.28 (t, *J* = 6.8 Hz, 3H).

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

Example 53: (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-(difluoromethyl)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide

Example 54: (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-(difluoromethyl)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00394] **Step A:** To a solution of 6-bromo-5-[(2-chloro-4-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-2-oxo-3H-benzo[d]imidazole-4-carbonitrile (300 mg, 0.654 mmol) in DMF (6 mL) was added K_2CO_3 (181 mg, 1.31 mmol) and methyl 2-bromo-2,2-difluoroacetate (185 mg, 0.981 mmol). The reaction mixture was stirred at 80 °C for 16 h. The cooled 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 triturated with EA: PE=1: 5 to afford 6-bromo-5-[(2-chloro-4-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-3-(difluoromethyl)-2-oxobenzo[d]imidazole-4-carbonitrile (170 mg, 0.334 mmol, 51%) as a brown solid. LCMS: ESI m/z 510.1 $[M + H]^+$.

[00395] **Step B:** A solution of 6-bromo-5-[(2-chloro-4-fluorophenyl)carbonyl]-1-(2,2-difluoroethyl)-3-(difluoromethyl)-2-oxobenzo[d]imidazole-4-carbonitrile (80 mg, 0.158 mmol), 5-fluoro-3-(trifluoromethyl)benzene-1-carboxamide (32.6 mg, 0.158 mmol), $Pd_2(dba)_3$ (14.4 mg, 16 μ mol), xantphos (18.22 mg, 32 μ mol), Cs_2CO_3 (154 mg, 0.473 mmol) in dioxane (4 mL) was

stirred at 100 °C for 2 h. The reaction mixture was concentrated in vacuo. The residue was purified using silica gel column chromatography eluted with MeOH in DCM (gradient: 0 ~ 10%) to afford N-(6-(2-chloro-5-fluorobenzoyl)-7-cyano-3-(2,2-difluoroethyl)-1-(difluoromethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (80 mg, 0.126 mmol, 80%) as a brown solid. (crude). LCMS: ESI m/z 635.1 [M + H]⁺.

[00396] **Step C:** To a solution of N-(6-(2-chloro-5-fluorobenzoyl)-7-cyano-3-(2,2-difluoroethyl)-1-(difluoromethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (100 mg, 0.158 mmol) in ACN (2 mL) and H₂O (0.2 mL) was added KOH (44.3 mg, 0.789 mmol). The reaction mixture was stirred at rt for 30 min. The mixture was diluted with water (10 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 N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-(difluoromethyl)-6-hydroxy-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (80 mg, 0.123 mmol, 78%) as a brown solid. LCMS: ESI m/z 653.2 [M – H]⁺.

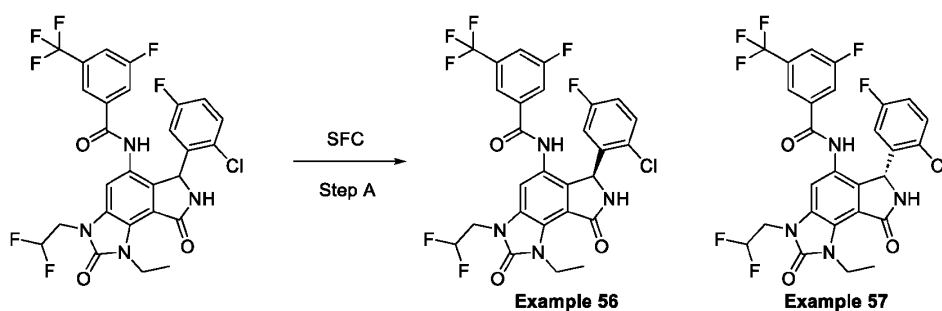
[00397] **Step D:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-(difluoromethyl)-6-hydroxy-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (15 mg, 23 μmol) in TFA (1 mL) was added Et₃SiH (0.2 mL). The reaction mixture was stirred at 60 °C for 30 min. The reaction mixture was concentrated to give a residue. The residue was purified by pre-HPLC to give N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-(difluoromethyl)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (4.3 mg, 7 μmol, 29%) as a white solid. LCMS: ESI m/z 637.0 [M + H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 9.11 (t, *J* = 56.0 Hz, 1H), 7.70 – 7.62 (m, 3H), 7.47 (s, 1H), 7.27 – 7.24 (m, 1H), 7.02 – 6.98 (m, 1H), 6.63 (brs, 1H), 6.39 – 6.10 (m, 2H), 4.45 – 4.35 (m, 2H).

[00398] **Step E:** N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-(difluoromethyl)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (120 mg, 0.19 mmol) was purified with SFC method 13 to afford (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-(difluoromethyl)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (26.3 mg, 0.041 mmol, 44%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.46 (s, 1H), 9.55 (s, 1H), 9.14 (t, *J* = 56.0 Hz, 1H), 7.98 – 7.89 (m, 1H), 7.79 – 7.72 (m, 1H), 7.70 (s, 1H), 7.51 (s, 1H), 7.36 –

7.24 (m, 1H), 7.15 – 7.05 (m, 1H), 6.93 – 6.63 (m, 1H), 6.59 – 6.24 (m, 1H), 6.20 – 5.93 (m, 1H), 4.53 – 4.31 (m, 2H). (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-(difluoromethyl)-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (26.8 mg, 0.042 mmol, 45%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.46 (s, 1H), 9.55 (s, 1H), 9.14 (t, *J* = 56.0 Hz, 1H), 7.98 – 7.89 (m, 1H), 7.79 – 7.72 (m, 1H), 7.70 (s, 1H), 7.51 (s, 1H), 7.36 – 7.24 (m, 1H), 7.15 – 7.05 (m, 1H), 6.93 – 6.63 (m, 1H), 6.59 – 6.23 (m, 1H), 6.20 – 5.93 (m, 1H), 4.54 – 4.31 (m, 2H).

