CEREBLON-BASED KRAS DEGRADING PROTACS AND USES RELATED THERETO

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is claims priority to U.S. Provisional Application Serial No. 63/592,814 filed October 24, 2023, U.S. Provisional Application Serial No. 63/486,528 filed February 23, 2023, and U.S. Provisional Application Serial No. 63/481,672, filed January 26, 2023, which are hereby incorporated herein by reference in their entireties.

BACKGROUND

E3 ubiquitin ligases like Cereblon confer substrate specificity for ubiquitination, and therefore are more attractive therapeutic targets than general proteasome inhibitors due to their specificity for certain protein substrates. Bifunctional compounds, such as those described in U.S. Patent Application Publication Nos. 2015/0291562 and 2014/0356322 (both incorporated herein by reference), function to recruit endogenous proteins to an E3 ubiquitin ligase for ubiquitination and degradation. In particular, these publications describe bifunctional or proteolysis targeting chimeric compounds (PROTAC® protein degraders), which find utility as modulators of targeted ubiquitination of a variety of polypeptides and proteins, which are then degraded via the proteasome system. These bifunctional compounds function to recruit endogenous proteins to an E3 ubiquitin ligase for degradation. In particular, the publications describe bifunctional or proteolysis targeting chimeric (PROTAC) compounds, which find utility as modulators of targeted ubiquitination of a variety of polypeptides and other proteins, which are then degraded and/or otherwise inhibited by the bifunctional compounds.

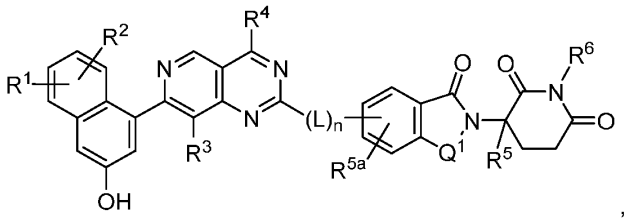
The Kirsten rat sarcoma (*KRAS*) gene is an oncogene encoding KRas, which is a small GTPase signal transduction protein. Ras proteins associate with the plasma membrane, and act as switches in the transduction of extracellular signals to intracellular response, thereby regulating, e.g., cell division. Numerous activating or gain-of-function mutations of the KRas gene are known, and in fact, KRas is the most frequently mutated gene in cancer. Gain-in-function KRas mutations are found in approximately 30% of all human cancers, including, e.g., pancreatic cancer (>80%), colon cancer (approximately 40–50%), lung cancer (approximately 30–50%), non-small cell lung cancer, biliary tract malignancies, endometrial cancer, cervical cancer, bladder cancer, liver cancer, myeloid leukemia, and breast cancer. These activating mutations impair the ability of KRas to switch between active and inactive states. Key roles for mutant KRas have been established in initiation, maintenance, progression, and metastasis of various cancers, and mutations are frequently correlated with poor prognosis and increased resistance to chemotherapy and biological therapies, including, e.g., therapies that target epidermal growth factor receptor. However, despite its key role and high rates prevalence in cancer, there is an absence of effective therapies that directly target this oncogene, leading to it being considered “undruggable.”

Thus, an ongoing need exists in the art for effective treatments for disease associated with overexpression, aggregation, and/or overactivation of KRas.

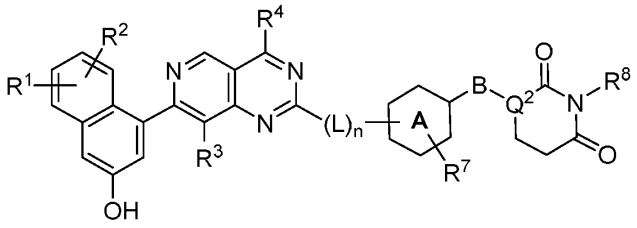
SUMMARY

Provided herein are compounds that target KRas and are thus useful in the treatment of cancer.

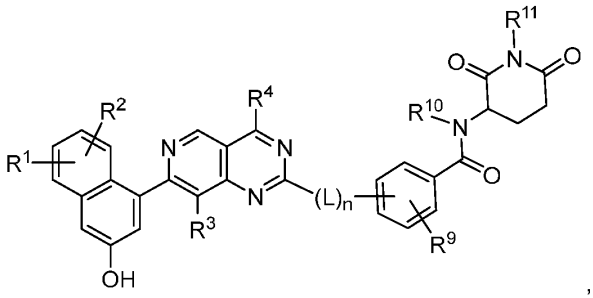
Provided herein are compounds of any one of Formula I–IV:



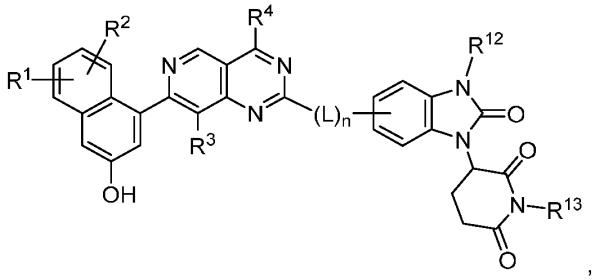
(I)



(II)



(III)

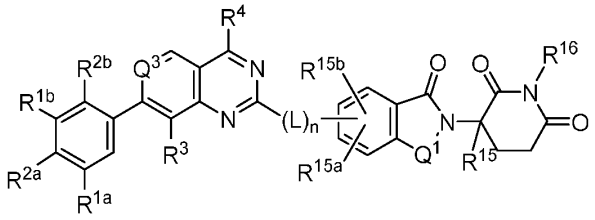


or

(IV)

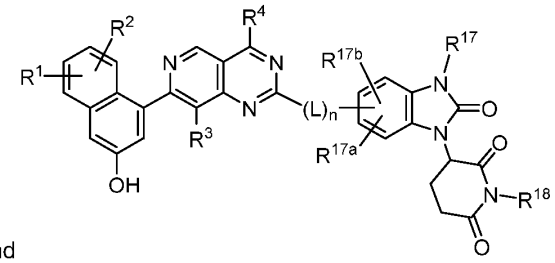
or a pharmaceutically acceptable salt thereof, wherein the variables are defined herein.

Also provided herein are compounds of Formula V and VI:



(V),

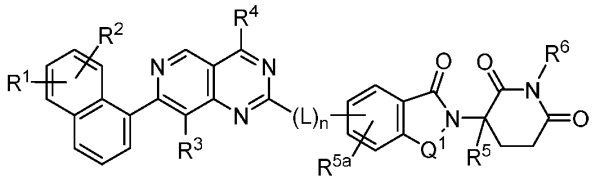
and



(VI)

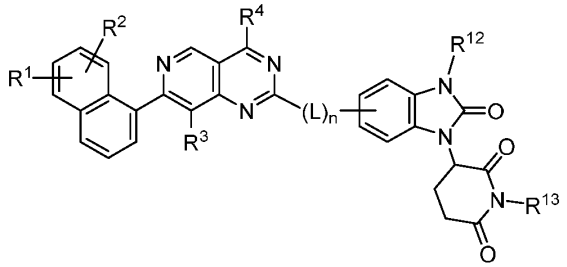
or a pharmaceutically acceptable salt thereof.

In an aspect, provided herein are compounds of Formula AI or AIV:



(AI)

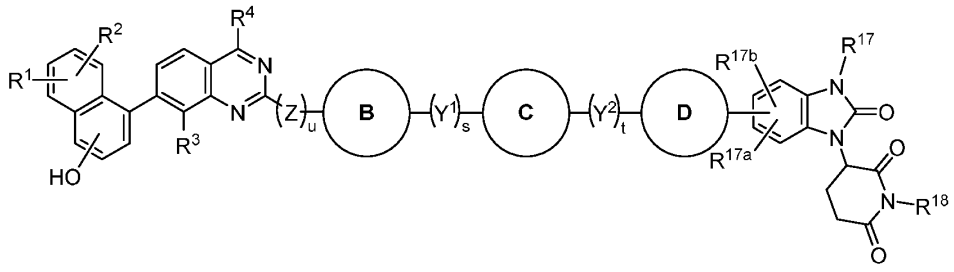
or



(AIV)

or a pharmaceutically acceptable salt thereof.

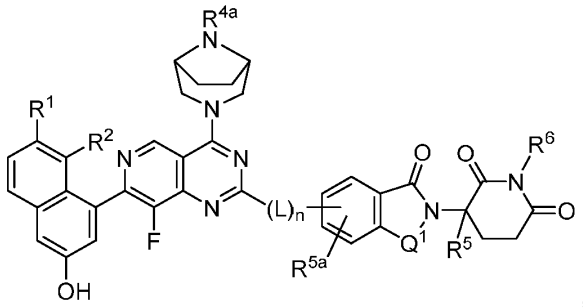
In another aspect, provided herein is a compound of Formula VII:



(VII)

or a pharmaceutically acceptable salt thereof.

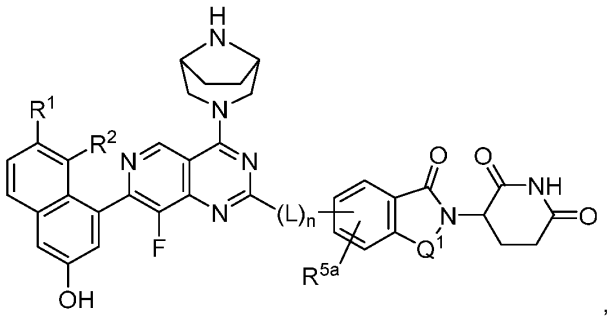
In embodiments, the compound of Formula I has a structure of Formula IA:



(IA)

or a pharmaceutically acceptable salt thereof.

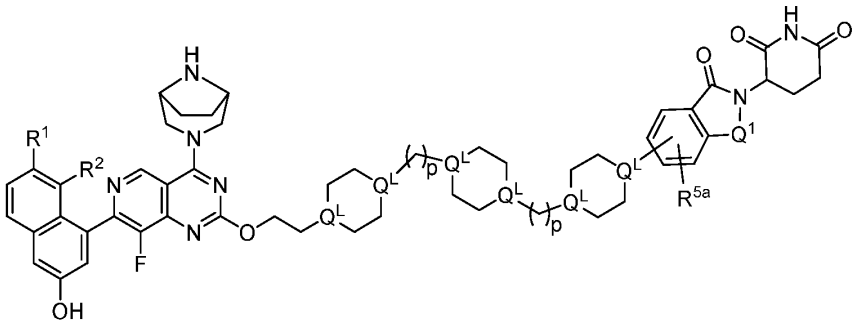
In embodiments, the compound of Formula I has a structure of Formula IB:



(IB)

or a pharmaceutically acceptable salt thereof.

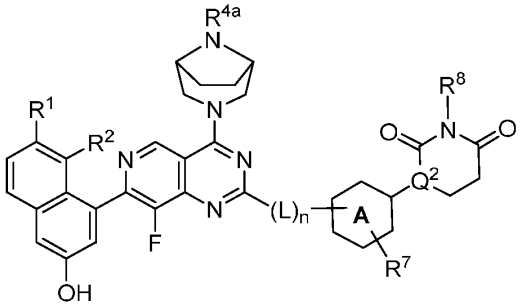
In embodiments, the compound of Formula I has a structure of Formula IB-i:



(IB-i)

or a pharmaceutically acceptable salt thereof.

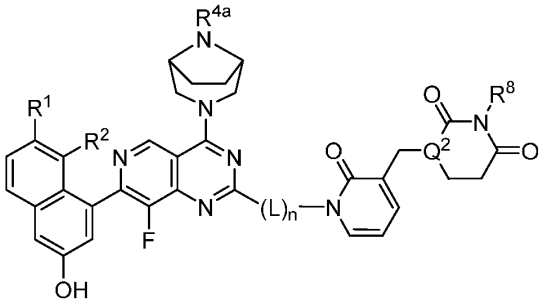
In embodiments, the compound of Formula II has a structure of Formula IIA:



(IIA)

or a pharmaceutically acceptable salt thereof.

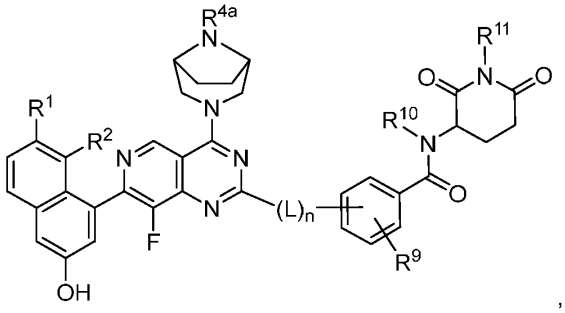
In embodiments, the compound of Formula II has a structure of Formula IIB:



(IIB)

or a pharmaceutically acceptable salt thereof.

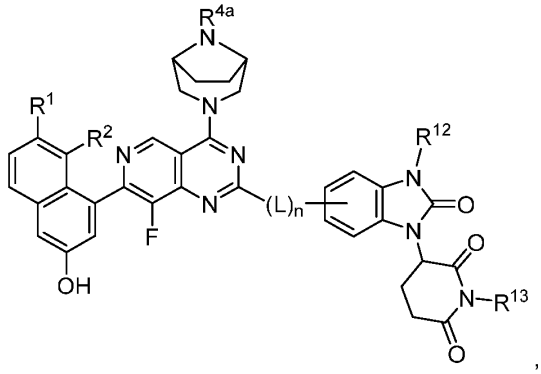
In embodiments, the compound of Formula III has a structure of Formula IIIA:



(IIIA)

or a pharmaceutically acceptable salt thereof.

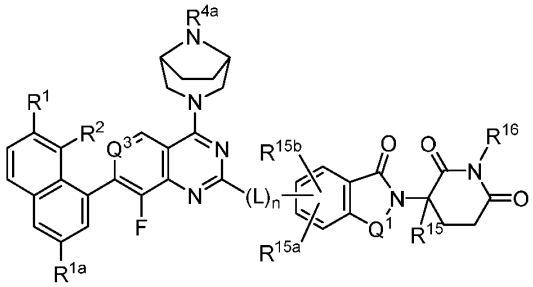
In embodiments, the compound of Formula IV has a structure of Formula IVA:



(IVA)

or a pharmaceutically acceptable salt thereof.

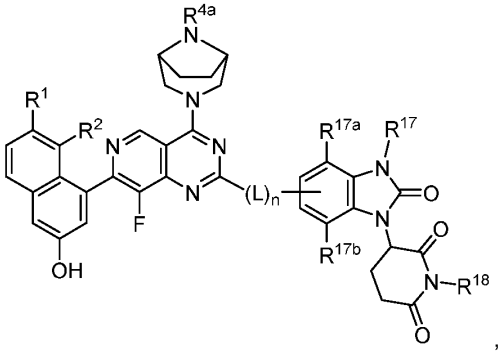
In embodiments, the compound of Formula V has a structure of Formula VA:



(VA)

or a pharmaceutically acceptable salt thereof.

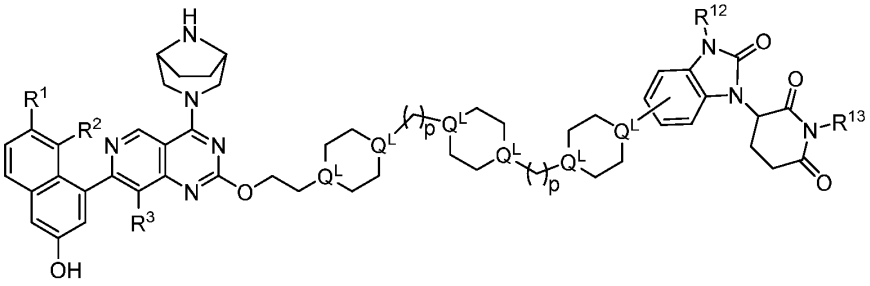
In embodiments, the compound of Formula VI has a structure of Formula VIA:



(VIA)

or a pharmaceutically acceptable salt thereof.

In yet another aspect, provided herein is a compound of Formula IVB:



(IVB)

or a pharmaceutically acceptable salt thereof.

Also provided herein are methods of treating or ameliorating a disease state or condition that are modulated through or causally related to the target protein, e.g., KRas.

Additionally, provided herein are methods comprising treating a disease or disorder in a subject, comprising administering to a subject an effective amount of a compound disclosed herein, or a therapeutically effective amount of a pharmaceutical composition disclosed herein.

In embodiments, the disease or disorder is cancer.

Also provided herein are methods for regulating KRas protein activity comprising administering to a subject an effective amount of any of the compounds disclosed herein or a pharmaceutical salt thereof, or a pharmaceutical composition comprising any of the compounds disclosed herein, and a pharmaceutically acceptable carrier.

Also provided herein are methods for regulating cereblon protein activity comprising administering to a subject an effective amount of any of compounds disclosed herein or a pharmaceutical salt thereof, or a pharmaceutical composition comprising any of the compounds disclosed herein, and a pharmaceutically acceptable carrier.

Also provided herein are methods of degrading a target protein in a cell comprising contacting the cell with an effective amount of any of the compounds disclosed herein or a

pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising any of the compounds disclosed herein, and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated into and form a part of the specification, illustrate several embodiments of the present disclosure and, together with the description, help explain the principles of the disclosure. The drawings are only for the purpose of illustrating an embodiment of the disclosure and are not to be construed as limiting the disclosure. Further objects, features and advantages of the disclosure will become apparent from the following detailed description taken in conjunction with the accompanying figures showing illustrative embodiments of the disclosure.

Figure 1 illustrates the HiBiT degradation of various KRAS cells treated with Compound 69.

Figure 2 illustrates the cell-free ubiquitination of KRAS G12D treated with a compound in accordance with one or more embodiments of the present disclosure.

Figure 3A and 3B (A) Proliferation in AsPC-1 cells treated with G12D Compound 69, E3-inactive Compound 69, and a control. (B) Proliferation in various cell types treated with active Compound 69.

Figure 4A and 4B (A) pERK suppression in AsPC-1 spheroids treated with G12D Compound 69 over time. (B) pERK suppression in AsPC-1 spheroids treated with E3-inactive Compound 69 over time.

Figure 5 illustrates caspase 3/7 activity in GP2d spheroids treated with G12D Compound 69, E3-inactive Compound 69 and KRAS-inactive Compound 69 after 16 hours.

Figure 6A and 6B (A) KRAS levels and cPARP induction in GP2d tumors treated with a single dose of G12D Compound 69. (B) Tumor concentration and KRAS levels in GP2d tumors treated with a single dose of G12D Compound 69.

Figure 7A and 7B (A) is a graph of GP2d tumor growth volumes after treatment with vehicle or Compound 69. (B) XB is a graph of GP2d tumor growth volumes after treatment with vehicle or Compound 102.

Figure 8 is a graph of LS180 tumor growth volumes after treatment with vehicle or Compound 102.

Figure 9A and Figure 9B (A) is a graph of AsPC-1 tumor growth volumes after treatment with vehicle or Compound 69. (B) is a graph of AsPC-1 tumor growth volumes after treatment with vehicle or Compound 102.

Figure 10A and 10B (A) is a graph of SW1990 tumor growth volumes after treatment with vehicle or Compound 69. (B) is a graph of SW1990 tumor growth volumes after treatment with vehicle or Compound 102.

Figure 11 is a graph of HPAC tumor growth volumes after treatment with vehicle or Compound 69.

Figure 12 is a graph of Panc04.03 tumor growth volumes after treatment with vehicle or Compound 69.

DETAILED DESCRIPTION

Definitions

Listed below are definitions of various terms used to describe the compounds and compositions disclosed herein. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, and peptide chemistry are those well-known and commonly employed in the art.

Specific compounds of the present invention may be identified in the present specification by chemical name and/or chemical structure. In the event of any conflict between the chemical name and chemical structure, the chemical structure will control.

As used herein, the articles “a” and “an” refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

As used herein, the term “about” will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. As used herein when referring to a measurable value such as an amount, a temporal duration, and the like, the term “about” is meant to encompass variations of ±20% or ±10%, including ±5%, ±1%, and ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

The term “administration” or the like as used herein refers to the providing a therapeutic agent to a subject. Multiple techniques of administering a therapeutic agent exist in the art including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

The term “treat,” “treated,” “treating,” or “treatment” includes the diminishment or alleviation of at least one symptom associated or caused by the state, disorder or disease being treated. In certain embodiments, the treatment comprises alleviating the symptoms of cancer.

As used herein, the term “prevent” or “prevention” means no disorder or disease development if none had occurred, or no further disorder or disease development if there had

already been development of the disorder or disease. Also considered is the ability of one to prevent some or all the symptoms associated with the disorder or disease.

As used herein, the term "cell" is meant to refer to a cell that is *in vitro*, *ex vivo*, or *in vivo*. In embodiments, an *ex vivo* cell can be part of a tissue sample excised from an organism such as a mammal. In embodiments, an *in vitro* cell can be a cell in a cell culture. In embodiments, an *in vivo* cell is a cell living in an organism such as a mammal.

As used herein, the term "subject" refers to a human or a non-human mammal. Non-human mammals include, for example, livestock and pets, such as ovine, bovine, porcine, canine, feline and marine mammals. Preferably the subject is human.