Example 56: (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-ethyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide

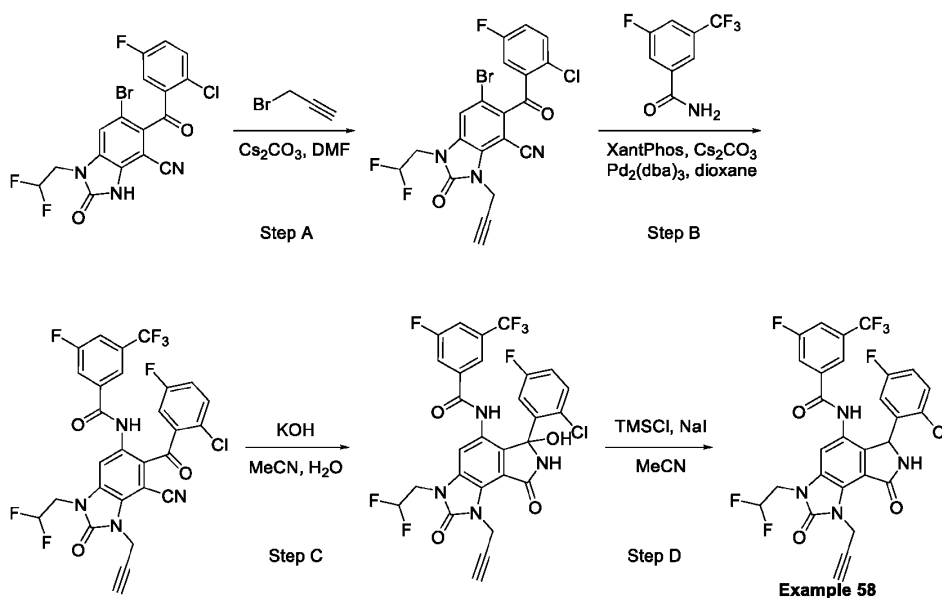
Example 57: (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-ethyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00399] **Step A:** N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-ethyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (16.3 mg, 0.03 mmol) was purified with SFC method 14 to afford (S)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-ethyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (5.2 mg, 0.01 mmol, 64%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.34 (s, 1H), 9.17 (s, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.77 – 7.66 (m, 2H), 7.41 (s, 1H), 7.33 – 7.25 (m, 1H), 7.13 – 7.04 (m, 1H), 6.77 – 5.73 (m, 3H), 4.64 – 4.49 (m, 2H), 4.46 – 4.31 (m, 2H), 1.31 – 1.25 (m, 3H). (R)-N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-1-ethyl-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (5.3 mg, 0.01 mmol, 65%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.34 (s, 1H), 9.17 (s, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.77 – 7.66 (m, 2H), 7.41 (s,

1H), 7.33 – 7.25 (m, 1H), 7.13 – 7.04 (m, 1H), 6.77 – 5.73 (m, 3H), 4.64 – 4.49 (m, 2H), 4.46 – 4.31 (m, 2H), 1.31 – 1.25 (m, 3H).

Example 58: N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-1-(prop-2-yn-1-yl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide



[00400] **Step A:** To a solution of 6-bromo-5-(2-chloro-5-fluorobenzoyl)-1-(2,2-difluoroethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (1 g, 2.18 mmol) in DMF (10 mL) was added 3-bromoprop-1-yne (0.29 g, 2.40 mmol) and Cs_2CO_3 (1.42 g, 4.36 mmol). The reaction mixture was stirred at 60 °C for 2 h. The mixture was diluted with H_2O , extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel flash chromatography eluted with 0 – 50% ethyl acetate in petroleum ether to afford 6-bromo-5-(2-chloro-5-fluorobenzoyl)-1-(2,2-difluoroethyl)-2-oxo-3-(prop-2-yn-1-yl)-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (0.9 g, 1.81 mmol, 83%) as a yellow solid. LCMS: ESI m/z 495.8/497.8 $[\text{M} + \text{H}]^+$.

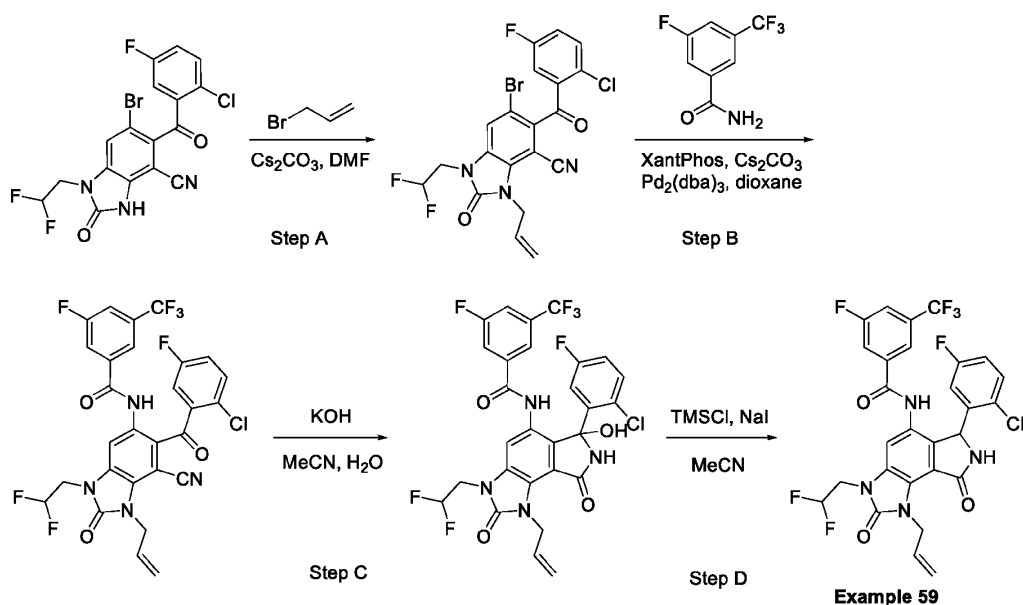
[00401] **Step B:** A solution of 6-bromo-5-(2-chloro-5-fluorobenzoyl)-1-(2,2-difluoroethyl)-2-oxo-3-(prop-2-yn-1-yl)-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (300 mg, 0.60 mmol), 3-fluoro-5-(trifluoromethyl)benzamide (150 mg, 0.72 mmol), $\text{Pd}_2(\text{dba})_3$ (55 mg, 0.06 mmol), XantPhos (70 mg, 0.12 mmol), Cs_2CO_3 (394 mg, 1.21 mmol) in dioxane (10 mL) was purged