As used herein, the terms "effective amount," "pharmaceutically effective amount," and "therapeutically effective amount" refer to a nontoxic but sufficient amount of an agent to provide the desired biological result. That result may be reduction or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An appropriate therapeutic amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

As used herein, the term "pharmaceutically acceptable" refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively non-toxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

As used herein, the term "pharmaceutically acceptable salt" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. The phrase "pharmaceutically acceptable salt" is not limited to a mono, or 1:1, salt. For example, "pharmaceutically acceptable salt" also includes bis-salts, such as a bis-hydrochloride salt. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and Journal of Pharmaceutical Science, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

As used herein, the term “composition” or “pharmaceutical composition” refers to a mixture of at least one compound useful within the disclosure with a pharmaceutically acceptable carrier. The pharmaceutical composition facilitates administration of the compound to a subject. Multiple techniques of administering a compound exist in the art including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

As used herein, the term “pharmaceutically acceptable carrier” means a pharmaceutically acceptable material, composition, or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening agent, solvent or encapsulating material, involved in carrying or transporting a compound useful within the disclosure within or to the subject such that it may perform its intended function. Typically, such constructs are carried or transported 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, including the compound useful within the disclosure, and not injurious to the subject. Some examples of materials that may 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; surface active agents; 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.

As used herein, “pharmaceutically acceptable carrier” also includes any and all coatings, antibacterial and antifungal agents, and absorption delaying agents, and the like that are compatible with the activity of the compound useful within the present disclosure and are physiologically acceptable to the subject. Supplementary active compounds may also be incorporated into the compositions. The “pharmaceutically acceptable carrier” may further include a pharmaceutically acceptable salt of the compound disclosed herein. Other additional ingredients that may be included in the pharmaceutical compositions are known in the art and described, for example, in Remington’s Pharmaceutical Sciences (Genaro, Ed., Mack Publishing Co., 1985, Easton, PA), which is incorporated herein by reference.

As used herein, the term “alkyl,” by itself or as part of another substituent means, unless otherwise stated, a straight or branched chain hydrocarbon having the number of carbon atoms designated (i.e., C_{1-6} alkyl means an alkyl having one to six carbon atoms) and includes straight and branched chains. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert

butyl, pentyl, neopentyl, and hexyl. Other examples of C_{1-6} alkyl include ethyl, methyl, isopropyl, isobutyl, n-pentyl, and n-hexyl.

The term "alkenyl" employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more double carbon-carbon bonds. An alkenyl group formally corresponds to an alkene with one C-H bond replaced by the point of attachment of the alkenyl group to the remainder of the compound. The term "C_{n-m} alkenyl" refers to an alkenyl group having n to m carbons. In some embodiments, the alkenyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms. Example alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl and the like.

The term "alkynyl" employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more triple carbon-carbon bonds. An alkynyl group formally corresponds to an alkyne with one C-H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. The term "C_{n-m} alkynyl" refers to an alkynyl group having n to m carbons. Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl and the like. In some embodiments, the alkynyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

As used herein, the term "haloalkyl" refers to an alkyl group, as defined above, substituted with one or more halo substituents, wherein alkyl and halo are as defined herein. Haloalkyl includes, by way of example, chloromethyl, trifluoromethyl, bromoethyl, chlorofluoroethyl, and the like.

As used herein, the term "halo" or "halogen" alone or as part of another substituent means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably, fluorine, chlorine, or bromine, more preferably, fluorine or chlorine.

As used herein, the term "cycloalkyl" means a non-aromatic carbocyclic system that is fully saturated having 1, 2 or 3 rings wherein such rings may be fused. The term "fused" means that a second ring is present (i.e., attached or formed) by having two adjacent atoms in common (i.e., shared) with the first ring. Cycloalkyl also includes bicyclic structures that may be bridged or spirocyclic in nature with each individual ring within the bicycle varying from 3-8 atoms. The term "cycloalkyl" includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[3.1.0]hexyl, spiro[3.3]heptanyl, and bicyclo[1.1.1]pentyl. In embodiments, cycloalkyl refers to C_{3-10} cycloalkyl. In another embodiment, cycloalkyl refers to C_{3-6} cycloalkyl.

As used herein, the term "heterocycloalkyl" means a non-aromatic carbocyclic system containing 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S and having 1, 2, or 3 rings wherein such rings may be fused, wherein fused is defined above. The term "heterocycloalkyl" includes unsaturated compounds such as dihydropyridinyl, dihydropyridazinyl, dihydropyrimidinyl, and dihydropyrazinyl. Heterocycloalkyl also includes bicyclic structures that may be bridged or spirocyclic in nature with each individual ring within

the bicycle varying from 3–8 atoms, and containing 0, 1, or 2 N, O, or S atoms. The term "heterocycloalkyl" includes cyclic esters (i.e., lactones) and cyclic amides (i.e., lactams) and also specifically includes, but is not limited to, epoxidyl, oxetanyl, tetrahydro-furanyl, tetrahydropyranyl (i.e., oxanyl), pyranyl, dioxanyl, aziridinyl, azetidinyl, pyrrolidinyl, 2,5-dihydro-1H-pyrrolyl, oxazolidinyl, thiazolidinyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl, 1,3-oxazinanyl, 1,3-thiazinanyl, 2-azabicyclo[2.1.1]hexanyl, 5-azabicyclo[2.1.1]-hexanyl, 6-azabicyclo[3.1.1] heptanyl, 2-azabicyclo[2.2.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 2-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.0]hexanyl, 2-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 3-oxa-7-azabicyclo[3.3.1]nonanyl, 3-oxa-9-azabicyclo[3.3.1]nonanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 6-oxa-3-azabicyclo[3.1.1]heptanyl, 2-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2-oxaspiro[3.3]heptanyl, 2-oxaspiro[3.5]nonanyl, 3-oxaspiro[5.3]nonanyl, and 8-oxabicyclo[3.2.1]octanyl. In embodiments, heterocycloalkyl refers to 3–12 membered heterocycloalkyl. In embodiments, heterocycloalkyl refers to 6–12 membered heterocycloalkyl. In embodiments, heterocycloalkyl refers to 3–10 membered heterocycloalkyl. In embodiments, heterocycloalkyl refers to 6–8 membered heterocycloalkyl. In embodiments, heterocycloalkyl refers to 6-membered heterocycloalkyl. In embodiments, heterocycloalkyl refers to 7-membered heterocycloalkyl. In embodiments, heterocycloalkyl refers to 9-membered heterocycloalkyl. In embodiments, heterocycloalkyl refers to 9-membered heterocycloalkyl.

A 6-membered heterocycloalkyl ring is a heteroaryl group having six ring atoms wherein one or more (*e.g.*, 1, 2, or 3) ring atoms are independently selected from N, O, and S. Exemplary 6-membered ring heterocycloalkyls include piperidinyl, piperazinyl, dioxanyl thianyl, dithianyl, morpholinyl, thiomorpholinyl, and dihydropyridinyl.

A 7-membered heterocycloalkyl ring is a heteroaryl group having seven ring atoms wherein one or more (*e.g.*, 1, 2 or 3) ring atoms are independently selected from N, O and S. Exemplary 7-membered ring heterocycloalkyls include azepinyl, oxepanyl, thiepanyl, oxathiepanyl, diazaspiro[3.3]heptanyl, and azaspiro[3.3]heptanyl.

A 9-membered heterocycloalkyl ring is a heterocycloalkyl group having nine ring atoms wherein one or more (*e.g.*, 1, 2 or 3) ring atoms are independently selected from N, O and S. Exemplary 9-membered ring heterocycloalkyls are 2-azaspiro[3.5]nonanyl and 2,7-diazaspiro[3.5]nonanyl.

An 11-membered heterocycloalkyl ring is a heteroaryl group having eleven ring atoms wherein one or more (*e.g.*, 1, 2, or 3) ring atoms are independently selected from N, O and S. Exemplary 11-membered ring heterocycloalkyls include 3,9-diazaspiro[5.5]undecanyl and 3-azaspiro[5.5]undecanyl.

As used herein, the term "aromatic" refers to a carbocycle or heterocycle with one or more polyunsaturated rings and having aromatic character, i.e., having (4n + 2) delocalized π (pi) electrons, where n is an integer.

As used herein, the term “aryl” means an aromatic carbocyclic system containing 1, 2 or 3 rings, wherein such rings may be fused, wherein fused is defined above. If the rings are fused, one of the rings must be fully unsaturated and the fused ring(s) may be fully saturated, partially unsaturated, or fully unsaturated. The term “aryl” includes, but is not limited to, phenyl, naphthyl, indanyl, and 1,2,3,4-tetrahydronaphthalenyl. In some embodiments, aryl groups have 6 carbon atoms. In embodiments, aryl groups have from six to ten carbon atoms. In embodiments, aryl groups have from six to sixteen carbon atoms. In embodiments, the aryl group has six to ten carbon atoms.

As used herein, the term “heteroaryl” means an aromatic carbocyclic system containing 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S and having 1, 2, or 3 rings wherein such rings may be fused, wherein fused is defined above. The term “heteroaryl” includes, but is not limited to, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazo[1,2-a]pyridinyl, pyrazolo[1,5-a]pyridinyl, 5,6,7,8-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydroquinolinyl, 6,7-dihydro-5H-cyclopenta[b]pyridinyl, 6,7-dihydro-5H-cyclopenta-[c]pyridinyl, 1,4,5,6-tetrahydrocyclopenta[c]pyrazolyl, 2,4,5,6-tetrahydrocyclopenta[c]pyrazolyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, 6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazolyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridinyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridinyl, 4,5,6,7-tetrahydro-1H-indazolyl and 4,5,6,7-tetrahydro-2H-indazolyl. In embodiment, heteroaryl is 5-10 membered heteroaryl. In embodiments, heteroaryl is 5-7 membered heteroaryl. In embodiments, heteroaryl is 6-7 membered heteroaryl. In embodiments, heteroaryl is 6-membered heteroaryl.

A 5-membered heteroaryl ring is a heteroaryl group having five ring atoms wherein one or more (*e.g.*, 1, 2, or 3) ring atoms are independently selected from N, O and S. Exemplary 5-membered ring heteroaryls include thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl.

A 6-membered heteroaryl ring is a heteroaryl group having six ring atoms wherein one or more (*e.g.*, 1, 2, or 3) ring atoms are independently selected from N, O, and S. Exemplary 6-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl, isoindolyl, and pyridazinyl.

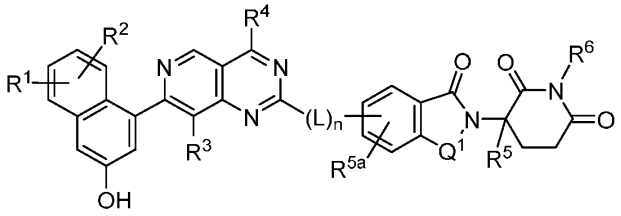
It is to be understood that if an aryl, heteroaryl, cycloalkyl, or heterocyclyl moiety may be bonded or otherwise attached to a designated moiety through differing ring atoms (i.e., shown or described without denotation of a specific point of attachment), then all possible points are intended, whether through a carbon atom or, for example, a trivalent nitrogen atom. For example, the term “pyridinyl” means 2-, 3- or 4-pyridinyl, the term “thienyl” means 2- or 3-thienyl, and so forth.

The term "independently selected" is used herein to indicate that, for a variable which occurs in more than one location in a genus, the identity of the variable is determined separately in each instance. For example, if R^x appears as a substituent on two different atoms, the two instances of R^x may be the same moiety, or different moieties. The same is true if a single atom is substituted with more than one instance of R^x. The identity of R^x in each instance is determined independently of the identity of the other(s).

Compounds

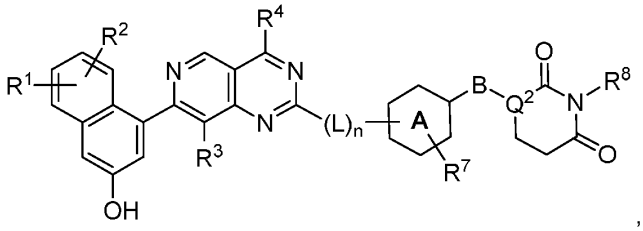
Provided herein are compounds that target Kras and are thus useful in the treatment of cancer.

In particular, provided herein are compounds of any one of Formula I–IV:



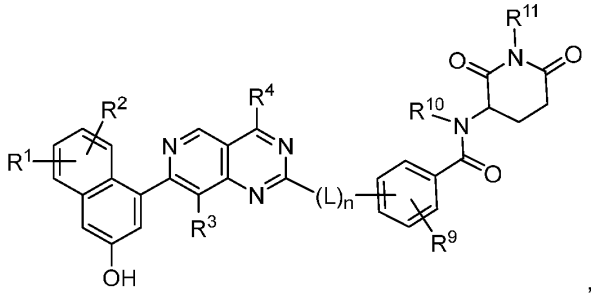
,

(I)



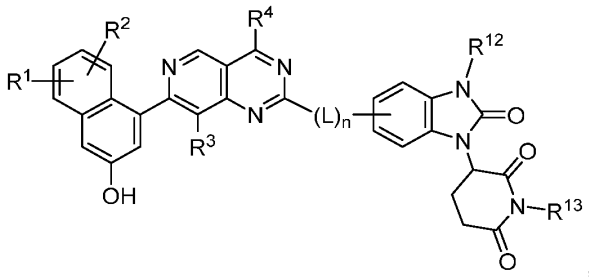
,

(II)



,

(III)



or , **(IV)**

or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is selected from $C(R^{14})_2$, C(O), and NR^{14};

Q^2 is CR^{14} or N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^3 is selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^4 is selected from C_{3-11} cycloalkyl, 3–10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl, wherein C_{3-11} cycloalkyl, 3–10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl are optionally substituted with R^{4a};

R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{5a}, R^5, R^6, R^8, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

Ring A is selected from phenyl, 6-membered heteroaryl, C_6 cycloalkyl, and 6-membered heterocycloalkyl;

B is a bond or C_{1-6} alkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.In embodiments of Formulae I–IV,

Q^1 is $C(R^{14})_2$ or C(O);

Q^2 is N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^3 is selected from H, halo, and CN;

R^4 is C_{3-11} cycloalkyl or 3–10 membered heterocycloalkyl, wherein C_{3-11} cycloalkyl and 3-10 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{5a}, R^5, R^6, R^8, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

Ring A is selected from phenyl, 6-membered heteroaryl, and 6-membered heterocycloalkyl;

B is a bond or C_{1-6} alkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, and 5–10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formulae I–IV,

Q^1 is $C(R^{14})_2$ or C(O);

Q^2 is N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{5a}, R^5, R^6, R^8, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

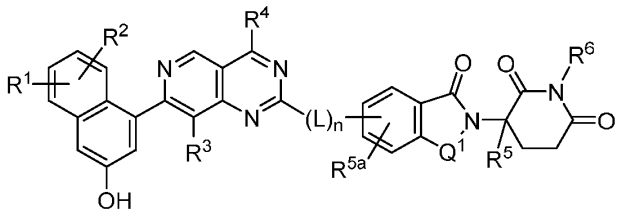
Ring A is phenyl or 6-membered heterocycloalkyl;

B is a bond or C_{1-6} alkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5–12 membered heterocycloalkyl, and 6–7 membered heteroaryl, wherein 5–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In an embodiment, the compound has a structure of Formula I,



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is $C(R^{14})_2$ or C(O);

R^1 and R^2 are each independently selected from halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6-8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6-8 membered heterocycloalkyl are optionally substituted with R^{4a};

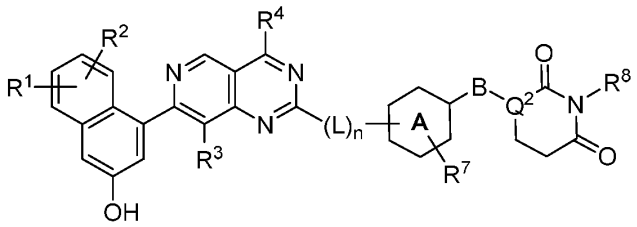
R^{4a} is H or C_{1-6} alkyl;

R^{5a}, R^5, R^6, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In another embodiment, the compound has a structure of Formula II,



(II)

or a pharmaceutically acceptable salt thereof,

wherein:

Q^2 is N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6-8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6-8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^8 and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

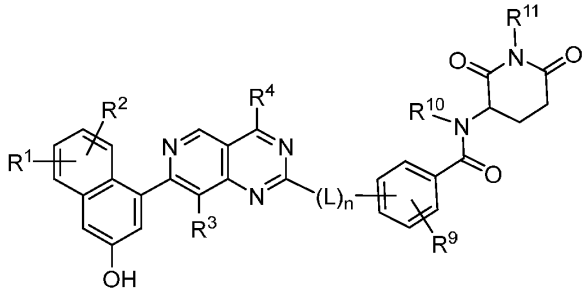
Ring A is phenyl or 6-membered heterocycloalkyl;

B is a bond or C_{1-6} alkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In yet another embodiment, the compound has a structure of Formula III,



(III)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6-8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6-8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

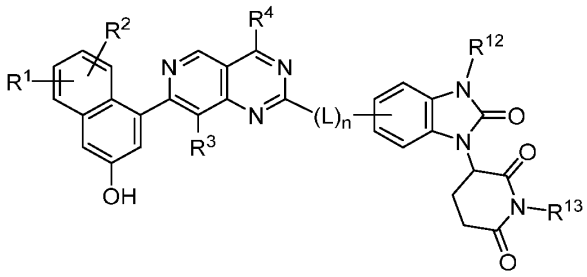
R^{10} and R^{11} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In still another embodiment, the compound has a structure of Formula IV,



(IV)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

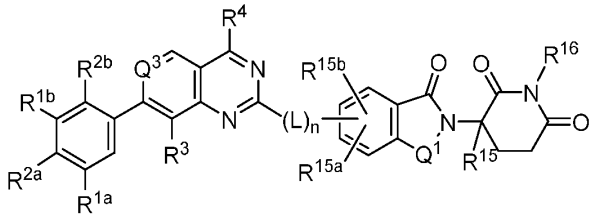
R^4 is C_{6-8} cycloalkyl or 6-8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6-8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{12} and R^{13} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

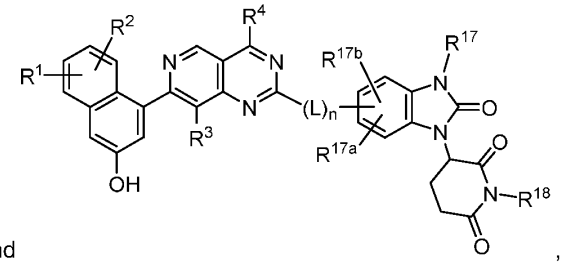
each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.Also provided herein are compounds of Formula V and VI:



,

(V),



and ,

(VI)

or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is selected from $C(R^{14})_2$, C(O), and NR^{14};

Q^3 is CR^{14} or N;

R^{1a} and R^{2a} are each independently selected from OH, H, and halo;

R^{1b} and R^{2b} are each independently selected from halo and C_{3-6} cycloalkyl,

or R^{1b} and R^{2b}, together with the phenyl to which they attach, form C_{8-12} aryl, wherein C_{8-12} aryl is optionally substituted with R^1 and R^2;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^3 is selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^4 is selected from C_{3-11} cycloalkyl, 3–10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl, wherein C_{3-11} cycloalkyl, 3–10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl are optionally substituted with 1 or 2 R^{4a};

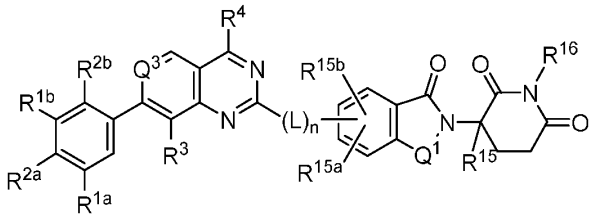
each R^{4a} is independently selected from H, OH, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{14}, R^{15a}, R^{15b}, R^{15}, R^{16}, R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3–12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

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

In an embodiment, the compound has a structure of Formula V,



(V)

or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is $C(R^{14})_2$ or C(O);

Q^3 is CH or N;

R^{1a} and R^{2a} are each independently selected from H, OH, and halo;

R^{1b} and R^{2b}, together with the phenyl to which they attach, form naphthyl substituted with R^1 and R^2;

R^1 and R^2 are each independently selected from H, halo, C_{1-3} alkyl, C_{3-5} cycloalkyl and C≡CH;

R^3 is H or halo;

R^4 is selected from C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with 1 or 2 R^{4a};

each R^{4a} is independently selected from H, OH, and C_{1-6} alkyl;

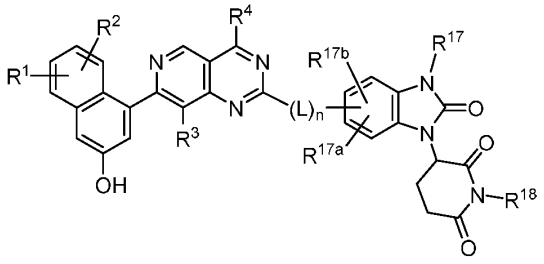
R^{14}, R^{15}, and R^{16} are each independently selected from H, halo, C_{1-3} alkyl, and C_{1-3} alkoxy;

R^{15a} and R^{15b} are each independently selected from halo, C_{1-3} alkyl, and C_{1-3} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In another embodiment, the compound has a structure of Formula VI,