with nitrogen three times and stirred at 100 °C for 2 h. The cooled mixture was filtered, and the filter cake was washed with EtOAc. The filtrate was concentrated and the residue was purified by silica gel flash chromatography, eluted with a gradient of 0 -100 % ethyl acetate in petroleum ether to afford N-(6-(2-chloro-5-fluorobenzoyl)-7-cyano-3-(2,2-difluoroethyl)-2-oxo-1-(prop-2-yn-1-yl)-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (150 mg, 0.24 mmol, 40%) as a yellow solid. LCMS: ESI m/z 623.0 [M + H]⁺.

[00402] **Step C:** To a stirred mixture of N-(6-(2-chloro-5-fluorobenzoyl)-7-cyano-3-(2,2-difluoroethyl)-2-oxo-1-(prop-2-yn-1-yl)-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (150 mg, 0.24 mmol) in MeCN (2 mL) and H₂O (0.5 mL) was added KOH (68 mg, 1.20 mmol), and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with EtOAc, washed with brine, and organic layer was separated. The aqueous layer was extracted with EtOAc, then the combined extracts were dried over anhydrous MgSO₄, filtered and evaporated. The crude product was purified by flash silica chromatography, eluting with a gradient of 0~100% EtOAc in petroleum ether to afford N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-6-hydroxy-2,8-dioxo-1-(prop-2-yn-1-yl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (110 mg, 0.17 mmol, 71%) as a yellow solid. LCMS: ESI m/z 641.4 [M + H]⁺.

[00403] **Step D:** To a solution of N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-6-hydroxy-2,8-dioxo-1-(prop-2-yn-1-yl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (50 mg, 0.08 mmol) in MeCN (2 mL) were added NaI (59 mg, 0.39 mmol) and TMSCl (42 mg, 0.39 mmol). The reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated to give a residue. The residue was purified by pre-HPLC to give N-(6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-2,8-dioxo-1-(prop-2-yn-1-yl)-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (7 mg, 0.01 mol, 14%) as a yellow solid. LCMS: ESI m/z 625.0 [M + H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.77 – 7.57 (m, 3H), 7.42 (s, 1H), 7.25 (dd, *J* = 8.8, 5.0 Hz, 1H), 6.99 (td, *J* = 8.2, 3.0 Hz, 1H), 6.57 – 6.07 (m, 2H), 5.56 (dd, *J* = 17.2, 2.4 Hz, 1H), 5.45 (dd, *J* = 17.2, 2.4 Hz, 1H), 4.39 (td, *J* = 15.0, 3.2 Hz, 2H), 2.67 (s, 1H).

Example 59: N-(1-allyl-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



[00404] **Step A:** To a solution of 6-bromo-5-(2-chloro-5-fluorobenzoyl)-1-(2,2-difluoroethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (1 g, 2.18 mmol) in DMF (10 mL) was added 3-bromoprop-1-ene (286 mg, 2.40 mmol) and Cs_2CO_3 (1.42 g, 4.36 mmol). The reaction mixture was stirred at 50 °C for 2 h. The mixture was diluted with H_2O , extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel flash chromatography eluted with 0 – 50% ethyl acetate in petroleum ether to afford 3-allyl-6-bromo-5-(2-chloro-5-fluorobenzoyl)-1-(2,2-difluoroethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (0.9 g, 1.81 mmol, 83%) as a yellow solid. LCMS: ESI m/z 497.9/499.9 $[\text{M} + \text{H}]^+$.

[00405] **Step B:** A solution of 3-allyl-6-bromo-5-(2-chloro-5-fluorobenzoyl)-1-(2,2-difluoroethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile (100 mg, 0.26 mmol), 3-fluoro-5-(trifluoromethyl)benzamide (50 mg, 0.24 mmol), $\text{Pd}_2(\text{dba})_3$ (18 mg, 0.02 mmol), XantPhos (23 mg, 0.04 mmol), Cs_2CO_3 (131 mg, 0.40 mmol) in dioxane (5 mL) was purged with nitrogen three times and stirred at 100 °C for 2 h. The cooled mixture was filtered and the filter cake was washed with EtOAc. The filtrate was concentrated and the residue was purified by silica gel flash chromatography, eluted with a gradient of 0 -100 % ethyl acetate in petroleum ether to afford N-(1-allyl-6-(2-chloro-5-fluorobenzoyl)-7-cyano-3-(2,2-difluoroethyl)-2-oxo-2,3-

dihydro-1H-benzo[d]imidazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (80 mg, 0.13 mmol, 63%) as a yellow solid. LCMS: ESI m/z 625.0 $[M + H]^+$.

[00406] **Step C:** To a stirred mixture of N-(1-allyl-6-(2-chloro-5-fluorobenzoyl)-7-cyano-3-(2,2-difluoroethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (80 mg, 0.13 mmol) in MeCN (2 mL) and H₂O (0.5 mL) was added KOH (36 mg, 0.64 mmol), and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with EtOAc, washed with brine, and organic layer was separated. The aqueous layer was extracted with EtOAc, then the combined extracts were dried over anhydrous MgSO₄, filtered and evaporated to afford N-(1-allyl-6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-6-hydroxy-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (60 mg, 0.09 mmol, 73%) as a yellow solid. LCMS: ESI m/z 643.0 $[M + H]^+$.

[00407] **Step D:** To a solution of N-(1-allyl-6-(2-chloro-5-fluorophenyl)-3-(2,2-difluoroethyl)-6-hydroxy-2,8-dioxo-1,2,3,6,7,8-hexahydroimidazo[4,5-e]isoindol-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide (60 mg, 0.09 mmol) in MeCN (2 mL) were added NaI (70 mg, 0.47 mmol) and TMSCl (51 mg, 0.47 mmol). The reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated to give a residue. The residue was purified by pre-HPLC to give N-(1-allyl-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 (33 mg, 0.05 mol, 56%) as a yellow solid. LCMS: ESI m/z 627.0 $[M + H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.35 (s, 1H), 9.17 (s, 1H), 7.94 (d, J = 8.3 Hz, 1H), 7.80 – 7.63 (m, 2H), 7.43 (s, 1H), 7.28 (dd, J = 8.9, 5.0 Hz, 1H), 7.13 – 7.05 (m, 1H), 6.56 – 5.92 (m, 3H), 5.32 – 5.20 (m, 1H), 5.17 – 5.08 (m, 2H), 5.06 – 4.89 (m, 1H), 4.56 – 4.29 (m, 2H).

PI3K α enzymatic ADP-Glo assay

Table 2. Materials

Reagent/Material	Source	Cat. No.	Lot. No.
PI3K α (WT)	Invitrogen	PV4788	616250A
PI3K α (H1047R)	Carna	11-415-20N	20CBS-0866 C
PI3K α (E545K)	Carna	11-414-20N	20CBS-0402 C
PI3K α (E542K)	Carna	11-413-20N	20CBS-0488 C
ADP-Glo Kinase Assay	Promega	v9102/3	314795

PIP2:PS	Invitrogen	PR8982B	2533745B
HEPES, pH7.5	Gibco	11344-041	1653630
CHAPS	Sigma	C3023-25G	050M5300V
MgCl ₂	Sigma	M2670-500g	BCBM7703V
DTT	Sigma	D0632-10G	SLBK4951V
EGTA	Sigma	E3889-100G	SLBG8546V
384 well Echo plate	Labcyte	PP-0200	6386422
PROXIPLATE-384 PLUS	Revvity	6008289	8310-19401

Table 3. Instruments

Instrument	Model	Manufacturer	SN
Precision	PRC384U	BioTek	214145
Centrifuge	Avanti J-15R	BECKMAN COULTRE	JBR20A055
Acoustic Liquid Handler	Echo650	LABCYTE	E6XX-21146
Envision	2104 Multilabel Reader	Perkin Elmer	1041604

[00408] 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 μ L 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.

[00409] Results of the ADP-Glo Biochemical PI3K α enzymatic assays using PI3K α H1047R, E545K, E542K and WT enzymes are presented in **Table 4**. 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 4. 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	C	D	C	C
Example 3	A	A	A	B
Example 4	C	C	C	C
Example 5	C	C	C	C
Example 6	A	A	A	B
Example 7	A	A	A	C
Example 8	C	C	C	D
Example 9	A	A	A	A
Example 10	A	A	A	B
Example 11	C	C	C	C
Example 12	A	A	A	B
Example 13	A	A	A	B
Example 14	A	A	A	B
Example 15	A	A	A	B
Example 16	A	A	A	B
Example 17	A	A	A	B
Example 18	A	A	A	B
Example 19	A	A	A	B
Example 20	D	C	D	D
Example 21	A	A	A	A
Example 22	A	A	A	C
Example 23	A	A	A	C
Example 24	B	A	B	C
Example 25	A	A	A	B

Example 26	C	D	D	D
Example 27	A	A	A	A
Example 28	D	D	D	D
Example 29	A	A	A	A
Example 30	C	D	D	C
Example 31	A	A	A	A
Example 32	A	A	A	B
Example 33	D	C	C	C
Example 34	A	A	A	B
Example 35	A	A	A	B
Example 36	A	A	A	B
Example 37	D	D	C	D
Example 38	A	A	A	A
Example 39	A	A	A	B
Example 40	A	A	A	B
Example 41	A	A	A	B
Example 43	A	A	A	B
Example 44	C	C	C	D
Example 45	C	C	C	D
Example 46	A	A	A	B
Example 47	A	A	A	B
Example 48	A	A	A	B
Example 49	A	A	A	A
Example 50	A	A	A	B
Example 51	A	A	A	B
Example 52	A	A	A	B
Example 53	C	C	C	D
Example 54	A	A	A	B
Example 56	D			
Example 57	A			
Example 58	A			
Example 59	A			

Material and instrument information for cellular assays**Table 5. Materials**

Reagents/Material	Vendor	Catalog	Lot Number
FBS	BI	04-002-1A	2144325
Penicillin-Streptomycin solution	Hyclone	SV30010	J170012
0.25%Trypsine-EDTA	Invitrogen	25200072	2360145
96-well plate	Corning	3903	09423049
384-well plate	Corning	3765	35423032
DMSO	SIGMA	D4540-1L	BCCG0991
Phospho-AKT1/2/3 (Ser473) cellular kit	Perkin Elmer	64AKSPEH	-
RPMI 1640	Invitrogen	11875085	2449512
CellTiter-Glo Luminescent Cell Viability Assay	Promega	G7573	0000584202
DMEM/F-12(1:1)	Invitrogen	11320033	2458377
Insulin, Human Recombinant Zinc	Invitrogen	12585014	2451711
Insulin - Transferrin-Selenium-X	Invitrogen	51500056	2415099
Insulin - Transferrin-Selenium	Invitrogen	41400045	2423505
Glutamax	Invitrogen	35050061	2523109
Hydrocortisone	SIGMA	H08881G	061M1140V
Beta-estradiol	SIGMA	E2758-1G	-

Table 6. Instruments

Instrument	Model	Vendor	Serial number
CO ₂ Incubator	3111	Thermo	300557319
Cell Counter	Vi-CELL XR	Beckman	BF04081
Plate reader Envision	EnVision 2105	PerkinElmer	2301000507MDF-86V690D(AD)
Vortex finder	S0200-230V-EU	Labnet	NA
Centrifuge	Sorvall ST4R Plus	Thermo	42899760
D300e Digital Dispenser	D300e	Tecan	SG23Q12002

HTRF PHOSPHO-AKT (SER473) assay

[00410] HCC1954 cells (American Type Culture Collection, Catalog#: CRL-2338, Lot #: 70032967) 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 RPMI1640 culture medium with 10%FBS. 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.