(VI)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 are each independently selected from H, halo, C_{1-3} alkyl, C_{3-5} cycloalkyl, and C≡CH;

R^3 is H or halo;

R^4 is selected from C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with 1 or 2 R^{4a};

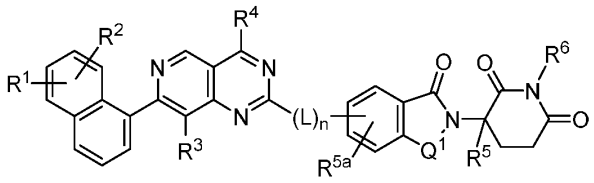
each R^{4a} is independently selected from H, OH, and C_{1-6} alkyl;

R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-3} alkyl, and C_{1-3} alkoxy;

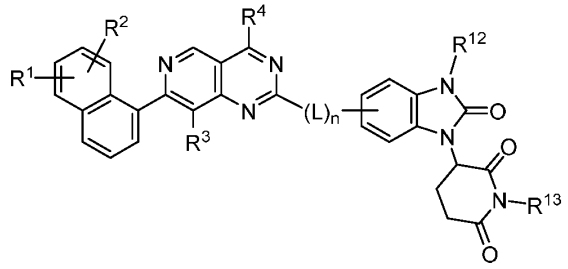
each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In an aspect, provided herein is a compound of Formula AI or AIV:



(AI)



or

(AIV)

or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is selected from $C(R^{14})_2$, C(O), and NR^{14};

Q^2 is CR^{14} or N;

R^1 and R^2 are each independently halo or C_{2-6} alkynyl;

R^3 is selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^4 is selected from C_{3-11} cycloalkyl, 3-10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl, wherein C_{3-11} cycloalkyl, 3-10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl are optionally substituted with R^{4a};

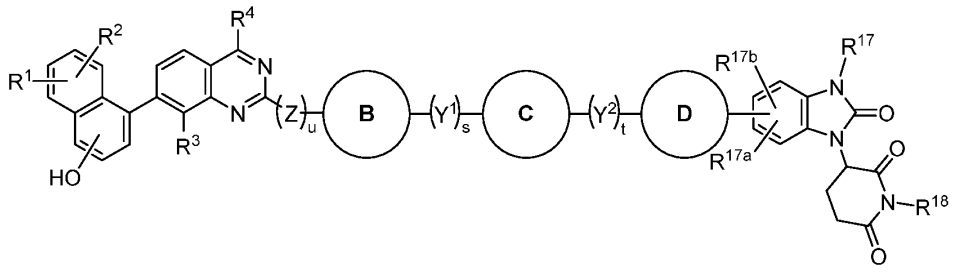
R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{5a}, R^5, R^6, R^{12}, R^{13}, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In another aspect, provided herein is a compound of Formula VII:



(VII)

or a pharmaceutically acceptable salt thereof,

wherein:

Ring B and Ring C are each independently selected from 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl;

Ring D is selected from a bond, C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl, provided that when Ring D is a bond, then Y^2 is also a bond and t is 0;

Y^1 and Y^2 are each independently selected from a bond, O, C(O), N(H), N(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

Z is selected from N(H), N(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^3 is selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^4 is selected from C_{3-11} cycloalkyl, 3-10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl, wherein C_{3-11} cycloalkyl, 3-10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl are optionally substituted with R^{4a};

R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

s and t are each independently 0, 1, 2, or 3; and

u is 1 or 2.

In embodiments of Formula I–VI:

Q^1 is $C(R^{14})_2$ or C(O);

Q^2 is N;

Q^3 is CR^{14} or N;

R^{1a} and R^{2a} are each independently selected from OH, H, and halo;

R^{1b} and R^{2b}, together with the phenyl to which they attach, form C_{8-12} aryl, wherein the C_{8-12} aryl is optionally substituted with R^1 and R^2;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^3 is selected from H, halo, and CN;

R^4 is selected from C_{3-11} cycloalkyl and 3–10 membered heterocycloalkyl, wherein C_{3-11} cycloalkyl and 3–10 membered heterocycloalkyl are optionally substituted with 1 or 2 R^{4a};

each R^{4a} is independently selected from H, OH, and C_{1-6} alkyl;

R^{5a}, R^5, R^6, R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15a}, R^{15b}, R^{15}, R^{16}, R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

Ring A is selected from phenyl, 6-membered heteroaryl, and 6-membered heterocycloalkyl;

B is a bond or C_{1-6} alkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula I-VI:

Q^1 is $C(R^{14})_2$ or C(O);

Q^2 is N;

Q^3 is CR^{14} or N;

R^{1a} and R^{2a} are each independently selected from H, OH, and halo;

R^{1b} and R^{2b}, together with the phenyl to which they attach, form naphthyl substituted with R^1 and R^2;

R^1 and R^2 are each independently selected from H, halo, C_{1-3} alkyl, C_{3-5} cycloalkyl and C≡CH;

R^3 is H or halo;

R^4 is selected from C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with 1 or 2 R^{4a};

each R^{4a} is independently selected from H, OH, and C_{1-6} alkyl;

R^{5a}, R^5, R^6, R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15a}, R^{15b}, R^{15}, R^{16}, R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-3} alkyl and C_{1-3} alkoxy;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

Ring A is phenyl or 6-membered heterocycloalkyl;

B is a bond or C_{1-6} alkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, O, C(O), N(H), $N(C_{1-6}$ alkyl), C_{4-7} cycloalkyl, 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments of Formula I,

Q^1 is $C(R^{14})_2$ or C(O);

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{3-11} cycloalkyl or 3–10 membered heterocycloalkyl, wherein C_{3-11} cycloalkyl and 3-10 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{5a}, R^5, R^6, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), $N(C_{1-6}$ alkyl), C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, and 5–10 membered heteroaryl, wherein 3–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula I,

Q^1 is $C(R^{14})_2$ or C(O);

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{5a}, R^5, R^6, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5–12 membered heterocycloalkyl, and 6–7 membered heteroaryl, wherein 5–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments of Formula II,

Q^2 is N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{3-11} cycloalkyl or 3–10 membered heterocycloalkyl, wherein C_{3-11} cycloalkyl and 3-10 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^8 is selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

Ring A is selected from phenyl, 6-membered heteroaryl, and 6-membered heterocycloalkyl;

B is a bond or C_{1-6} alkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, and 5–10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula II,

Q^2 is N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^8 is selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

Ring A is phenyl or 6-membered heterocycloalkyl;

B is a bond or C_{1-6} alkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 6–12 membered heterocycloalkyl, and 6–7 membered heteroaryl, wherein 6–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments of Formula III,

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{3-11} cycloalkyl or 3–10 membered heterocycloalkyl, wherein C_{3-11} cycloalkyl and 3-10 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^{10} and R^{11} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, and 5–10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula III,

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^{10} and R^{11} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 6–12 membered heterocycloalkyl, and 6–7 membered heteroaryl, wherein 6–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments of Formula IV,

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{3-11} cycloalkyl or 3–10 membered heterocycloalkyl, wherein C_{3-11} cycloalkyl and 3-10 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{12} and R^{13} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, and 5–10 membered heteroaryl, wherein 3–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula IV,

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{12} and R^{13} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 6–12 membered heterocycloalkyl, and 6–7 membered heteroaryl, wherein 6–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments of Formula IV:

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6-8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6-8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{12} and R^{13} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments of Formula V:

Q^1 is $C(R^{14})_2$ or C(O);

Q^3 is CR^{14} or N;

R^{1a} and R^{2a} are each independently selected from OH, H, and halo;

R^{1b} and R^{2b}, together with the phenyl to which they attach, form C_{8-12} aryl, wherein the C_{8-12} aryl is optionally substituted with R^1 and R^2;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^3 is selected from H, halo, and CN;

R^4 is selected from C_{3-11} cycloalkyl and 3–10 membered heterocycloalkyl, wherein C_{3-11} cycloalkyl and 3–10 membered heterocycloalkyl are optionally substituted with 1 or 2 R^{4a};

each R^{4a} is independently selected from H, OH, and C_{1-6} alkyl;

R^{14}, R^{15a}, R^{15b}, R^{15}, and R^{16}, are each independently selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3–12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula V:

Q^1 is $C(R^{14})_2$ or C(O);

Q^3 is CH or N;

R^{1a} and R^{2a} are each independently selected from H, OH, and halo;

R^{1b} and R^{2b}, together with the phenyl to which they attach, form naphthyl substituted with R^1 and R^2;

R^1 and R^2 are each independently selected from H, halo, C_{1-3} alkyl, C_{3-5} cycloalkyl and C≡CH;

R^3 is H or halo;

R^4 is selected from C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with 1 or 2 R^{4a};

each R^{4a} is independently selected from H, OH, and C_{1-6} alkyl;

R^{14}, R^{15a}, R^{15b}, R^{15}, and R^{16}, are each independently selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5–12 membered heterocycloalkyl, and 5-7 membered heteroaryl, wherein 5–12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments of Formula VI:

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^3 is selected from H, halo, and CN;

R^4 is selected from C_{3-11} cycloalkyl and 3–10 membered heterocycloalkyl, wherein C_{3-11} cycloalkyl and 3–10 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, C_{6-10}

aryl, and 5-10 membered heteroaryl, wherein 3–12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula VI:

R^1 and R^2 are each independently selected from H, halo, C_{1-3} alkyl, and C≡CH;

R^3 is H or halo;

R^4 is selected from C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-3} alkyl and C_{1-3} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5–12 membered heterocycloalkyl, and 5-7 membered heteroaryl, wherein 5–12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments of Formula VI:

R^1 and R^2 are each independently selected from H, halo, C_{1-3} alkyl, C_{3-5} cycloalkyl, and C≡CH;

R^3 is H or halo;

R^4 is selected from C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with 1 or 2 R^{4a};

each R^{4a} is independently selected from H, OH, and C_{1-6} alkyl;

R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-3} alkyl, and C_{1-3} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments of Formula AI,

Q^1 is $C(R^{14})_2$ or C(O);

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{3-11} cycloalkyl or 3–10 membered heterocycloalkyl, wherein C_{3-11} cycloalkyl and 3-10 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{5a}, R^5, R^6, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, and 5–10 membered heteroaryl, wherein 3–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula AI,

Q^1 is $C(R^{14})_2$ or C(O);

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{5a}, R^5, R^6, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5–12 membered heterocycloalkyl, and 6–7 membered heteroaryl, wherein 5–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments of Formula AIV,

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{3-11} cycloalkyl or 3–10 membered heterocycloalkyl, wherein C_{3-11} cycloalkyl and 3-10 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{12} and R^{13} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, and 5–10 membered heteroaryl, wherein 3–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula AIV,

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{12} and R^{13} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 6–12 membered heterocycloalkyl, and 6–7 membered heteroaryl, wherein 6–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments of Formula AIV:

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6-8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6-8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{12} and R^{13} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments of Formula VII, Ring B and Ring C are each independently selected from 3-6 membered heterocycloalkyl and 5- or 6-membered heteroaryl, wherein 3-6 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl;

Ring D is selected from a bond, 3-6 membered heterocycloalkyl, and 5- or 6-membered heteroaryl, wherein 3-6 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl, provided that when Ring D is a bond, then Y^2 is also a bond and t is 0;

Y^1 and Y^2 are each independently selected from a bond, O, C(O), N(H), N(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

Z is selected from N(H), N(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^3 is selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^4 is 6-8 membered heterocycloalkyl, optionally substituted with R^{4a};

R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

s and t are each independently 0, 1, 2, or 3; and

u is 1 or 2.

In embodiments of Formula VII, Ring B and Ring C are each independently 3-6 membered heterocycloalkyl optionally substituted with halo, CN, and C_{1-6} alkyl;

Ring D is a bond or 3-6 membered heterocycloalkyl optionally substituted with halo, CN, and C_{1-6} alkyl, provided that when Ring D is a bond, then Y^2 is also a bond and t is 0;

Y^1 and Y^2 are each independently selected from a bond, O, C(O), N(H), N(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

Z is selected from N(H), N(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^3 is selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^4 is 6-8 membered heterocycloalkyl, optionally substituted with R^{4a};

R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

s and t are each independently 0, 1, 2, or 3; and

u is 1 or 2.

In embodiments of Formula VII, Ring B and Ring C are each independently 3-6 membered heterocycloalkyl optionally substituted with halo, CN, and C_{1-6} alkyl;

Ring D is 3-6 membered heterocycloalkyl optionally substituted with halo, CN, and C_{1-6} alkyl;

Y^1 and Y^2 are each independently selected from a bond, O, C(O), N(H), and C_{1-6} alkyl;

Z is selected from N(H) and C_{1-6} alkyl;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^3 is selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^4 is 6-8 membered heterocycloalkyl, optionally substituted with R^{4a};

R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

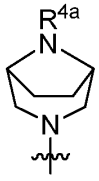
s and t are each independently 0, 1, or 2; and

u is 1.

In embodiments of Formula VII, Ring B, Ring C, and Ring D are each independently 5- or 6-membered heterocycloalkyl optionally substituted with halo, CN, and C_{1-6} alkyl.

In embodiments of Formulae I–VI, R^4 is bridged 8-membered heterocycloalkyl optionally substituted with R^{4a}.

In embodiments of Formulae I–VI, R^4 is:



.

In embodiments of Formulae I–IV, R^6 is H.

In embodiments of Formulae I–IV, R^8 is H.

In embodiments of Formulae I–IV, R^{11} is H.

In embodiments of Formulae I–IV, R^{13} is H.

In embodiments of Formulae I–IV, R^{15} is H.

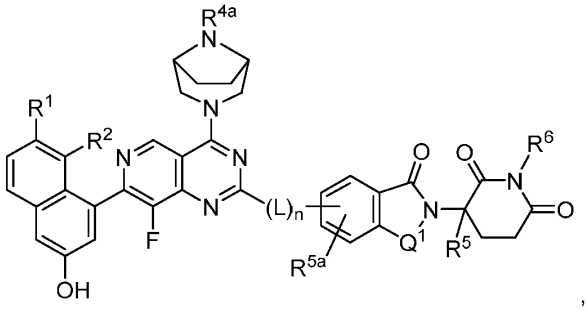
In embodiments of Formulae I–IV, R^{16} is H.

In embodiments of Formulae I–IV R^6, R^8, R^{11}, and R^{13} are each H.

In embodiments of Formulae I–IV, R^{15} and R^{16} are each H.

In embodiments of Formula V, R^4 is a 6-7 membered heterocycloalkyl optionally substituted with 1 or 2 R^{4a}.

In embodiments, the compounds of Formula I have a structure of Formula IA:



(IA)

or a pharmaceutically acceptable salt thereof, wherein:

Q^1 is selected from $C(R^{14})_2$, C(O), and NR^{14};

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{5a}, R^5, R^6, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula IA,

Q^1 is $C(R^{14})_2$ or C(O);

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^{4a} is H or C_{1-6} alkyl;

R^{5a}, R^5, R^6, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, and 5–10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula IA,

Q^1 is $C(R^{14})_2$ or C(O);

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

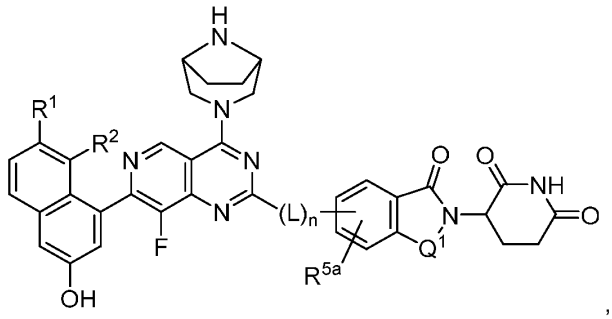
R^{4a} is H or C_{1-6} alkyl;

R^{5a}, R^5, R^6, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5–12 membered heterocycloalkyl, and 6–7 membered heteroaryl, wherein 5–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments, the compounds of Formula I have a structure of Formula IB:



(IB)

or a pharmaceutically acceptable salt thereof, wherein:

Q^1 is selected from $C(R^{14})_2$, C(O), and NR^{14};

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{5a} and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula IB,

Q^1 is CH_2 or C(O);

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^{5a} is independently selected from H, halo, and C_{1-6} alkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, and 5–12 membered heterocycloalkyl, wherein 5–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 4, 5, or 6.

In embodiments of Formula IB, n is 6, and each L forms the following linker: (C_{1-6} alkoxy)-(6–12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(6–12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl).

In embodiments of Formula IB, n is 6, and each L forms the following linker: (C_{1-6} alkoxy)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl).

In embodiments of Formula IB, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(5–12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(5–12 membered heterocycloalkyl).

In embodiments of Formula IB, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(11-membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl).

In embodiments of Formula IB, 11-membered heterocycloalkyl is spirocyclic 11-membered heterocycloalkyl.

In embodiments of Formula IB, n is 6, and each L forms the following linker: (C_{1-6} alkoxy)-(5–12 membered heterocycloalkyl)-(O)-(5–12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(5–12 membered heterocycloalkyl), wherein 5–12 membered heterocycloalkyl is optionally substituted with C_{1-6} alkyl.

In embodiments of Formula IB, n is 6, and each L forms the following linker: (C_{1-6} alkoxy)-(5-membered heterocycloalkyl)-(O)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl), wherein 5-membered heterocycloalkyl is optionally substituted with C_{1-6} alkyl.

In embodiments of Formula IB, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(5–12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(5–12 membered heterocycloalkyl).

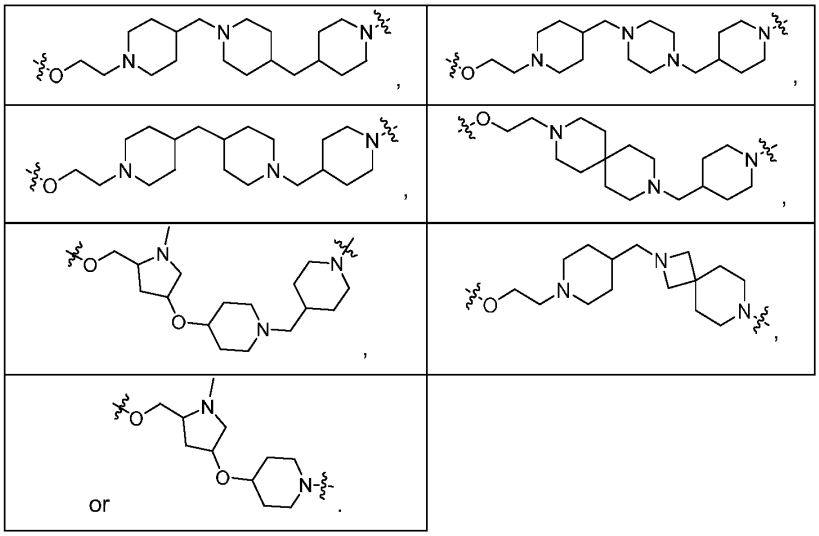
In embodiments of Formula IB, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(9-membered heterocycloalkyl).

In embodiments of Formula IB, 9-membered heterocycloalkyl is spirocyclic 9-membered heterocycloalkyl.

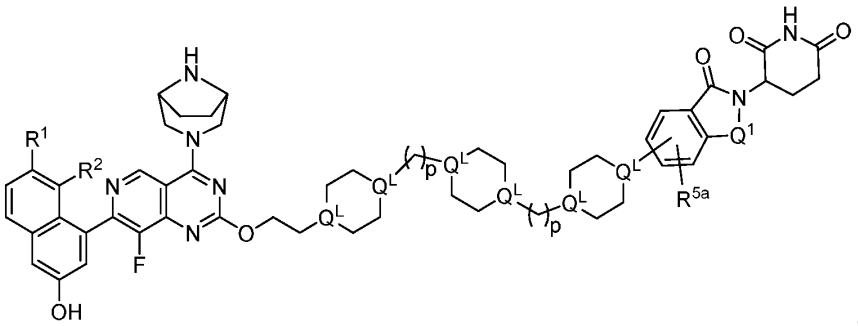
In embodiments of Formula IB, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(5–12 membered heterocycloalkyl)-(O)-(5–12 membered heterocycloalkyl), wherein 5–12 membered heterocycloalkyl is optionally substituted with C_{1-6} alkyl.

In embodiments of Formula IB, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(5-membered heterocycloalkyl)-(O)-(6-membered heterocycloalkyl), wherein 5-membered heterocycloalkyl is optionally substituted with C_{1-6} alkyl.

In embodiments of Formula IB, each L forms the linker:



In embodiments, the compounds of Formula I have a structure of Formula IB-i:



(IB-i)

or a pharmaceutically acceptable salt thereof,

wherein,

Q^1 is selected from $C(R^{14})_2$, C(O), and NR^{14};

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl,

R^{5a} and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each Q^L is independently CR^L or N;

each R^L is independently H, halo, or CN; and

each p is independently 1, 2, 3, 4, 5, or 6.

In embodiments of Formula IB-i,

each Q^L is independently CR^L or N;

each R^L is independently H or halo;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

R^3 is selected from H, halo, and CN;

R^{5a} and R^{14} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy; and

each p is 1, 2, 3, or 4.