[00411] Data analysis: Calculate the ratio of the acceptor and donor emission signals for each individual well.

$$\text{Ratio} = \frac{\text{Signal 665 nm}}{\text{Signal 620 nm}} \times 10^4$$

Cell Proliferation Assay

[00412] NCIH1048 cells (American Type Culture Collection, Catalog#: CRL-5853, Lot #: 70026468) 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.

[00413] 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.

[00414] XLfit software (Fit model: Dose response one site/ $\text{fit} = \frac{A + (B-A)}{1 + ((C/x)^D)}$) was used for curve fitting and IC₅₀ calculation.

[00415] Results of the HTRF pAKT assay on HCC1954 cell line and CTG cell proliferation assay on NCI-H1048 cell line are presented in **Table 7**. 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 uM are represented as “B”; Compounds having an IC₅₀ greater than 1 uM but less than 10 uM are represented as “C”; Compounds having an IC₅₀ greater than or equal to 10 uM are represented as “D”.

Table 7. Cellular Potency for Exemplary Compounds

Example #	HTRF pAKT IC ₅₀ HCC1954	CTG cell proliferation IC ₅₀ NCI-H1048
Example 1	A	A
Example 2	D	C
Example 3	A	A
Example 4	D	C
Example 5	C	C
Example 6	A	A
Example 7	A	A
Example 8	D	C
Example 9	A	A
Example 10	A	A
Example 11	C	B
Example 12	A	A
Example 13	A	A
Example 14	A	A
Example 15	A	A
Example 16	A	A
Example 17	A	A
Example 18	A	A
Example 19	A	A
Example 20	D	C
Example 21	A	A

Example 22	B	A
Example 23	B	A
Example 24	C	B
Example 25	A	A
Example 26	D	C
Example 27	A	A
Example 28	D	C
Example 29	A	A
Example 30	D	C
Example 31	A	A
Example 32	A	A
Example 33	D	D
Example 34	A	A
Example 35	C	B
Example 36	A	A
Example 37	D	C
Example 38	A	A
Example 39	A	A
Example 40	A	A
Example 41	A	A
Example 43	A	A
Example 44	C	C
Example 45	D	C
Example 46	A	A
Example 47	C	A
Example 48	A	A
Example 49	A	A
Example 50	A	A
Example 51	A	A
Example 52	A	A
Example 53	D	B
Example 54	A	A
Example 56	D	C
Example 57	A	A
Example 58	A	A
Example 59	A	A

[00416] 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.

[00417] 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.

[00418] 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.

[00419] 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

[00420] 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.

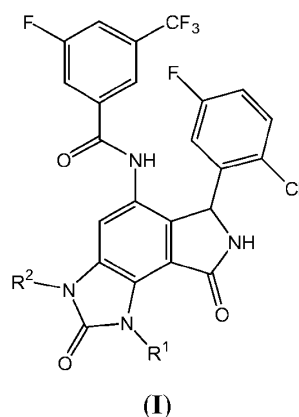
Equivalents

[00421] 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):

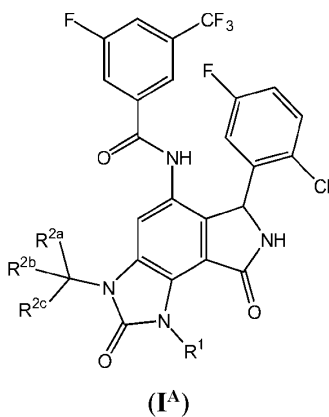


or a pharmaceutically acceptable form or an isotope derivative thereof,
wherein

each of R^1 and R^2 is independently a C_{1-6} alkyl, C_{2-5} alkenyl, or C_{2-5} alkynyl group, substituted with 0-8 R^A , wherein each R^A is independently D, halogen, CN, OR, SR, NRR' , an unsubstituted or substituted C_{3-6} carbocyclic or heterocyclic group, or an unsubstituted or substituted 5- or 6-membered aryl or heteroaryl group; and

each of R and R' is independently H, unsubstituted or substituted C_{1-4} alkyl, or unsubstituted or substituted 3- 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.

2. The compound of claim 1, wherein R^2 is $CR^{2a}R^{2b}R^{2c}$, having the structural formula (I^A):



wherein

R^{2a} is H, D or halogen;

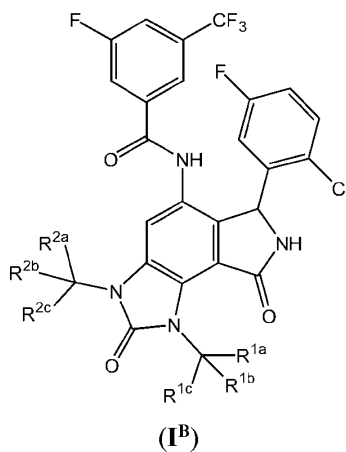
R^{2b} is H, D or halogen; and

R^{2c} is

H, D, halogen, CN, OR, SR, or NRR' ; or

an unsubstituted or substituted C_{1-5} alkyl, C_{3-6} carbocyclic or heterocyclic group, or 5- or 6-membered aryl or heteroaryl group.

3. The compound of claim 2, wherein R^1 is $CR^{1a}R^{1b}R^{1c}$, having the structural formula (**I^B**):



wherein

R^{1a} is H, D or halogen;

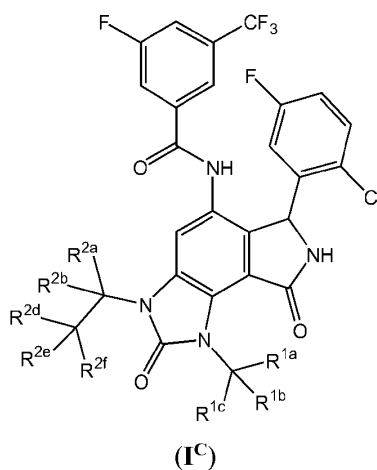
R^{1b} is H, D or halogen; and

R^{1c} is

H, D, halogen, CN, OR, SR, or NRR' ; or

an unsubstituted or substituted C_{1-5} alkyl, C_{3-6} carbocyclic or heterocyclic group, or 5- or 6-membered aryl or heteroaryl group.

4. The compound of claim 3, wherein R^{2c} is $CR^{2d}R^{2e}R^{2f}$, having the structural formula (**I^c**):



wherein

R^{2d} is H, D or halogen; and

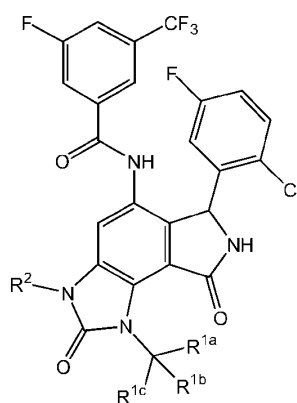
each of R^{2e} and R^{2f} is independently

H, D, halogen, CN, OR, SR, or NRR' ; or

an unsubstituted or substituted C_{1-5} alkyl, C_{3-6} carbocyclic or heterocyclic group, or 5- or 6-membered aryl or heteroaryl group.

5. The compound of any one of claims 2-4, wherein each of R^{2a} and R^{2b} is H.
6. The compound of any one of claims 2-4, wherein each of R^{2a} and R^{2b} is D.
7. The compound of any one of claims 4-6, wherein at least one of R^{2d} , R^{2e} and R^{2f} is a halogen atom.
8. The compound of claim 7, wherein one of R^{2d} , R^{2e} and R^{2f} is F.

9. The compound of claim 7, wherein two of R^{2d} , R^{2e} and R^{2f} is F.
10. The compound of claim 7, wherein each of R^{2d} , R^{2e} and R^{2f} is F.
11. The compound of any one of claims 4-6, wherein at least one of R^{2d} , R^{2e} and R^{2f} is a D.
12. The compound of claim 11, wherein one of R^{2d} , R^{2e} and R^{2f} is D.
13. The compound of claim 11, wherein two of R^{2d} , R^{2e} and R^{2f} is D.
14. The compound of claim 11, wherein each of R^{2d} , R^{2e} and R^{2f} is D.
15. The compound of any one of claims 1-14, wherein R^1 is CH_3 .
16. The compound of any one of claims 1-14, wherein R^1 is CD_3 .
17. The compound of any one of claims 1-14, wherein R^1 is not CH_3 .
18. The compound of any one of claims 1-14, wherein R^1 is not CD_3 .
19. The compound of claim 1, wherein R^1 is $CR^{1a}R^{1b}R^{1c}$, having the structural formula (**1P**):



(I^D)

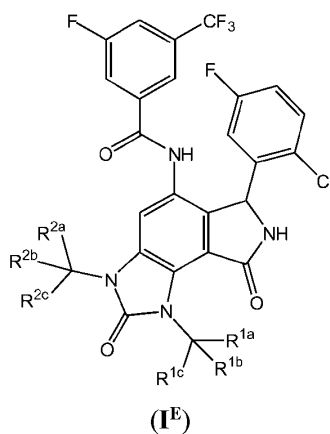
wherein

R^{1a} is H, D or halogen;R^{1b} is H, D or halogen; andR^{1c} is

H, D, halogen, CN, OR, SR, or NRR'; or

an unsubstituted or substituted C₁₋₅ alkyl, C₃₋₆ carbocyclic or heterocyclic group, or 5- or 6-membered aryl or heteroaryl group.

20. The compound of claim 19, wherein R² is CR^{2a}R^{2b}R^{2c}, having the structural formula (I^E):



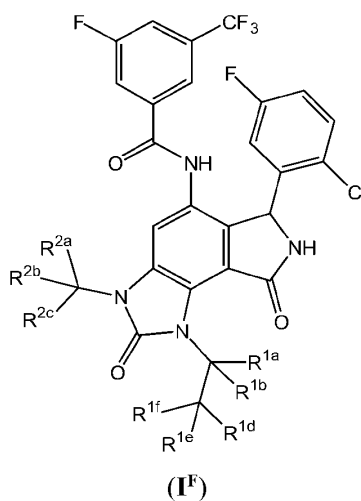
wherein

R^{2a} is H, D or halogen;R^{2b} is H, D or halogen; andR^{2c} is

H, D, halogen, CN, OR, SR, or NRR'; or

an unsubstituted or substituted C₁₋₅ alkyl, C₃₋₆ carbocyclic or heterocyclic group, or 5- or 6-membered aryl or heteroaryl group.

21. The compound of claim 20, wherein R^{1c} is CR^{1d}R^{1e}R^{1f}, having the structural formula (I^F):



wherein

R^{1d} is H, D or halogen; and

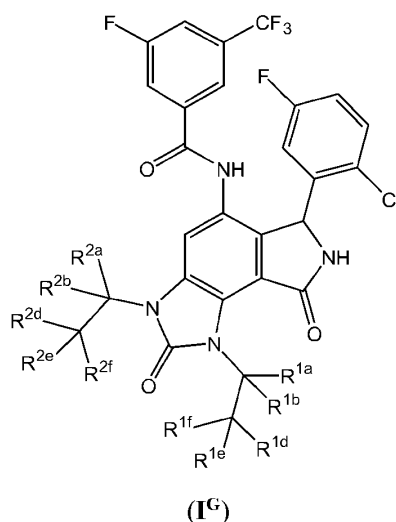
each of R^{1e} and R^{1f} is independently

H, D, halogen, CN, OR, SR, or NRR'; or

an unsubstituted or substituted C₁₋₅ alkyl, C₃₋₆ carbocyclic or heterocyclic group, or a 5- or 6-membered aryl or heteroaryl group.