In embodiments of Formula IB-i,

each Q^L is independently CH or N;

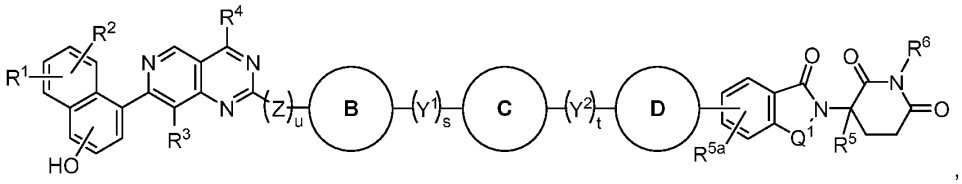
R^1 and R^2 are each independently selected from H, halo, C_{1-3} alkyl, and C≡CH;

R^3 is halo;

R^{5a} and R^{14} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} alkoxy; and

each p is 1, 2, or 3.

In embodiments, the compounds of Formula I have a structure of Formula IC:



,

(IC)

or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is selected from $C(R^{14})_2$, C(O), and NR^{14};

Ring B and Ring C are each independently selected from 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl;

Ring D is selected from a bond, C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl, provided that when Ring D is a bond, then Y^2 is also a bond and t is 0;

Y^1 and Y^2 are each independently selected from a bond, O, C(O), N(H), $N(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

Z is selected from N(H), $N(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

R^3 is selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^4 is selected from C_{3-11} cycloalkyl, 3-10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl, wherein C_{3-11} cycloalkyl, 3-10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl are optionally substituted with R^{4a};

R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{5a}, R^5, R^6, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

s and t are each independently 0, 1, 2, or 3; and

u is 1 or 2.

In embodiments of Formula IC, Ring B and Ring C are each independently selected from 3-12 membered heterocycloalkyl and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl.

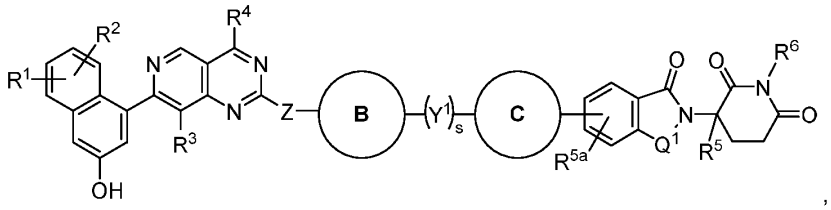
In embodiments of Formula IC, Ring B and Ring C are each independently 3-12 membered heterocycloalkyl optionally substituted with halo, CN, and C_{1-6} alkyl.

In embodiments of Formula IC, at least one of Y^1 and Y^2 is a bond and at least one of s and t is 0.

In embodiments of Formula IC, Ring D is selected from a bond, 3-12 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl.

In embodiments of Formula IC, Ring D is selected from a bond, 3-6 membered heterocycloalkyl, and 5- or 6-membered heteroaryl, wherein 3-6 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl.

In embodiments, the compounds of Formula IC have a structure of Formula IC-i:



,

(IC-i)

or a pharmaceutically acceptable salt thereof,

wherein:

Ring B and Ring C are each independently selected from 5- or 6-membered heterocycloalkyl, 9-11 membered spirocyclic heterocycloalkyl, and 8-membered bridged heterocycloalkyl, wherein 5- or 6-membered heterocycloalkyl, 9-11 membered spirocyclic heterocycloalkyl, and 8-membered bridged heterocycloalkyl are optionally substituted with halo, CN, and C_{1-6} alkyl;

Y^1 is selected from a bond, O, C(O), N(H), N(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

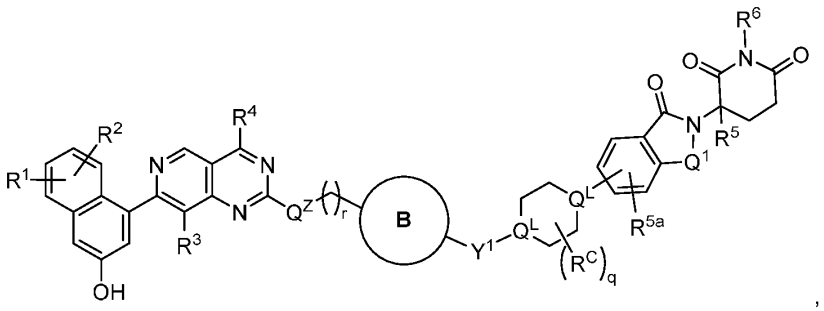
Z is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl; and

s is 0, 1, 2, or 3.

In embodiments, the compounds of Formula IC-i have a structure of Formula IC-ia:



(IC-ia)

or a pharmaceutically acceptable salt thereof

wherein:

Ring B is selected from 5- or 6-membered heterocycloalkyl, 9- or 11-membered spirocyclic heterocycloalkyl, and 8-membered fused heterocycloalkyl, wherein 5- or 6-membered heterocycloalkyl, 9- or 11-membered spirocyclic heterocycloalkyl, and 8-membered fused heterocycloalkyl are optionally substituted with halo, CN, and C_{1-6} alkyl;

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

each R^C is independently halo or C_{1-6} alkyl;

Y^1 is selected from O, C_{1-6} alkyl, and C_{1-6} haloalkyl;

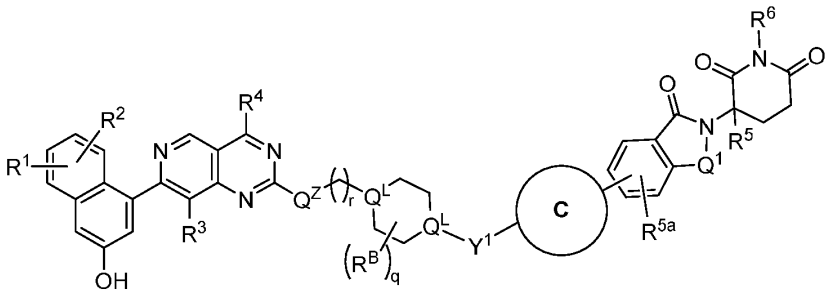
R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

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

q is 0, 1, or 2.

In embodiments, the compound of Formula IC-i has a structure of Formula IC-ib:



(IC-ib)

or a pharmaceutically acceptable salt thereof

wherein:

Ring B is selected from 5- or 6-membered heterocycloalkyl, 9- or 11-membered spirocyclic heterocycloalkyl, and 8-membered fused heterocycloalkyl, wherein 5- or 6-membered heterocycloalkyl, 9- or 11-membered spirocyclic heterocycloalkyl, and 8-membered fused heterocycloalkyl are optionally substituted with halo, CN, and C_{1-6} alkyl;

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

R^B is halo or C_{1-6} alkyl;

Y^1 is selected from O, C_{1-6} alkyl, and C_{1-6} haloalkyl;

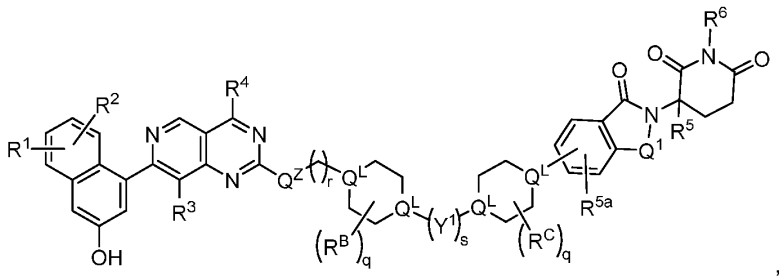
R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

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

q is 0, 1, or 2.

In embodiments, the compound of Formula IC-ia has a structure of Formula IC-iai:



(IC-iai)

or a pharmaceutically acceptable salt thereof

wherein:

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

R^B and R^C are each independently halo or C_{1-6} alkyl;

Y^1 is C_{1-6} alkyl or C_{1-6} haloalkyl;

R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

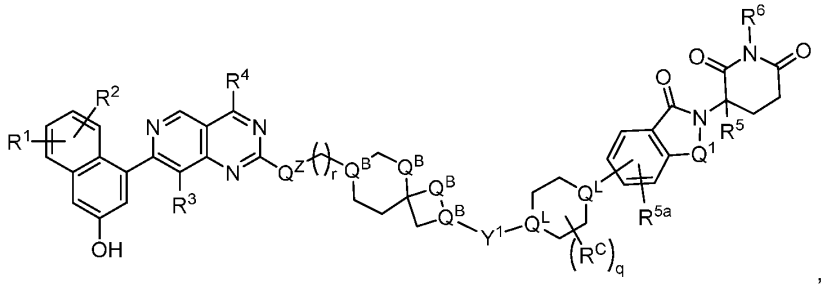
r is 1, 2, 3, 4, 5, or 6;

s is 0, 1, 2, or 3; and

each q is independently 0, 1, or 2.

In embodiments of Formula IC-iai, Ring B is 9 or 11-membered spirocyclic heterocycloalkyl.

In embodiments, the compound of Formula IC-ia has a structure of Formula IC-iaii:



(IC-iaii)

or a pharmaceutically acceptable salt thereof

wherein:

each Q^B is independently selected from CH, CH_2, N, NH, and N(C_{1-6} alkyl), provided that at least one Q^B is N, NH, or N(C_{1-6} alkyl);

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N, provided that at least one Q^L is N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

each R^C is independently halo or C_{1-6} alkyl;

Y^1 is selected from O, C_{1-6} alkyl, and C_{1-6} haloalkyl;

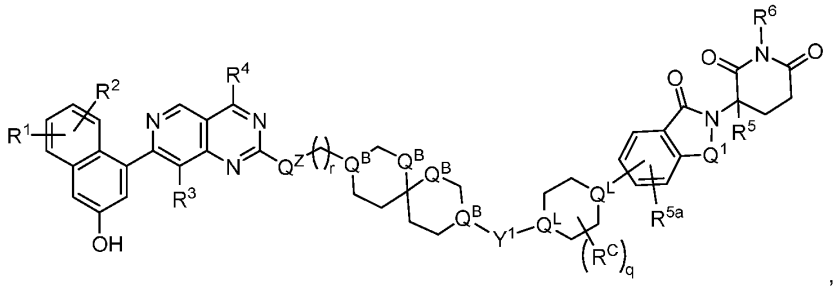
R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

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

q is 0, 1, or 2.

In embodiments, the compound of Formula IC-ia has a structure of Formula IC-iaiii:



(IC-iaiii)

or a pharmaceutically acceptable salt thereof

wherein:

each Q^B is independently selected from CH, CH_2, N, NH, and N(C_{1-6} alkyl), provided that at least one Q^B is N, NH, or N(C_{1-6} alkyl);

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N, provided that at least one Q^L is N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

each R^C is independently halo or C_{1-6} alkyl;

Y^1 is selected from O, C_{1-6} alkyl, and C_{1-6} haloalkyl;

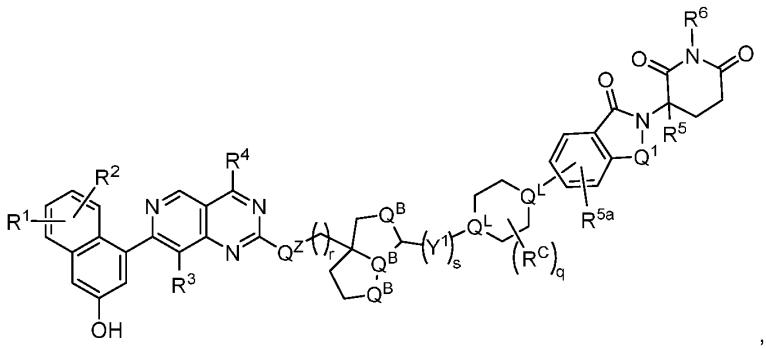
R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

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

q is 0, 1, or 2.

In embodiments, the compound of Formula IC-ia has a structure of Formula IC-iaiv:



(IC-iaiv)

or a pharmaceutically acceptable salt thereof

wherein:

each Q^B is independently selected from CH_2, N, NH, and N(C_{1-6} alkyl), provided that at least one Q^B is N, NH, or N(C_{1-6} alkyl);

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

each R^C is independently halo or C_{1-6} alkyl;

Y^1 is selected from O, C(O), N(H), N(C_{1-6} alkyl), C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^1 is halo or C_{2-6} alkynyl;

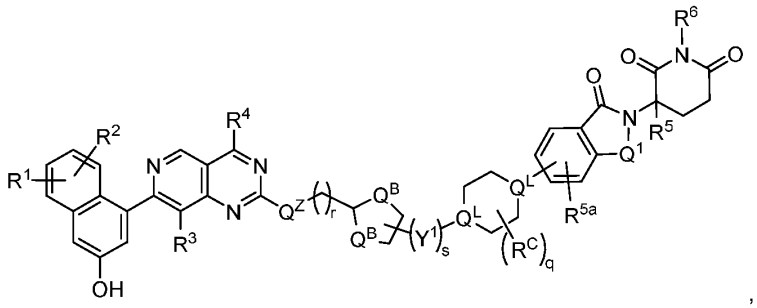
R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

r is 1, 2, 3, 4, 5, or 6;

s is 0, 1, 2, or 3; and

q is 0, 1, or 2.

In embodiments, the compound of Formula IC-ia has a structure of Formula IC-iav:



(IC-iav)

or a pharmaceutically acceptable salt thereof

wherein:

each Q^B is independently selected from CH_2, NH, and $N(C_{1-6}$ alkyl), provided that at least one Q^B is NH or $N(C_{1-6}$ alkyl);

Q^Z is O, NH, or $N(C_{1-6}$ alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

each R^C is independently halo or C_{1-6} alkyl;

Y^1 is selected from O, C(O), N(H), $N(C_{1-6}$ alkyl), C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^1 is halo or C_{2-6} alkynyl;

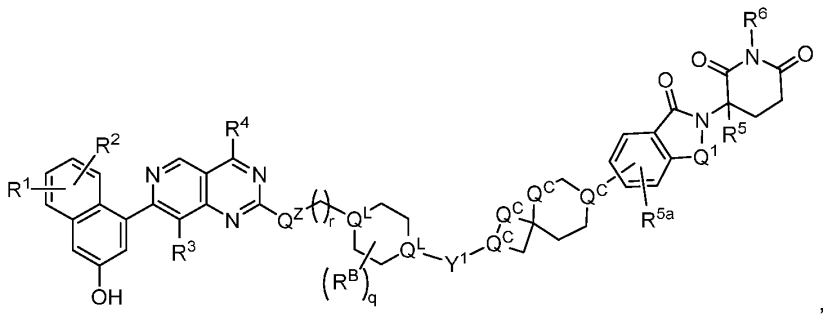
R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

r is 1, 2, 3, 4, 5, or 6;

s is 0, 1, 2, or 3; and

q is 0, 1, or 2.

In embodiments, the compound of Formula IC-ib has a structure of Formula IC-ibi:



(IC-ibi)

or a pharmaceutically acceptable salt thereof

wherein:

each Q^C is independently selected from CH, CH_2, N, NH, and $N(C_{1-6}$ alkyl), provided that at least one Q^C is N, NH, or $N(C_{1-6}$ alkyl);

Q^Z is O, NH, or $N(C_{1-6}$ alkyl);

each Q^L is independently CR^L or N, provided that at least one Q^L is N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

each R^B is independently halo or C_{1-6} alkyl;

Y^1 is selected from O, C_{1-6} alkyl, and C_{1-6} haloalkyl;

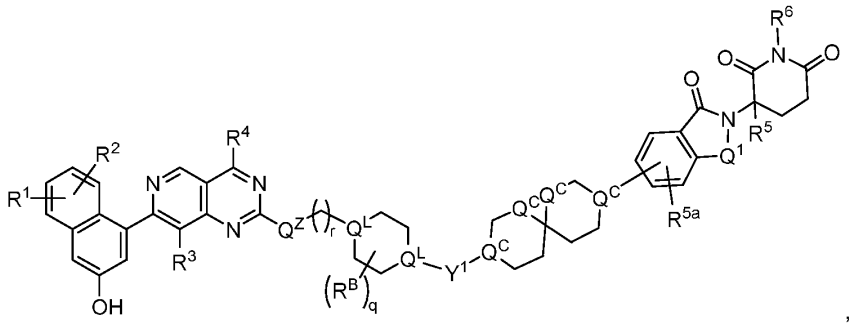
R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

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

q is 0, 1, or 2.

In embodiments, the compound of Formula IC-ib has a structure of Formula IC-ibii:



(IC-ibii)

or a pharmaceutically acceptable salt thereof

wherein:

each Q^C is independently selected from CH, CH_2, N, NH, and $N(C_{1-6}$ alkyl), provided that at least one Q^C is N, NH, or $N(C_{1-6}$ alkyl);

Q^Z is O, NH, or $N(C_{1-6}$ alkyl);

each Q^L is independently CR^L or N, provided that at least one Q^L is N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

each R^B is independently halo or C_{1-6} alkyl;

Y^1 is selected from O, C_{1-6} alkyl, and C_{1-6} haloalkyl;

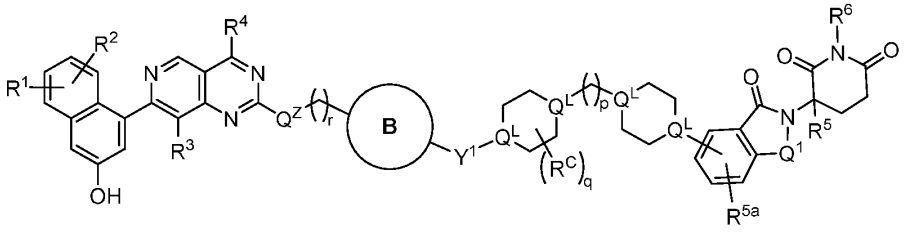
R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

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

q is 0, 1, or 2.

In embodiments, the compound of Formula IC has a structure of Formula IC-ii:



(IC-ii)

or a pharmaceutically acceptable salt thereof

wherein:

Ring B is 5- or 6-membered heterocycloalkyl or 8-membered fused heterocycloalkyl, wherein 5- or 6-membered heterocycloalkyl and 8-membered fused heterocycloalkyl are optionally substituted with halo, CN, and C_{1-6} alkyl;

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

each R^C is independently halo or C_{1-6} alkyl;

Y^1 is selected from O, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^1 is halo or C_{2-6} alkynyl;

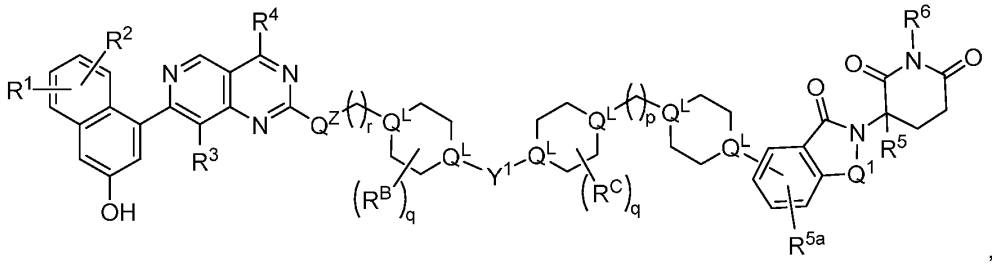
R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

p and r are each independently 1, 2, 3, 4, 5, or 6; and

q is 0, 1, or 2.

In embodiments of Formula IC-ii, Ring B is 8-membered fused heterocycloalkyl.

In embodiments, the compound of Formula IC-iia has a structure of Formula IC-iia:



(IC-iia)

or a pharmaceutically acceptable salt thereof

wherein:

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

R^B and R^C are each independently halo or C_{1-6} alkyl;

Y^1 is C_{1-6} alkyl or C_{1-6} haloalkyl;

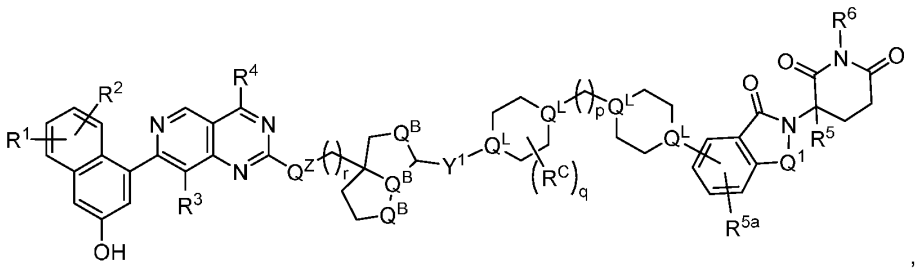
R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

p and r are each independently 1, 2, 3, 4, 5, or 6; and

each q is independently 0, 1, or 2.

In embodiments, the compound of Formula IC-ii, has a structure of Formula IC-iib:



(IC-iib)

or a pharmaceutically acceptable salt thereof

wherein:

each Q^B is independently selected from CH_2, N, NH, and N(C_{1-6} alkyl), provided that at least one Q^B is N, NH, or N(C_{1-6} alkyl);

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

each R^C is independently halo or C_{1-6} alkyl;

Y^1 is selected from O, C_{1-6} alkyl, and C_{1-6} haloalkyl;

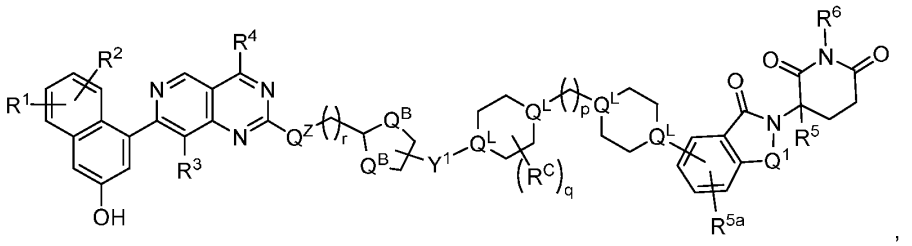
R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

p and r are each independently 1, 2, 3, 4, 5, or 6; and

q is 0, 1, or 2.