22. The compound of any one of claims 19-21, wherein each of R^{1a} and R^{1b} is H.
23. The compound of any one of claims 19-21, wherein each of R^{1a} and R^{1b} is D.
24. The compound of claim 22, wherein R^{1c} is H.
25. The compound of claim 23, wherein R^{1c} is D.
26. The compound of any one of claims 21-23, wherein at least one of R^{1d}, R^{1e} and R^{1f} is a halogen atom.
27. The compound of claim 26, wherein one of R^{1d}, R^{1e} and R^{1f} is F.

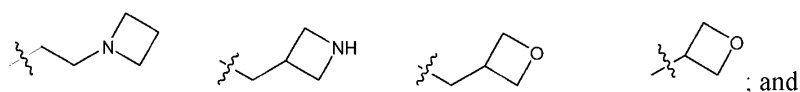
28. The compound of any one of claims 19-27, wherein R^2 is CH_3 or CD_3 .
29. The compound of any one of claims 19-27, wherein R^2 is not CH_3 or CD_3 .
30. The compound of claim 4 or 21, having the structural formula (I^G):



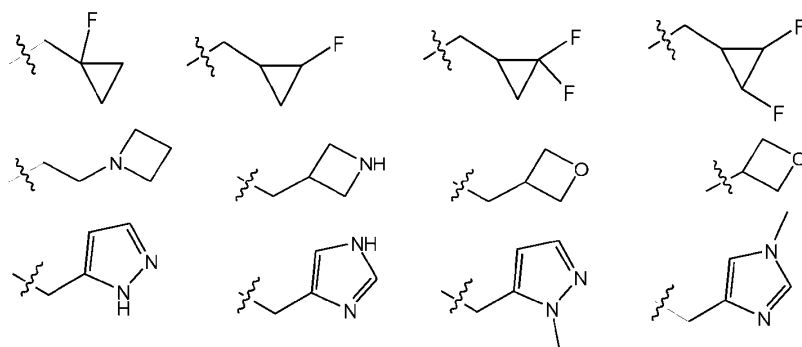
31. The compound of claim 30, wherein each of R^{2a} and R^{2b} is H.
32. The compound of claim 30, wherein each of R^{2a} and R^{2b} is D.
33. The compound of any one of claims 30-32, wherein at least one of R^{2d} , R^{2e} and R^{2f} is a halogen atom.
34. The compound of claim 33, wherein one of R^{2d} , R^{2e} and R^{2f} is F.
35. The compound of claim 33, wherein two of R^{2d} , R^{2e} and R^{2f} is F.
36. The compound of claim 33, wherein each of R^{2d} , R^{2e} and R^{2f} is F.
37. The compound of any one of claims 30-32, wherein at least one of R^{2d} , R^{2e} and R^{2f} is D.

38. The compound of claim 37, wherein one of R^{2d} , R^{2e} and R^{2f} is D.
39. The compound of claim 37, wherein two of R^{2d} , R^{2e} and R^{2f} is D.
40. The compound of claim 37, wherein each of R^{2d} , R^{2e} and R^{2f} is D.
41. The compound of any one of claims 30-40, wherein each of R^{1a} and R^{1b} is H.
42. The compound of any one of claims 30-40, wherein each of R^{1a} and R^{1b} is D.
43. The compound of claim 41 or 42, wherein each of R^{1d} , R^{1e} and R^{1f} is a H or D.
44. The compound of claim 1, wherein R^1 and R^2 are independently selected from:

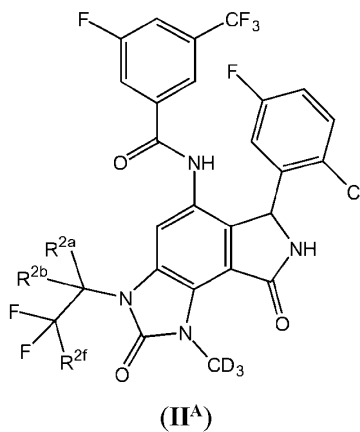
R^1 : CH_3 , CH_2D , CHD_2 , CD_3 , CH_2F , CHF_2 , CD_2F , CDF_2 , CF_3 , CH_2CH_3 , CD_2CH_3 , CH_2CD_3 , CD_2CD_3 , CH_2CN , $CH_2CH_2N(CH_3)_2$,



R^2 : CH_3 , CH_2D , CHD_2 , CD_3 , CH_2CH_3 , CH_2CH_2F , CD_2CH_2F , CH_2CD_2F , CD_2CD_3 , CD_2CD_2F , CH_2CHF_2 , CD_2CHF_2 , CH_2CDF_2 , CD_2CDF_2 , CH_2CF_3 , CD_2CF_3 , CH_2CN , $CH_2CH_2N(CH_3)_2$, CH_2CH_2OH , $CH_2CH_2OCH_3$, $CH_2CH_2CH_2F$, $CH_2CH_2CHF_2$, $CH_2CH_2CF_3$, propyl, isopropyl, n-butyl, isobutyl,



45. A compound of claim 1, having the structural formula (II^A):



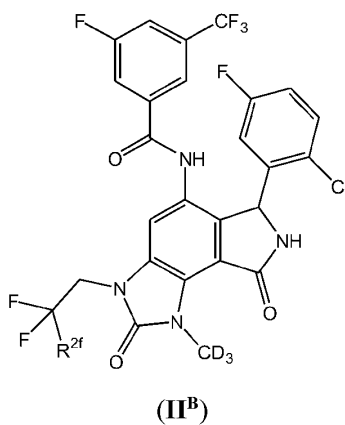
wherein

R^{2a} is H or D;

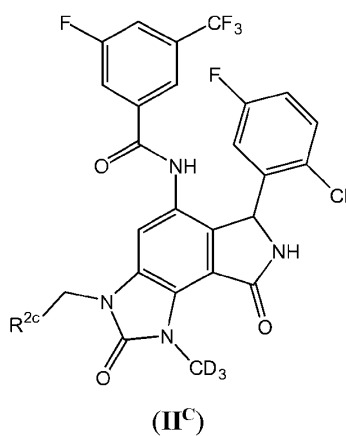
R^{2b} is H or D; and

R^{2f} is D, F, CN, OR, NRR', or an unsubstituted or substituted C₁₋₅ alkyl or C₃₋₅ carbocyclic or heterocyclic group.

46. The compound of claim 45, wherein each of R^{2a} and R^{2b} is H, having the structural formula (II^B):

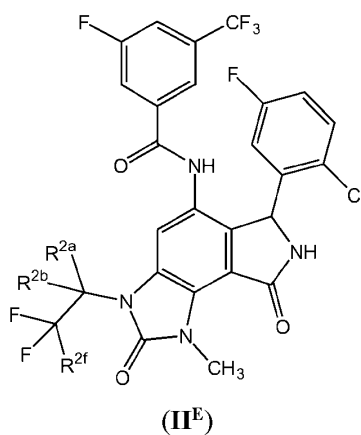


47. A compound of claim 1, having the structural formula (II^C):



wherein R^{2c} is CN, OR, SR, NRR', unsubstituted or substituted C₃₋₆ carbocyclic or heterocyclic group, or a 5- or 6-membered aryl or heteroaryl group.

48. A compound of claim 1, having the structural formula (II^E):



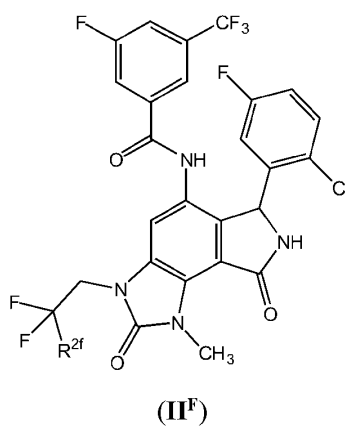
wherein

R^{2a} is H or D;

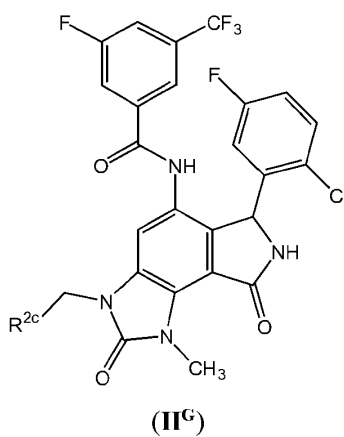
R^{2b} is H or D; and

R^{2f} is D, F, CN, OR, NRR', or an unsubstituted or substituted C₁₋₃ alkyl or C₃₋₅ carbocyclic or heterocyclic group.

49. The compound of claim 48, wherein each of R^{2a} and R^{2b} is H, having the structural formula (II^F):

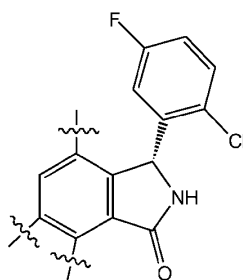


50. A compound of claim 1, having the structural formula (II^G):



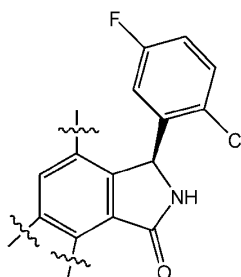
wherein R^{2c} is CN, OR, SR, NRR', unsubstituted or substituted C₃₋₆ carbocyclic or heterocyclic group, or a 5- or 6-membered aryl or heteroaryl group.

51. The compound of any one of claims 1-50, having the chirality shown in formula (III^A):



(III^A)

52. The compound of any one of claims 1-50, having the chirality shown in formula (III^B):

(III^B)

53. A compound selected from **Table 1**, or a pharmaceutically acceptable form or an isotope derivative thereof.
54. The compound of any of claims 1-53, having one or more deuterium atoms in place of hydrogen.
55. A pharmaceutical composition comprising a compound according to any one of claims 1-54 and a pharmaceutically acceptable excipient, carrier, or diluent.
56. The pharmaceutical composition of claim 55, being suitable for oral administration.
57. A unit dosage form comprising a pharmaceutical composition according to claim 55 or 56.
58. The unit dosage form of claim 57, being in the form of a tablet or capsule.
59. 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 1-54.
60. A method for modulating phosphoinositide 3-kinase α (PI3K α) activity in a cell,

comprising contacting the cell with a compound according to any one of claims 1-54.

61. A method for reducing phosphoinositide 3-kinase α (PI3K α) activity in a cell, comprising contacting the cell with a compound according to any one of claims 1-54.
62. 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 1-54.
63. The method of claim 62, wherein the disease or disorder is a cellular proliferative disease.
64. 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 1-54.
65. The method of claim 64, wherein the cancer is selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcoma, leukemia, neuroma, melanoma, and lymphoma.
66. The method of claim 64 or 65, 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.
67. The method of any one of claims 64-66, wherein the subject has a mutated class IA PI3K p110 α .
68. The method of any one of claims 64-67, wherein the subject has at least one of the following PI3K α mutations: H1047R, E542K, E545K and H1047X.
69. The method of any one of claims 64-68, wherein the subject being treated is further

administered one or more of chemotherapy, radiotherapy, targeted therapy, immunotherapy, and hormonal therapy.

70. Use of the compound according to any one of claims 1-54, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a disease or disorder.
71. The use of claim 70, wherein the disease or disorder is a cellular proliferative disease.
72. The use of claim 71, wherein the disease or disorder is cancer.
73. The use of claim 72, wherein the cancer is selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcoma, leukemia, neuroma, melanoma, and lymphoma.
74. The use of claim 72, 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.
75. The use of claim 72, wherein the cancer is selected from the group consisting of acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and glioblastomas.