In embodiments, the compound of Formula IC-ii has a structure of Formula IC-iic:



(IC-iic)

or a pharmaceutically acceptable salt thereof

wherein:

each Q^B is independently selected from CH_2, NH, and N(C_{1-6} alkyl), provided that at least one Q^B is NH or N(C_{1-6} alkyl);

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

each R^C is independently halo or C_{1-6} alkyl;

Y^1 is selected from O, C_{1-6} alkyl, and C_{1-6} haloalkyl;

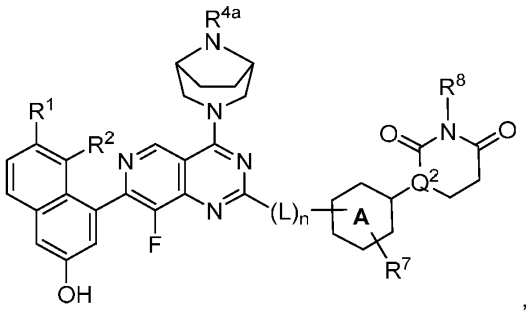
R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

p and r are each independently 1, 2, 3, 4, 5, or 6; and

q is 0, 1, or 2.

In embodiments, the compounds of Formula II have a structure of Formula IIA:



(IIA)

or a pharmaceutically acceptable salt thereof, wherein:

Q^2 is CR^{14} or N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl,

R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^8 and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

Ring A is selected from phenyl, 6-membered heteroaryl, C_6 cycloalkyl, and 6-membered heterocycloalkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula IIA,

Q^2 is N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^{4a} is H or C_{1-6} alkyl;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^8 is selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

Ring A is selected from phenyl, 6-membered heteroaryl, and 6-membered heterocycloalkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, and 5–10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula IIA,

Q^2 is N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^4 is C_{6-8} cycloalkyl or 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^8 is selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

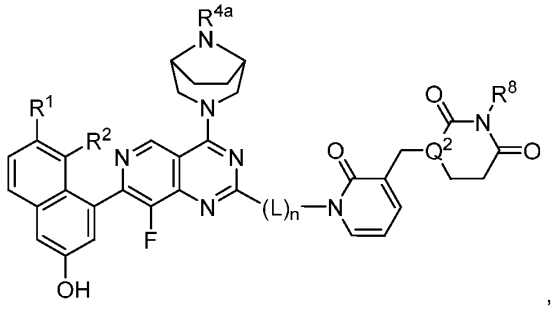
Ring A is phenyl or 6-membered heterocycloalkyl;

B is a bond or C_{1-6} alkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 6–12 membered heterocycloalkyl, and 6–7 membered heteroaryl, wherein 6–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments, the compounds of Formula II have a structure of Formula IIB:



,

(IIB)

or a pharmaceutically acceptable salt thereof, wherein:

Q^2 is CR^{14} or N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl,

R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^8 and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula IIB,

Q^2 is N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^{4a} is H or C_{1-6} alkyl;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^8 is selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

Ring A is selected from phenyl, 6-membered heteroaryl, and 6-membered heterocycloalkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, and 5–10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula IIB,

Q^2 is N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^4 is C_{6-8} cycloalkyl or 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with R^{4a};

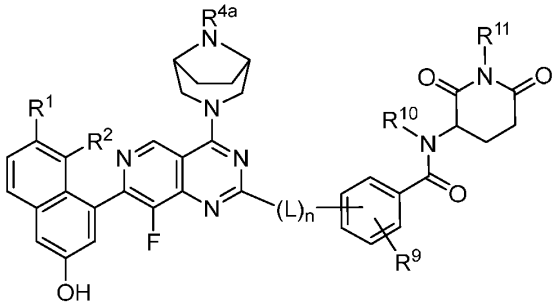
R^{4a} is H or C_{1-6} alkyl;

R^8 is selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 6–12 membered heterocycloalkyl, and 6–7 membered heteroaryl, wherein 6–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments, the compounds of Formula III have a structure of Formula IIIA:



(IIIA)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl,

R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^{10} and R^{11} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula IIIA,

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^{4a} is H or C_{1-6} alkyl;

R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^{10} and R^{11} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, and 5–10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula IIIA,

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^{4a} is H or C_{1-6} alkyl;

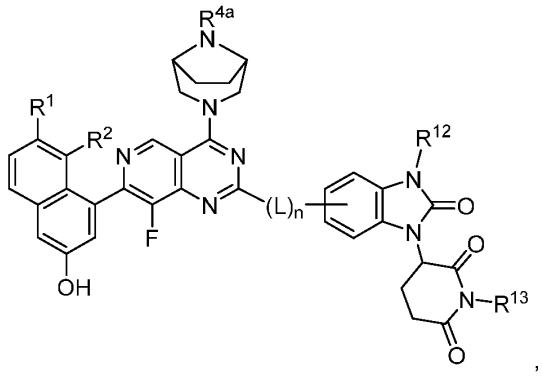
R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^{10} and R^{11} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 6–12 membered heterocycloalkyl, and 6–7 membered heteroaryl, wherein 6–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments, the compounds of Formula IV have a structure of Formula IVA:



(IVA)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl,

R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{12} and R^{13} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula IVA,

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^{4a} is H or C_{1-6} alkyl;

R^{12} and R^{13} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, and 5–10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula IVA,

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

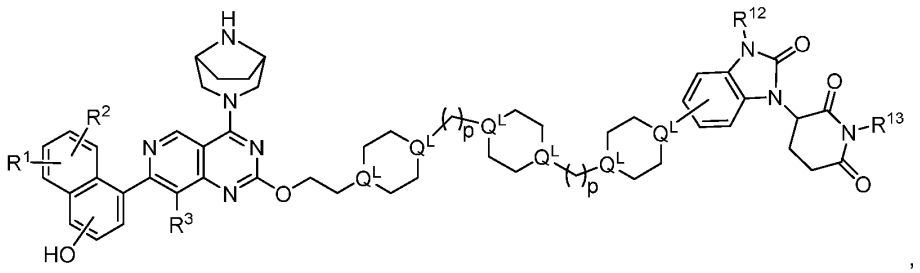
R^{4a} is H or C_{1-6} alkyl;

R^{12} and R^{13} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 6–12 membered heterocycloalkyl, and 6–7 membered heteroaryl, wherein 6–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments, the compounds of Formula IV have a structure of Formula IVB-a:



(IVB-a)

or a pharmaceutically acceptable salt thereof,

wherein:

each Q^L is independently CR^L or N;

each R^L is independently H, halo, or CN, and

each p is 1, 2, 3, 4, 5, or 6.

In embodiments of Formula IVB-a,

each Q^L is independently CR^L or N;

each R^L is independently H or halo;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

R^3 is selected from H, halo, and CN;

R^{12} and R^{13} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy; and

each p is 1, 2, 3, or 4.

In embodiments of Formula IVB-a,

each Q^L is independently CH or N;

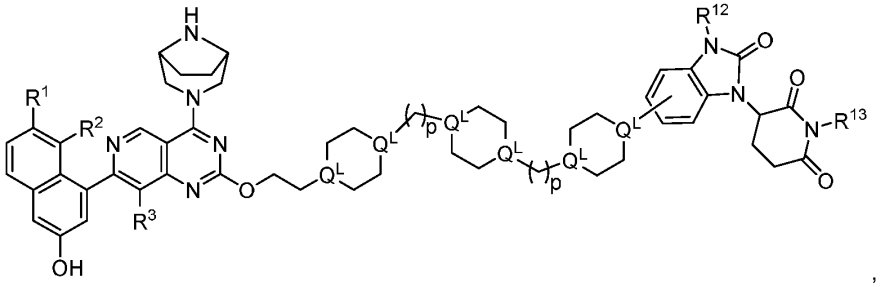
R^1 and R^2 are each independently selected from H, halo, C_{1-3} alkyl, and C≡CH;

R^3 is halo;

R^{12} and R^{13} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} alkoxy; and

each p is 1, 2, or 3.

In embodiments, the compounds of Formula IV have a structure of Formula IVB:



(IVB)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

R^3 is selected from H, halo, and CN;

each Q^L is independently CR^L or N;

each R^L is independently H, halo, or CN, and

each p is 1, 2, 3, 4, 5, or 6; and

R^{12} and R^{13} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy.

In embodiments of Formula IVB,

each Q^L is independently CR^L or N;

each R^L is independently H or halo;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

R^3 is selected from H, halo, and CN;

R^{12} and R^{13} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy; and

each p is 1, 2, 3, or 4.

In embodiments of Formula IVB,

each Q^L is independently CH or N;

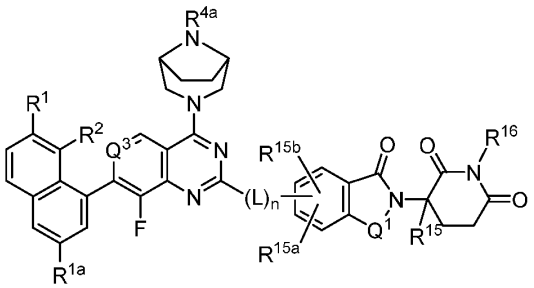
R^1 and R^2 are each independently selected from H, halo, C_{1-3} alkyl, and C≡CH;

R^3 is halo;

R^{12} and R^{13} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} alkoxy; and

each p is 1, 2, or 3.

In embodiments, the compounds of Formula V have the structure of Formula VA:



(VA)

or a pharmaceutically acceptable salt thereof, wherein:

Q^1 is selected from $C(R^{14})_2$, C(O), and NR^{14};

Q^3 is from CR^{14} or N;

R^{1a} is selected from OH, H, and halo;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{4a} is independently selected from H, OH, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{14}, R^{15a}, R^{15b}, R^{15}, and R^{16} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3–12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula VA,

Q^1 is $C(R^{14})_2$ or C(O);

Q^3 is CR^{14} or N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, and C≡CH;

R^{1a} is H or OH;

R^{4a} is H or C_{1-6} alkyl;

R^{14}, R^{15a}, R^{15b}, R^{15}, and R^{16} are each independently selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3–12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula VA:

Q^1 is $C(R^{14})_2$ or C(O);

Q^3 is CH or N;

R^1 and R^2 are each independently selected from H, halo, C_{1-3} alkyl, C_{3-5} cycloalkyl and C≡CH;

R^{1a} is H or OH;

R^3 is H or halo;

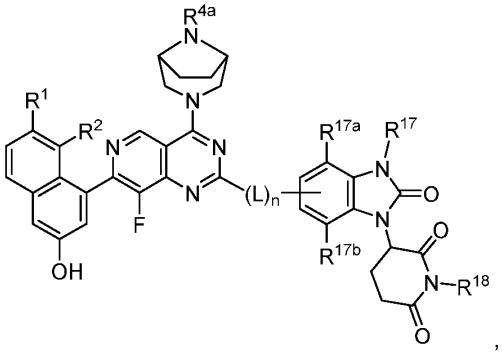
R^{4a} is H or C_{1-6} alkyl;

R^{14}, R^{15a}, R^{15b}, R^{15}, and R^{16} are each independently selected from H, halo, C_{1-3} alkyl and C_{1-3} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5–12 membered heterocycloalkyl, and 5-7 membered heteroaryl, wherein 5–12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments, the compounds of Formula VI have a structure of Formula VIA:



(VIA)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{4a} is independently selected from H, OH, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3–12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula VIA:

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, and C≡CH;

R^{4a} is H or C_{1-6} alkyl;

R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, C_{6-10}

aryl, and 5-10 membered heteroaryl, wherein 3–12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

In embodiments of Formula VIA:

R^1 and R^2 are each independently selected from H, halo, C_{1-3} alkyl, and C≡CH;

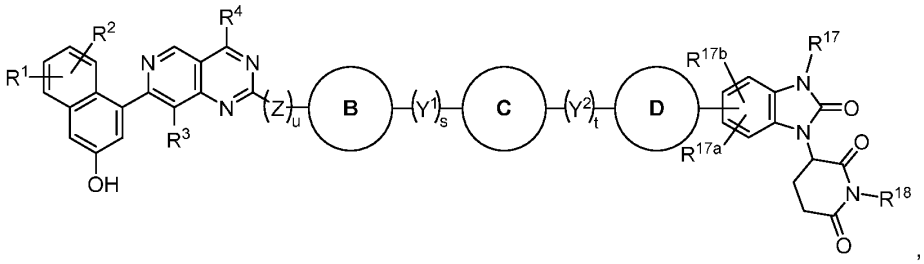
R^{4a} is H or C_{1-6} alkyl;

R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-3} alkyl and C_{1-3} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5–12 membered heterocycloalkyl, and 5-7 membered heteroaryl, wherein 5–12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

In embodiments, the compound of Formula VI has a structure of Formula VIAA:



,

(VIAA)

or a pharmaceutically acceptable salt thereof,

wherein:

Ring B and Ring C are each independently selected from 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl;

Ring D is selected from a bond, C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl, provided that when Ring D is a bond, then Y^2 is also a bond and t is 0;

Y^1 and Y^2 are each independently selected from a bond, O, C(O), N(H), N(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

Z is selected from N(H), N(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

R^3 is selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^4 is selected from C_{3-11} cycloalkyl, 3-10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl, wherein C_{3-11} cycloalkyl, 3-10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl are optionally substituted with R^{4a};

R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

s and t are each independently 0, 1, 2, or 3; and

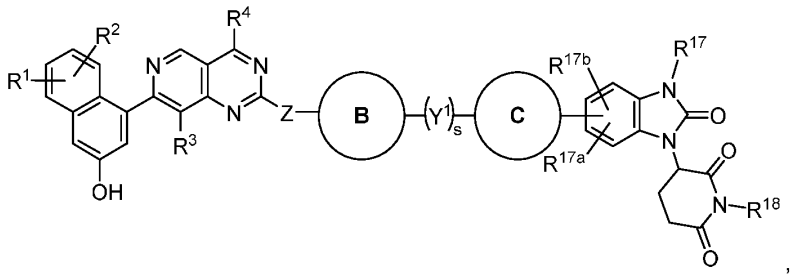
u is 1 or 2.

In embodiments of Formula VIAA, Ring D is selected from a bond, 3-12 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl.

In embodiments of Formula VIAA, Ring D is selected from a bond, 3-8 membered heterocycloalkyl, and 5- or 6-membered heteroaryl, wherein 3-8 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl.

In embodiments of Formula VIAA, Ring B is 8-membered fused heterocycloalkyl.

In embodiments, the compound of Formula VIAA has a structure of Formula VIAA-i:



(VIAA-i)

or a pharmaceutically acceptable salt thereof,

wherein:

Ring B and Ring C are each independently selected from 5- or 6-membered heterocycloalkyl, 9-11 membered spirocyclic heterocycloalkyl, and 8-membered bridged heterocycloalkyl, wherein 5- or 6-membered heterocycloalkyl, 9-11 membered spirocyclic heterocycloalkyl, and 8-membered bridged heterocycloalkyl are optionally substituted with halo, CN, and C_{1-6} alkyl;

Y^1 is selected from a bond, O, C(O), N(H), N(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

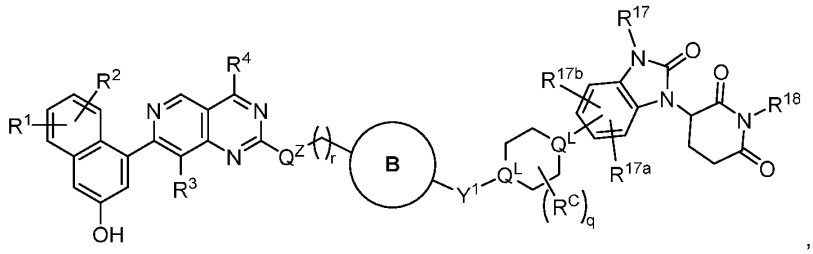
Z is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl; and

s is 0, 1, 2, or 3.

In embodiments, the compound of Formula VIAA-i has a structure of Formula VIAA-ia:



(VIAA-ia)

or a pharmaceutically acceptable salt thereof

wherein:

Ring B is selected from 5- or 6-membered heterocycloalkyl, 9- or 11-membered spirocyclic heterocycloalkyl, and 8-membered fused heterocycloalkyl, wherein 5- or 6-membered heterocycloalkyl, 9- or 11-membered spirocyclic heterocycloalkyl, and 8-membered fused heterocycloalkyl are optionally substituted with halo, CN, and C_{1-6} alkyl;

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

each R^C is independently halo or C_{1-6} alkyl;

Y^1 is selected from O, C_{1-6} alkyl, and C_{1-6} haloalkyl;

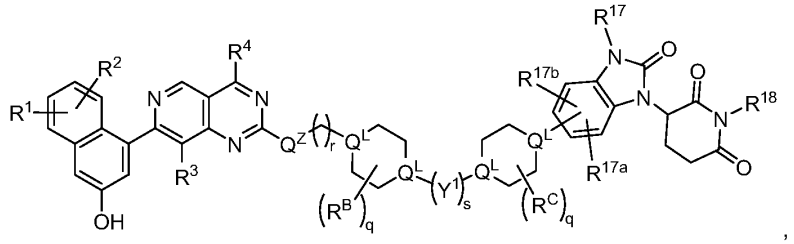
R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

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

q is 0, 1, or 2.

In embodiments, the compound of Formula VIAA-ia has a structure of Formula VIAA-iai:



(VIAA-iai)

or a pharmaceutically acceptable salt thereof

wherein:

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

R^B and R^C are each independently halo or C_{1-6} alkyl;

Y^1 is C_{1-6} alkyl or C_{1-6} haloalkyl;

R^1 is halo or C_{2-6} alkynyl;

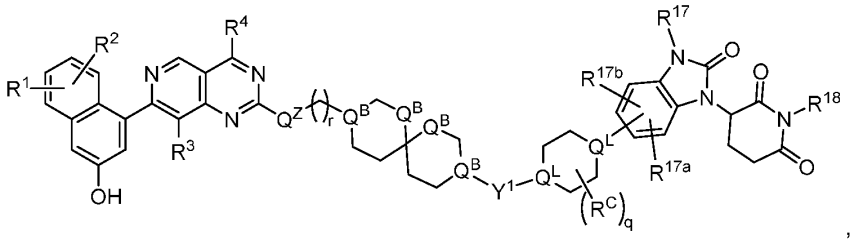
R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

r is 1, 2, 3, 4, 5, or 6;

s is 0, 1, 2, or 3; and

each q is independently 0, 1, or 2.

In embodiments, the compound of Formula VIAA-ia has a structure of Formula VIAA-iaii:



,

(VIAA-iaii)

or a pharmaceutically acceptable salt thereof

wherein:

each Q^B is independently selected from CH, CH_2, N, NH, and N(C_{1-6} alkyl), provided that at least one Q^B is N, NH, or N(C_{1-6} alkyl);

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N, provided that at least one Q^L is N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

each R^C is independently halo or C_{1-6} alkyl;

Y^1 is selected from O, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^1 is halo or C_{2-6} alkynyl;

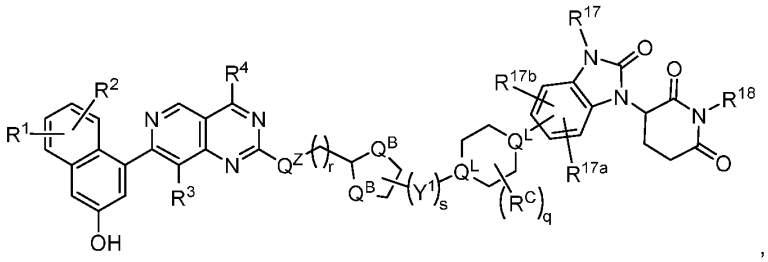
R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

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

q is 0, 1, or 2.

In embodiments of Formula VIAA-iaii, at least two Q^B are CH_2.

In embodiments, the compound of Formula VIAA-ia has a structure of Formula VIAA-iaiii:



,

(VIAA-iaiii)

or a pharmaceutically acceptable salt thereof

wherein:

each Q^B is independently selected from CH_2, NH, and $N(C_{1-6}$ alkyl), provided that at least one Q^B is NH or $N(C_{1-6}$ alkyl);

Q^Z is O, NH, or $N(C_{1-6}$ alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

each R^C is independently halo or C_{1-6} alkyl;

Y^1 is selected from O, C(O), N(H), $N(C_{1-6}$ alkyl), C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^1 is halo or C_{2-6} alkynyl;

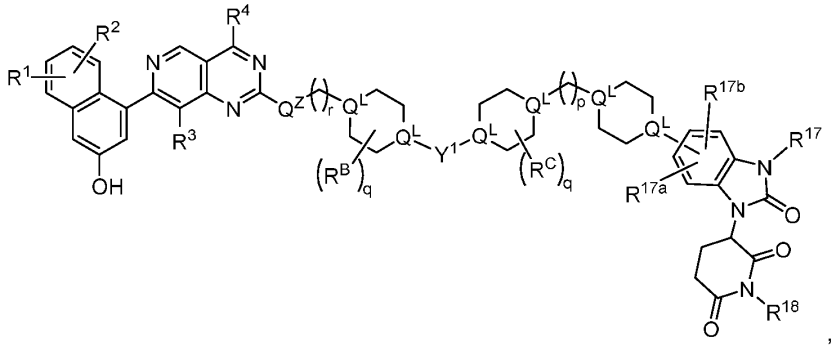
R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

r is 1, 2, 3, 4, 5, or 6;

s is 0, 1, 2, or 3; and

q is 0, 1, or 2.

In embodiments, the compound of Formula VIAA-ii has a structure of Formula VIAA-iia:



(VIAA-iia)

or a pharmaceutically acceptable salt thereof

wherein:

Q^Z is O, NH, or $N(C_{1-6}$ alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

R^B and R^C are each independently halo or C_{1-6} alkyl;

Y^1 is C_{1-6} alkyl or C_{1-6} haloalkyl;

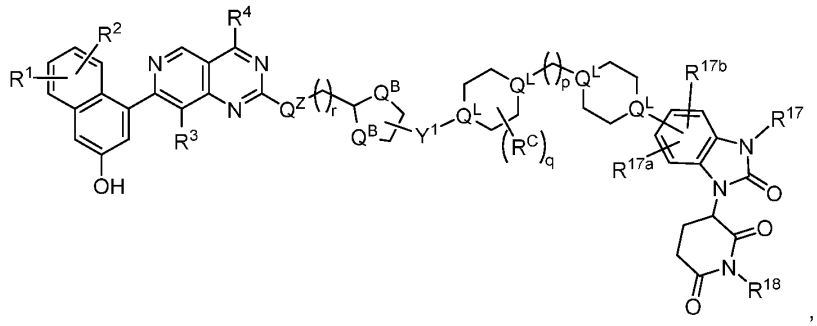
R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

p and r are each independently 1, 2, 3, 4, 5, or 6; and

each q is independently 0, 1, or 2.

In embodiments, the compound of Formula VIAA-ii has a structure of Formula VIAA-iib:



(VIAA-iib)

or a pharmaceutically acceptable salt thereof

wherein:

each Q^B is independently selected from CH_2, NH, and N(C_{1-6} alkyl), provided that at least one Q^B is NH or N(C_{1-6} alkyl);

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;

each R^C is independently halo or C_{1-6} alkyl;

Y^1 is selected from O, C_{1-6} alkyl, and C_{1-6} haloalkyl;

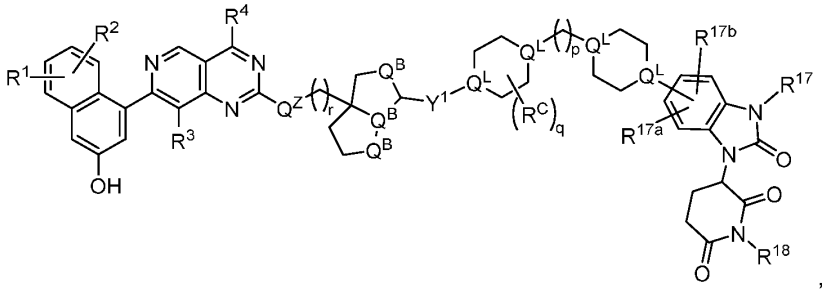
R^1 is halo or C_{2-6} alkynyl;

R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;

p and r are each independently 1, 2, 3, 4, 5, or 6; and

q is 0, 1, or 2.

In embodiments, the compound of Formula VIAA-ii has a structure of Formula VIAA-iic:



(VIAA-iic)

or a pharmaceutically acceptable salt thereof

wherein:

each Q^B is independently selected from CH_2, N, NH, and N(C_{1-6} alkyl), provided that at least one Q^B is N, NH, or N(C_{1-6} alkyl);

Q^Z is O, NH, or N(C_{1-6} alkyl);

each Q^L is independently CR^L or N;

each R^L is independently selected from H, halo, CN, and C_{1-6} alkyl;
each R^C is independently halo or C_{1-6} alkyl;
Y^1 is selected from O, C_{1-6} alkyl, and C_{1-6} haloalkyl;
R^1 is halo or C_{2-6} alkynyl;
R^2 is selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;
p and r are each independently 1, 2, 3, 4, 5, or 6; and
q is 0, 1, or 2.
In embodiments of Formula VIAA-iic, at least two Q^B are CH_2.

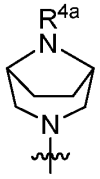
Various Embodiments of Formulae I-VIA, VIAA, VII, AI, AIV, and the Various Subgeneric Formulae Thereof, or Pharmaceutically Acceptable Salts Thereof

In embodiments, Q^1 is CH_2 or C(O). In embodiments, Q^2 is N. In embodiments, Q^3 is CH or N. In embodiments, R^{1a} is selected from H and OH. In embodiments, R^{1b} and R^{2b}, together with the phenyl to which they attach, form naphthyl substituted with R^1 and R^2. In embodiments, R^1 is selected from H, halo, and C_{1-6} alkyl. In embodiments, R^1 is H. In embodiments, R^1 is halo. In embodiments, R^1 is C_{1-6} alkyl. In embodiments, R^{2a} is selected from H and halo. In embodiments, R^2 is selected from H, C_{1-6} alkyl, and C≡CH. In embodiments, R^2 is C_{3-6} cycloalkyl.

In embodiments, R^2 is H. In embodiments, R^2 is C_{1-6} alkyl. In embodiments, R^2 is C≡CH. In embodiments, R^3 is halo.

In embodiments R^4 is bridged 8-membered heterocycloalkyl optionally substituted with R^{4a}.

In embodiments of Formulae I–VI, R^4 is:



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In embodiments, R^{4a} is H or C_{1-6} alkyl. In embodiments, R^{5a} is H, halo, or C_{1-6} alkoxy. In embodiments, R^5 is H or C_{1-6} alkyl. In embodiments, R^6 is H or C_{1-6} alkyl.

In embodiments, R^7 is selected from H, =O, halo, and C_{1-6} alkoxy. In embodiments, wherein R^7 is =O. In embodiments, R^7 is halo. In embodiments, R^7 is C_{1-6} alkoxy. In embodiments, R^8 is H or C_{1-6} alkyl. In embodiments, R^8 is H. In embodiments, R^9 is selected from H, halo, and C_{1-6} alkoxy. In embodiments, R^9 is halo.

In embodiments, R^9 is C_{1-6} alkoxy. In embodiments, R^{10} is H. In embodiments, R^{11} is H. In embodiments, R^{12} is C_{1-6} alkyl. In embodiments, R^{13} is H. In embodiments, R^{14} is H or C_{1-6} alkyl. In embodiments, R^{14} is H. In embodiments, R^{14} is C_{1-6} alkyl.

In embodiments, R^{15a} is H, halo, or C_{1-6} alkoxy. In embodiments, R^{15b} is H, halo, or C_{1-6} alkoxy. In embodiments, R^{15} is H or C_{1-6} alkyl. In embodiments, R^{16} is H or C_{1-6} alkyl. In embodiments, R^{17a} and R^{17b} are each independently H or halo. In embodiments, R^{17} is C_{1-6} alkyl. In embodiments, R^{18} is H.

In embodiments, Ring A is phenyl. In embodiments, Ring A is 6-membered heterocycloalkyl. In embodiments, Ring A is dihydropyridinyl. In embodiments, B is a bond. In embodiments, B is C_{1-6} alkyl.

In embodiments, each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C(O), 5–12 membered heterocycloalkyl, wherein 5–12 membered heterocycloalkyl is optionally substituted with halo. In embodiments, 5–12 membered heterocycloalkyl is fused 8 membered heterocycloalkyl.

In embodiments, each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, and 6–12 membered heterocycloalkyl, wherein 6–12 membered heterocycloalkyl is optionally substituted with halo.

In embodiments, each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, 6-8 membered heterocycloalkyl, and 5–6 membered heteroaryl, wherein 6–8 membered heterocycloalkyl is optionally substituted with halo.

In embodiments, L forms the following linker: (C_{1-6} alkoxy)-(6–12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(6–12 membered heterocycloalkyl).

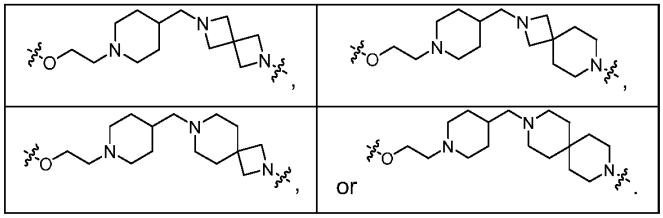
In embodiments, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(6–12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(6–12 membered heterocycloalkyl).

In embodiments, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(7-membered heterocycloalkyl).

In embodiments, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(9-membered heterocycloalkyl).

In embodiments, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(11-membered heterocycloalkyl).

In embodiments, each L forms the linker:



In embodiments, n is 6, and each L forms the following linker: (C_{1-6} alkoxy)-(6-12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl).

In embodiments, n is 6, and each L forms the following linker: (C_{1-6} alkoxy)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl).

In embodiments, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(5-12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(5-12 membered heterocycloalkyl).

In embodiments, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(11-membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl).

In embodiments, 11-membered heterocycloalkyl is spirocyclic 11-membered heterocycloalkyl.

In embodiments, n is 6, and each L forms the following linker: (C_{1-6} alkoxy)-(5-12 membered heterocycloalkyl)-(O)-(5–12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(5–12 membered heterocycloalkyl), wherein 5–12 membered heterocycloalkyl is optionally substituted with C_{1-6} alkyl.

In embodiments, n is 6, and each L forms the following linker: (C_{1-6} alkoxy)-(5-membered heterocycloalkyl)-(O)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl), wherein 5 membered heterocycloalkyl is optionally substituted with C_{1-6} alkyl.

In embodiments, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(5-12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(5-12 membered heterocycloalkyl).

In embodiments, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(9-membered heterocycloalkyl).

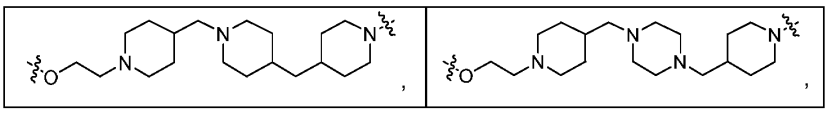
In embodiments, 9-membered heterocycloalkyl is spirocyclic 9-membered heterocycloalkyl.

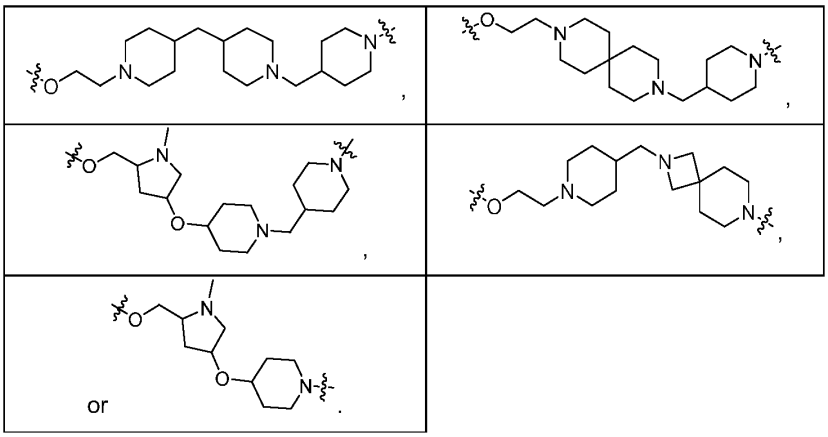
In embodiments, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(5-12 membered heterocycloalkyl)-(O)-(5-12 membered heterocycloalkyl), wherein 5-12 membered heterocycloalkyl is optionally substituted with C_{1-6} alkyl.

In embodiments, n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(5-membered heterocycloalkyl)-(O)-(6-membered heterocycloalkyl), wherein 5 membered heterocycloalkyl is optionally substituted with C_{1-6} alkyl.

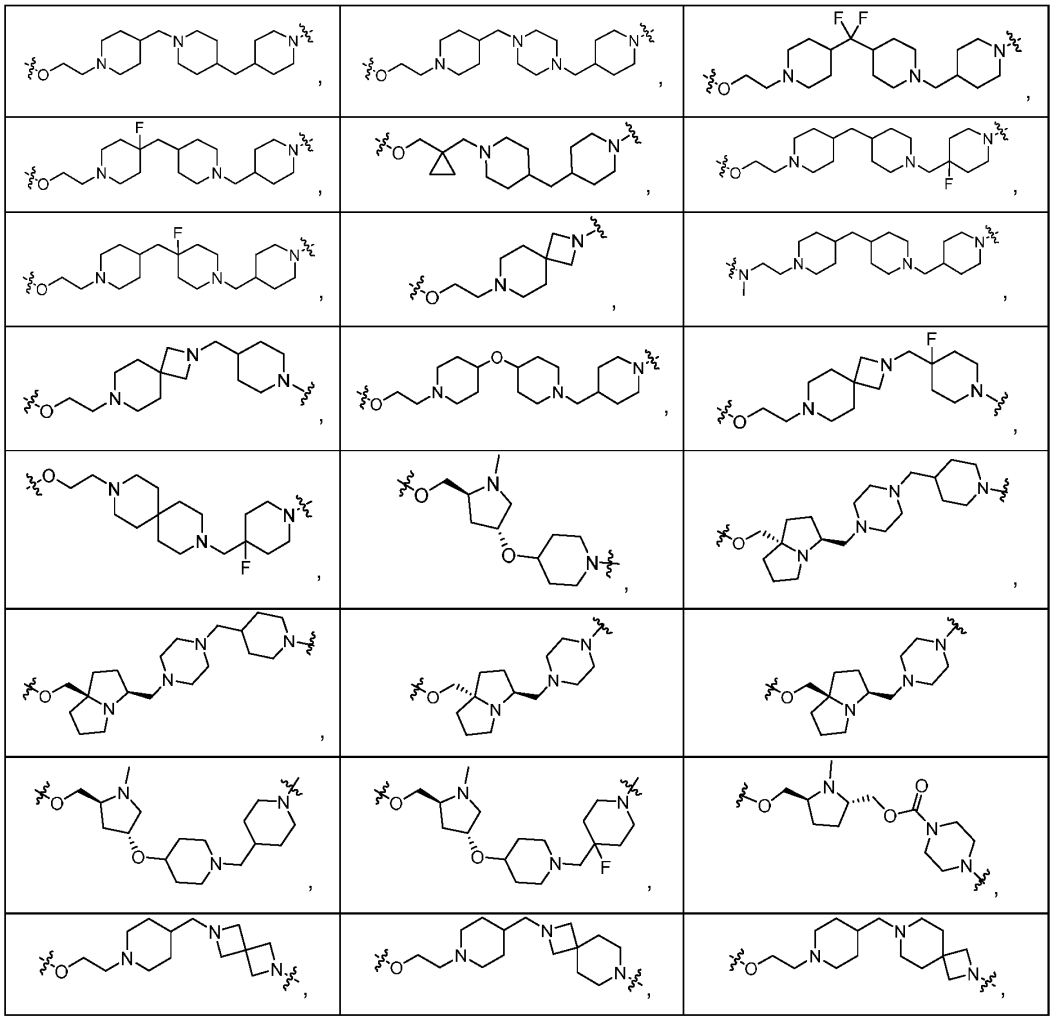
In embodiments, heterocycloalkyl contains 1, 2, or 3 heteroatoms independently selected from N, O, and S. In embodiments, heterocycloalkyl contains 1 or 2 heteroatoms independently selected from N, O, and S. In embodiments, heterocycloalkyl contains 1 or 2 heteroatoms independently selected from N and O. In embodiments, heterocycloalkyl contains 1 or 2 nitrogen heteroatoms.

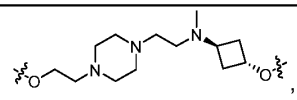
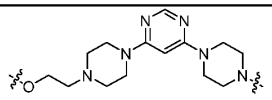
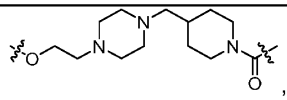
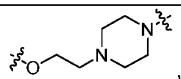
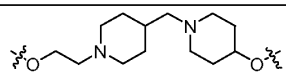
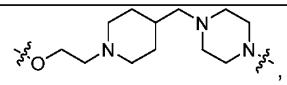
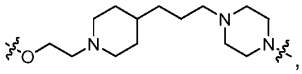
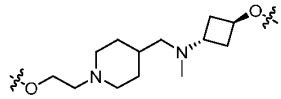
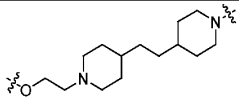
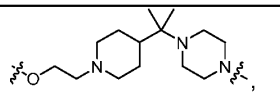
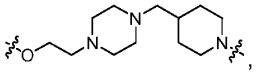
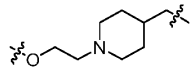
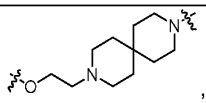
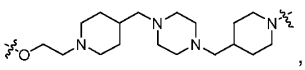
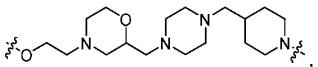
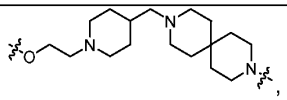
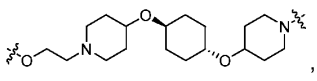
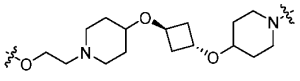
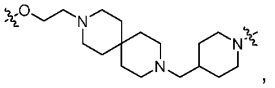
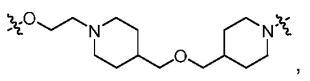
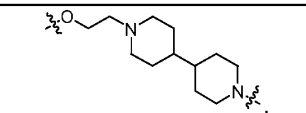
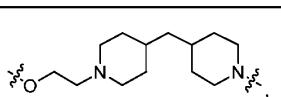
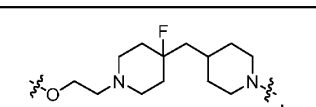
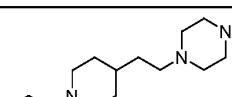
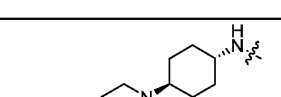
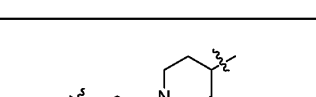
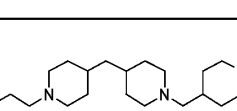
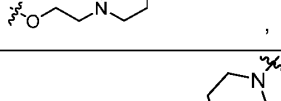
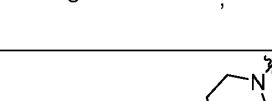
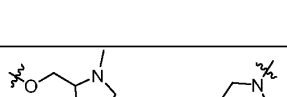
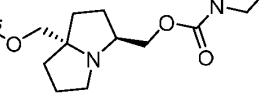
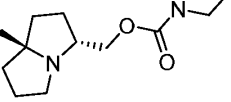
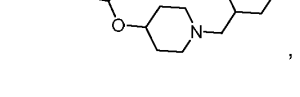
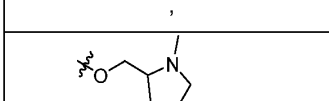
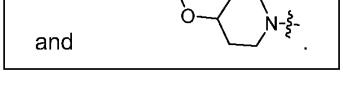
In embodiments, each L forms the linker:





In embodiments, $(L)_n$ is selected from:



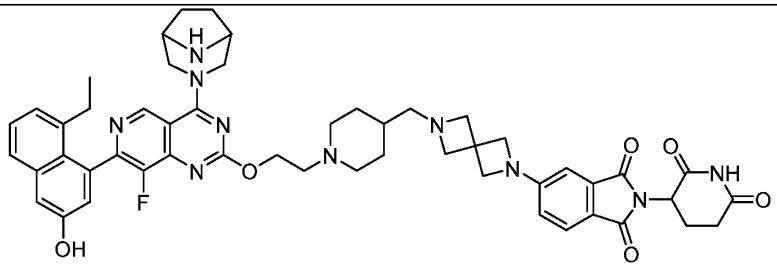
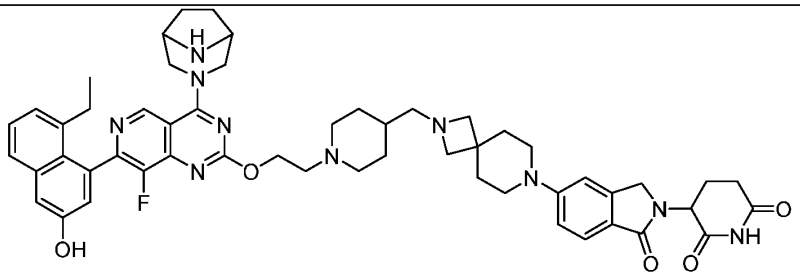
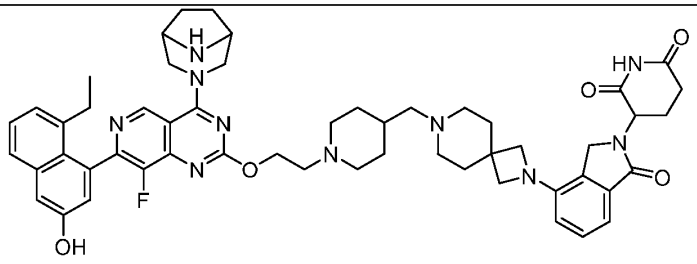
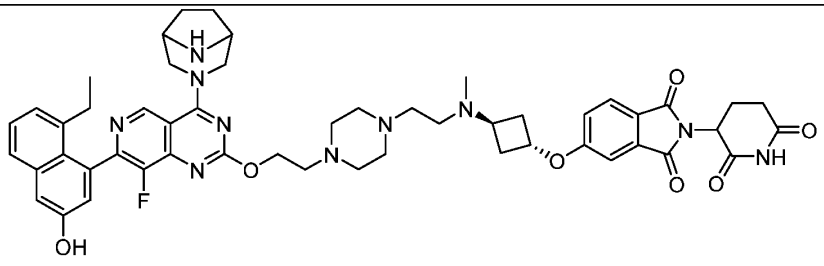
		
		
		
		
		
		
		
		
		
		
		
		
		

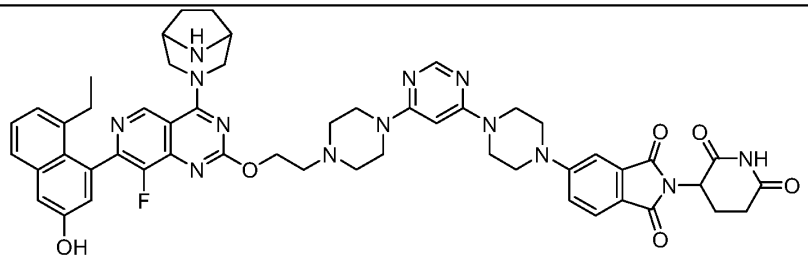
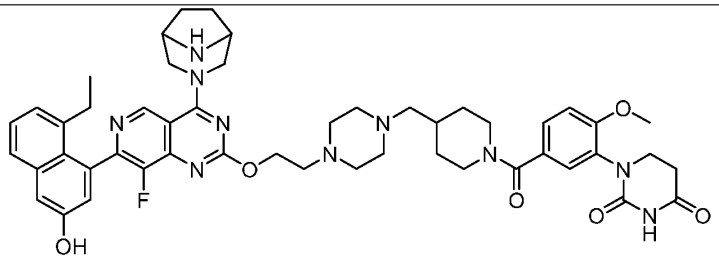
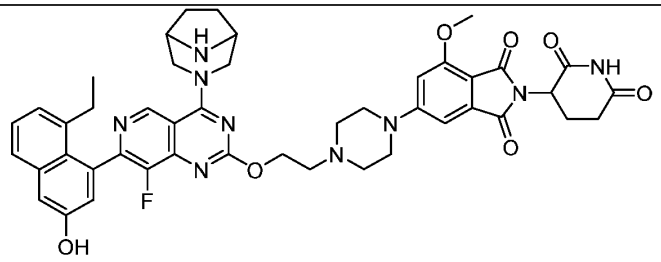
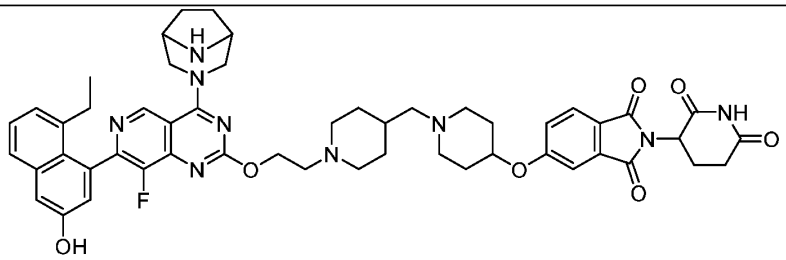
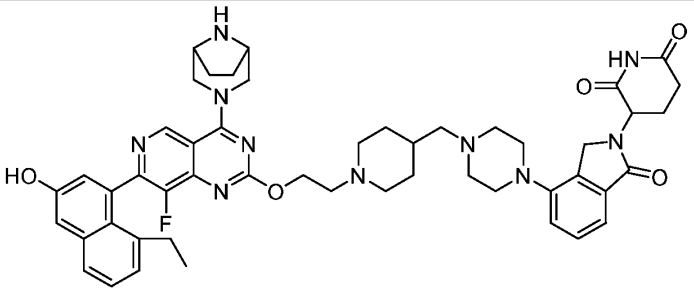
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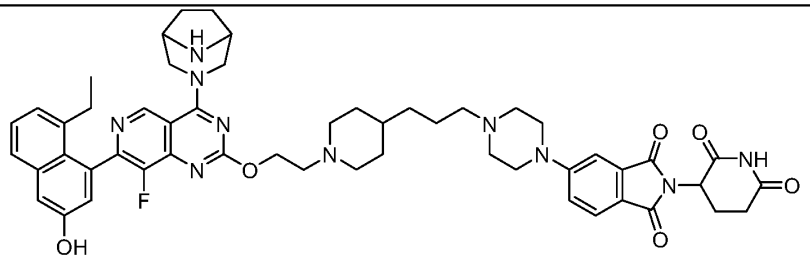
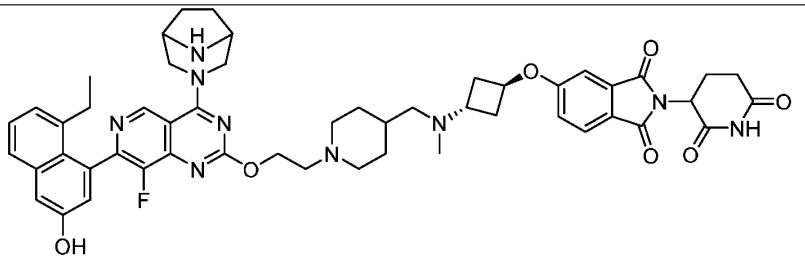
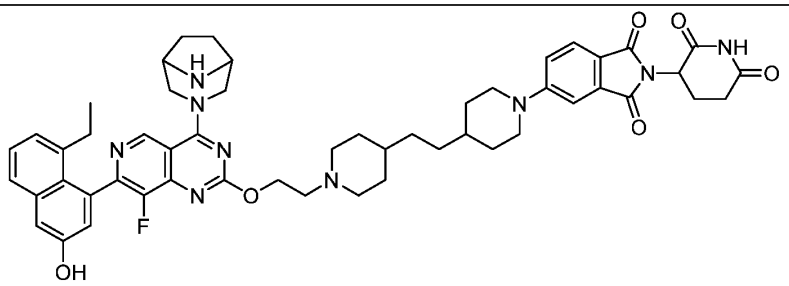
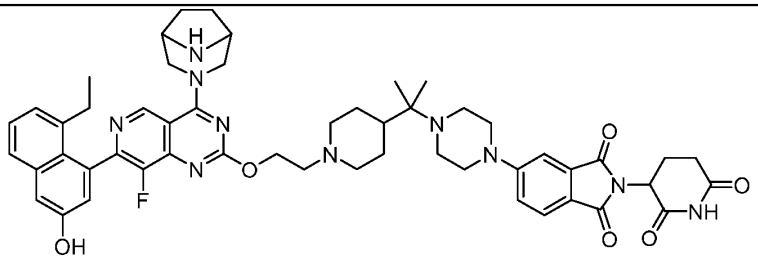
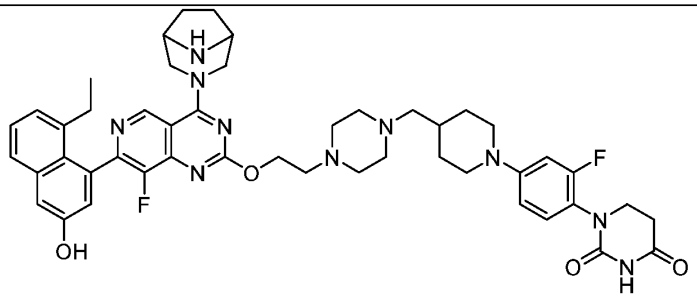
In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents are to be chosen in conformity with well-known principles of chemical structure connectivity and stability.

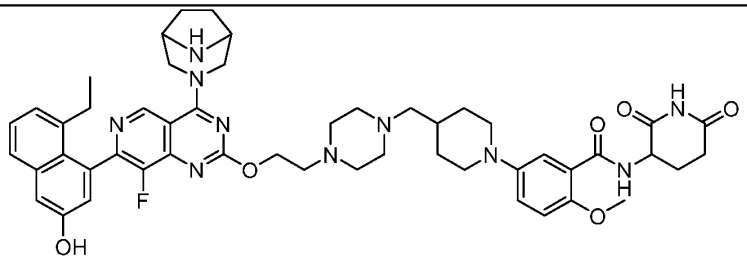
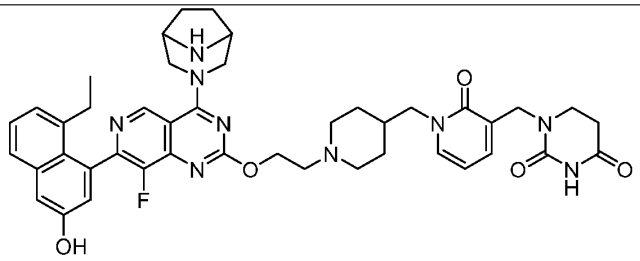
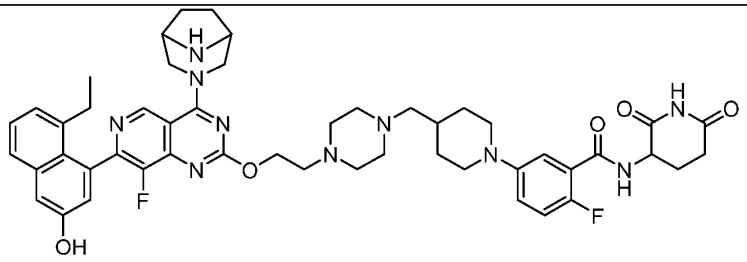
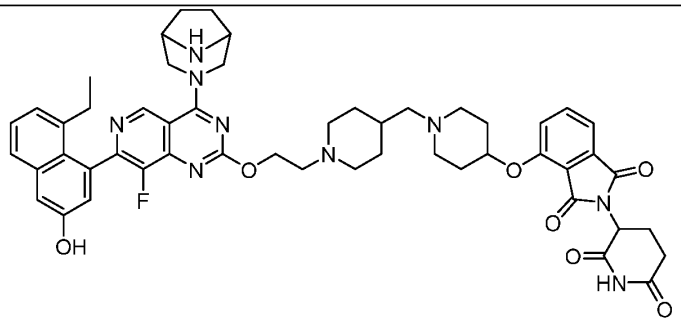
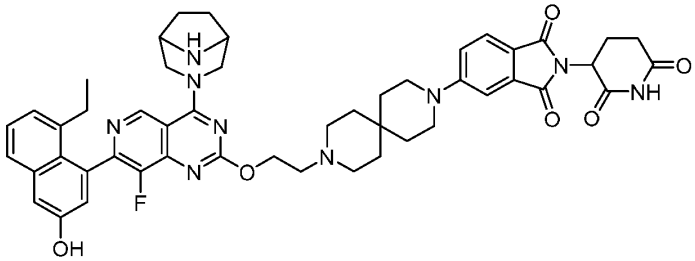
In embodiments, the compound of Formula I is selected from a compound in Table 1, or a pharmaceutically acceptable salt thereof.

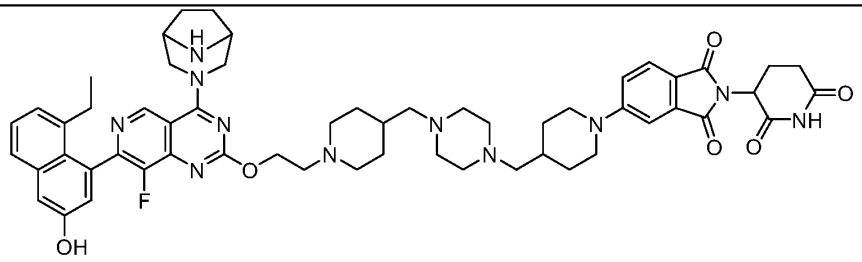
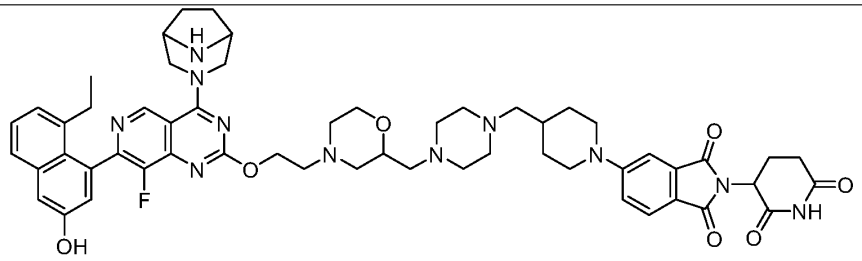
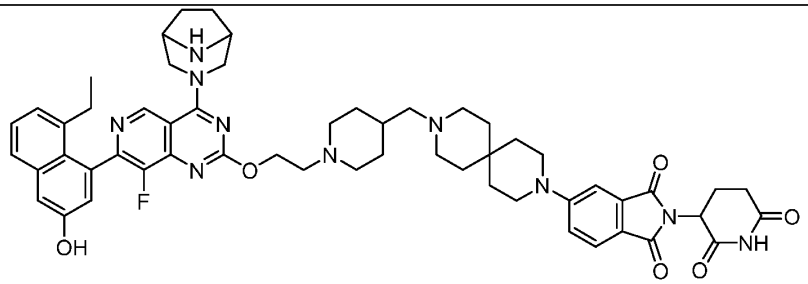
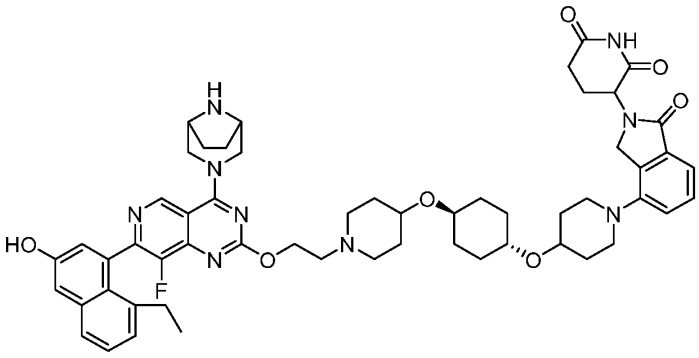
Table 1.

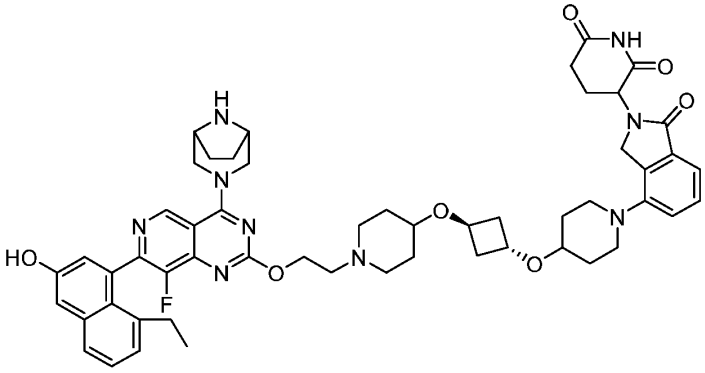
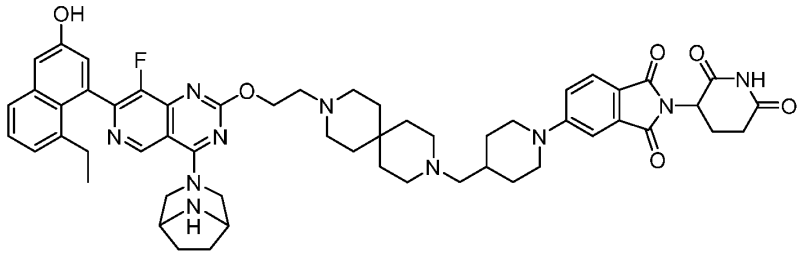
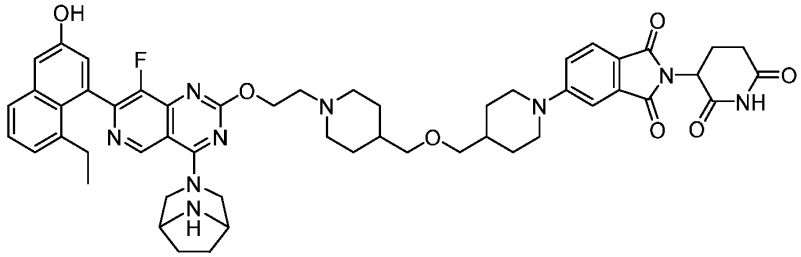
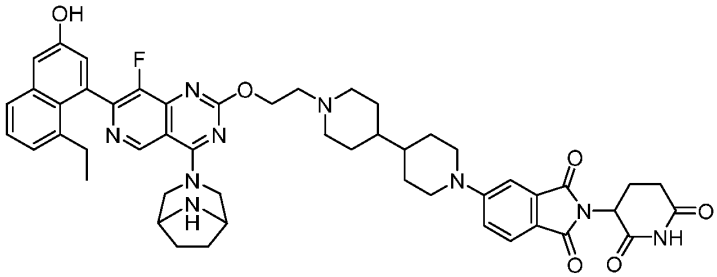
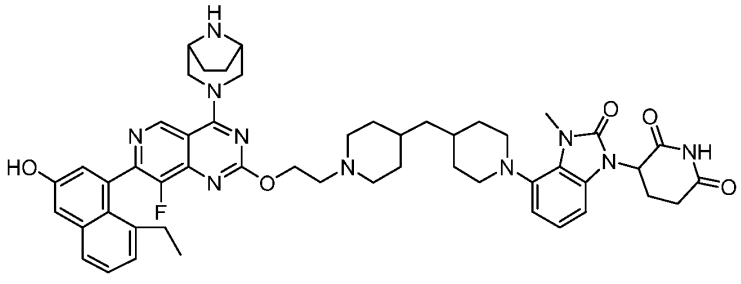
Compound	Structure
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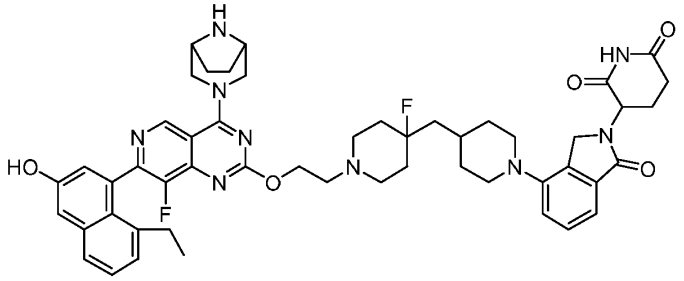
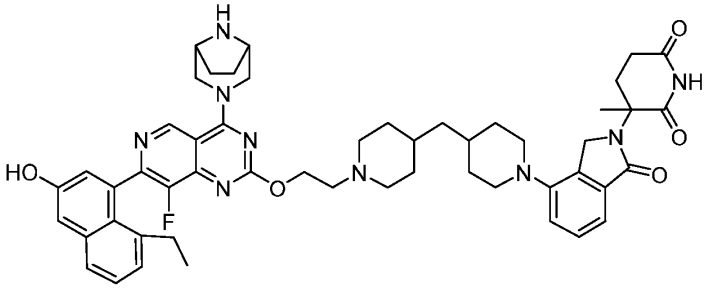
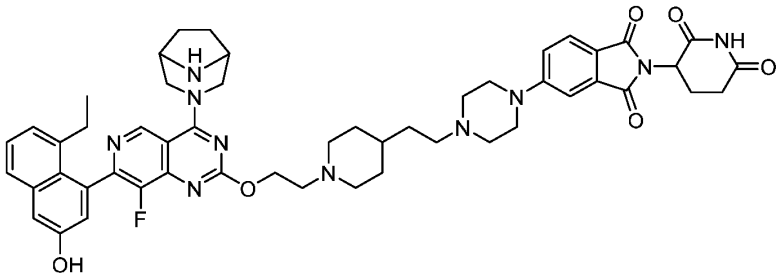
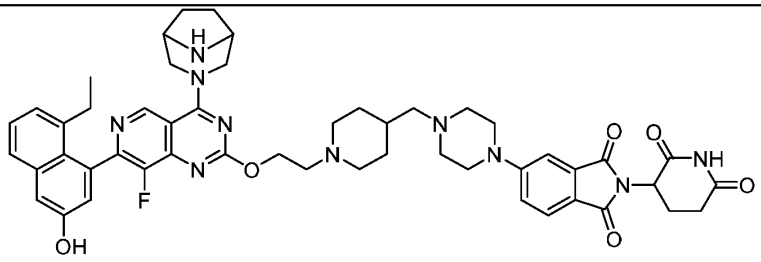
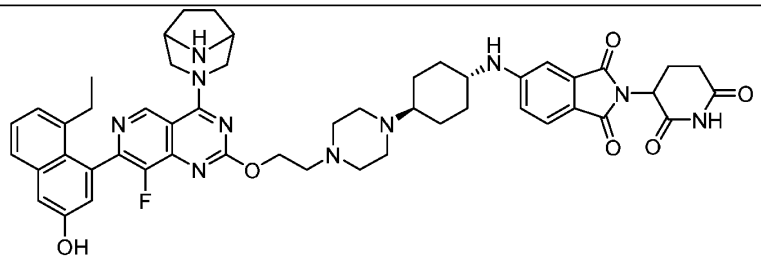
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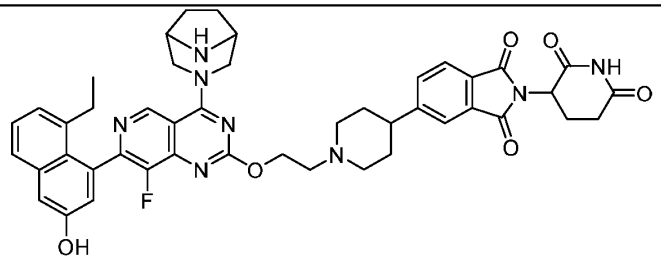
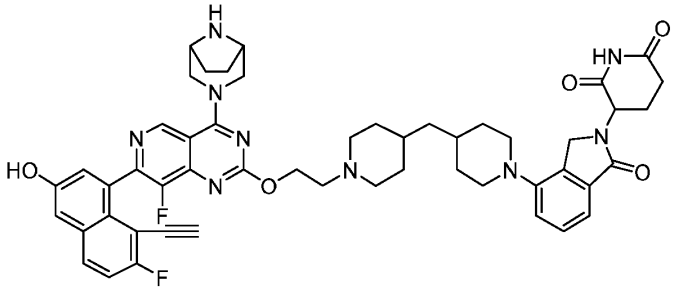
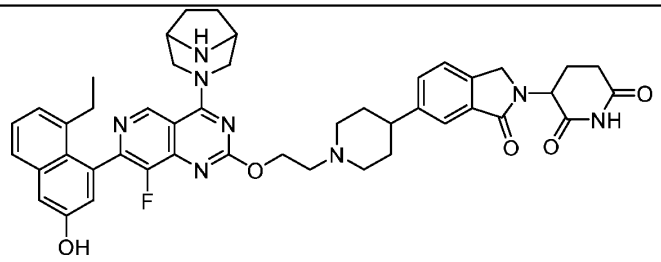
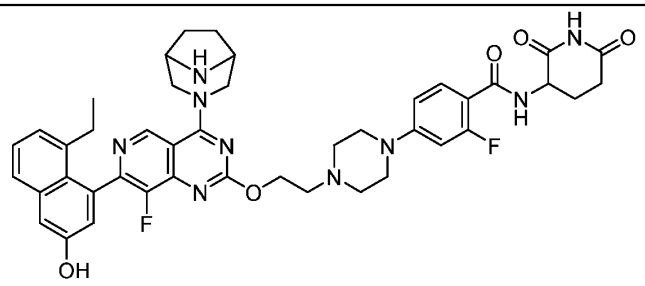
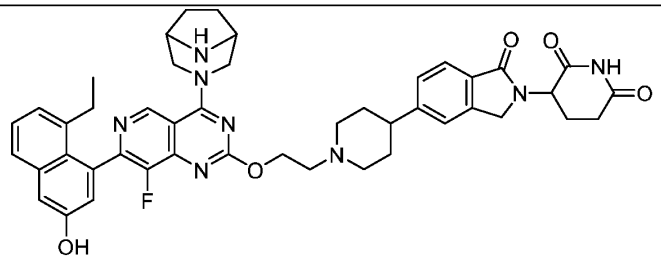
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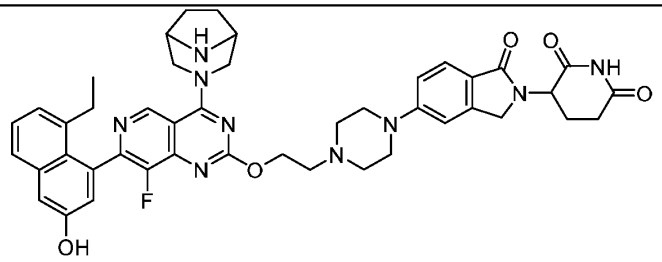
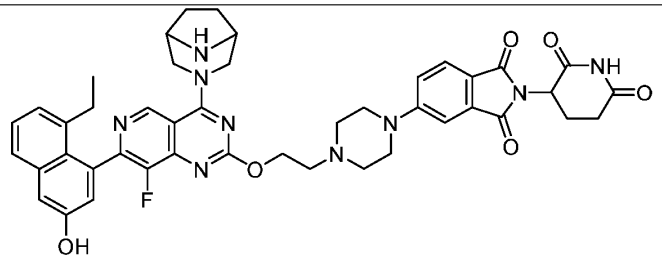
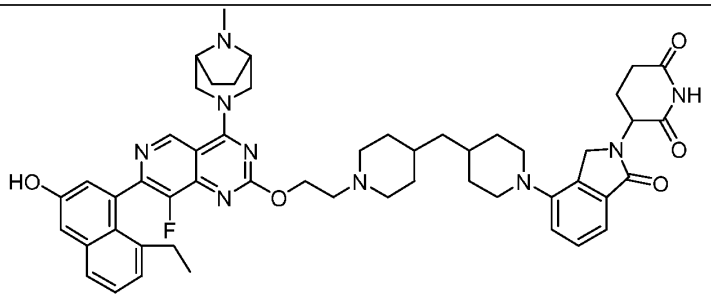
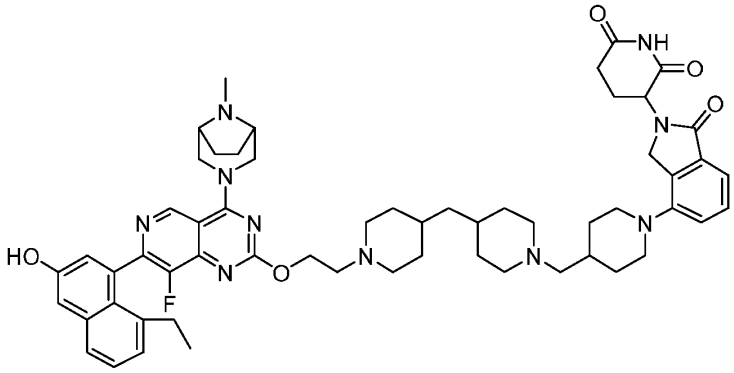
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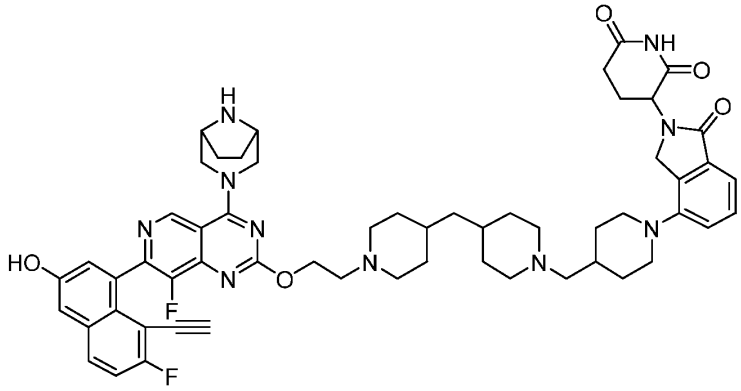
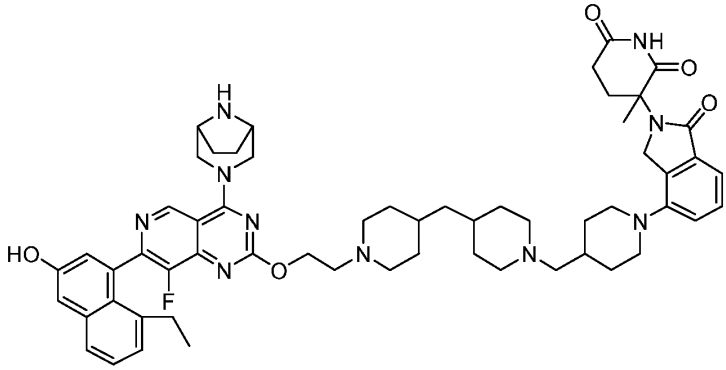
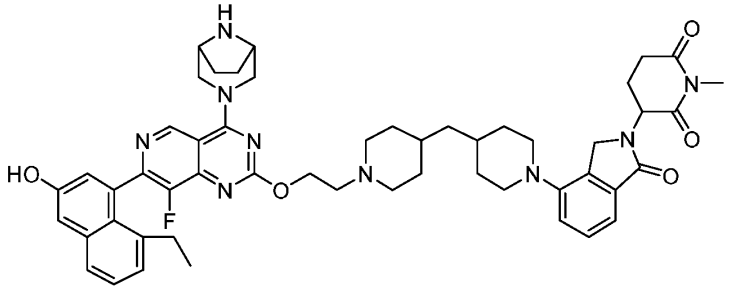
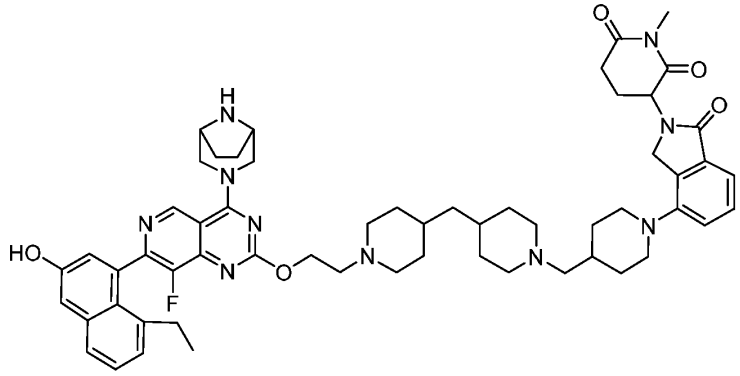
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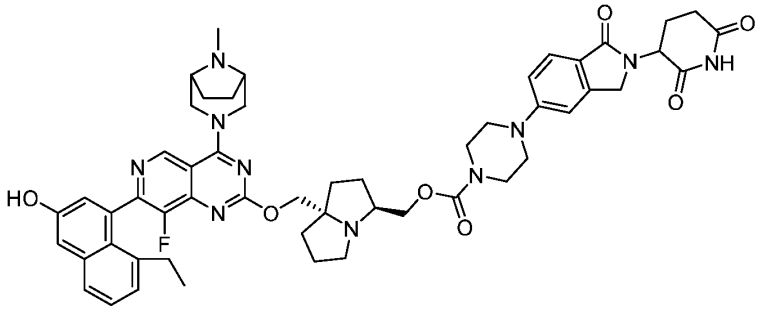
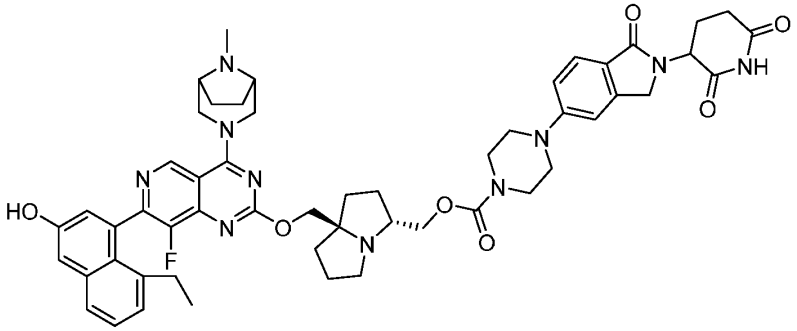
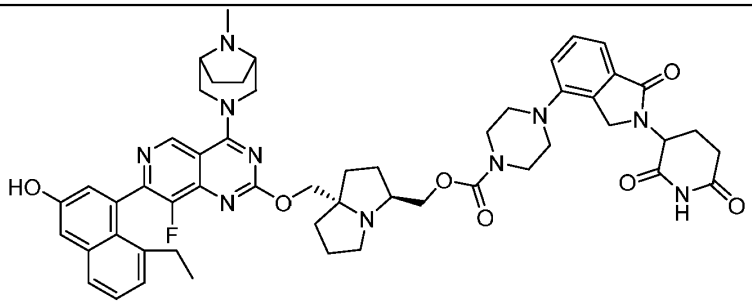
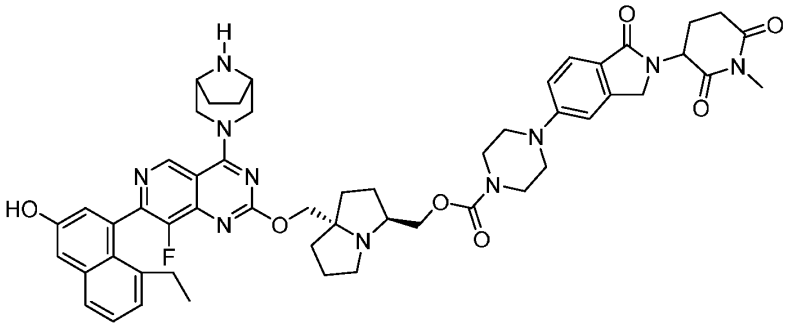
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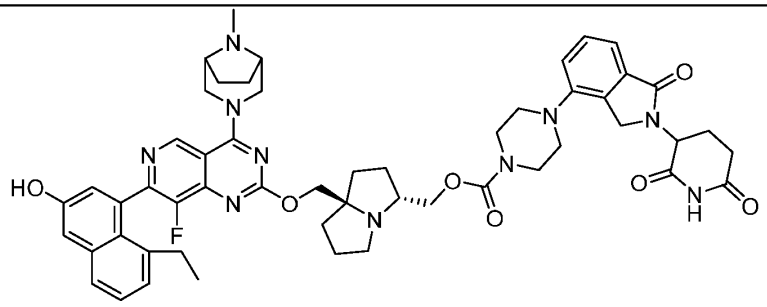
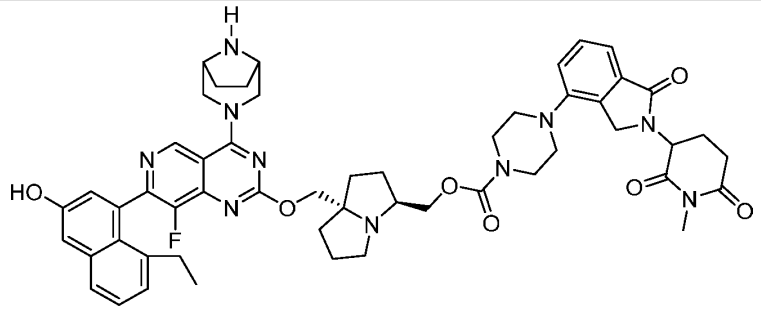
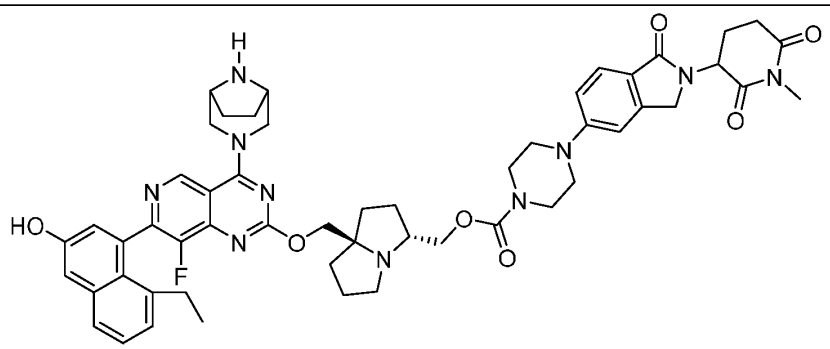
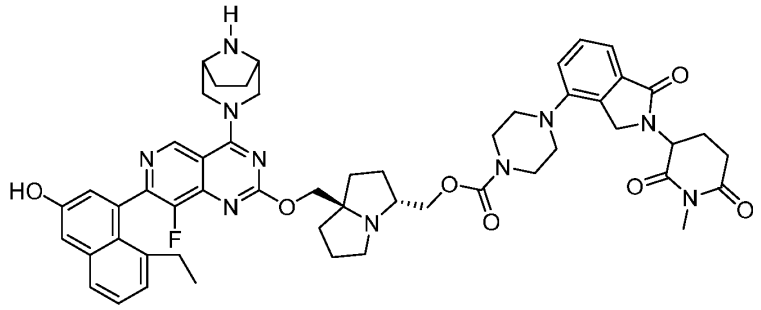
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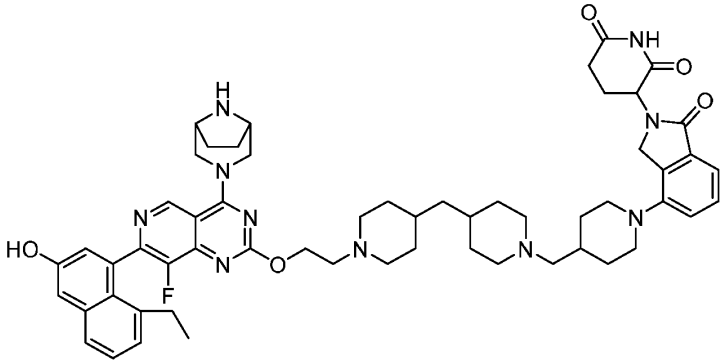
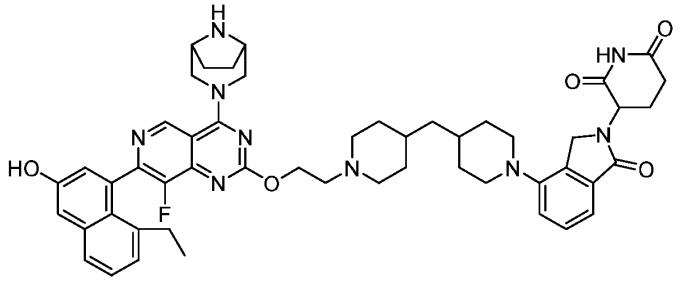
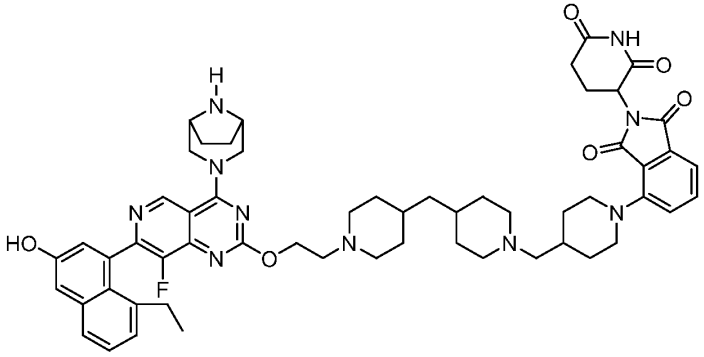
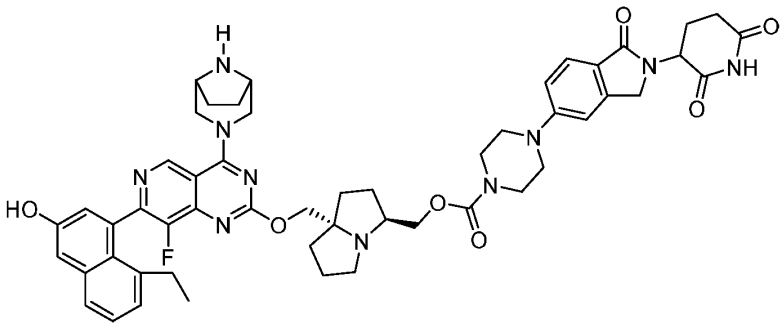
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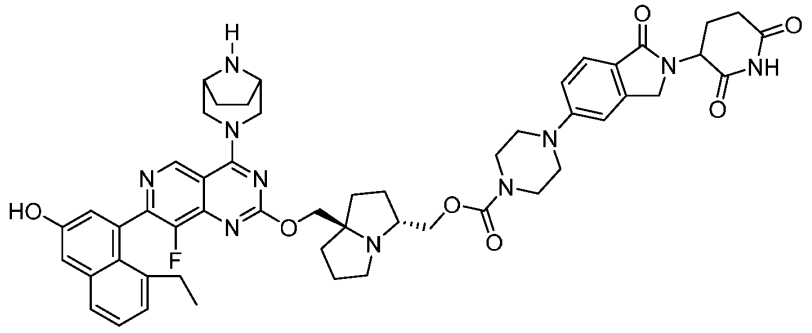
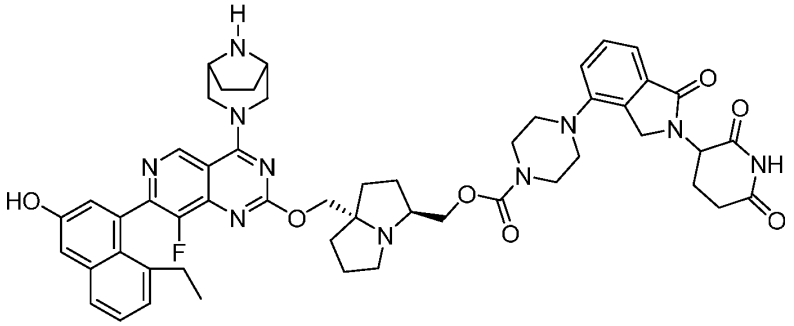
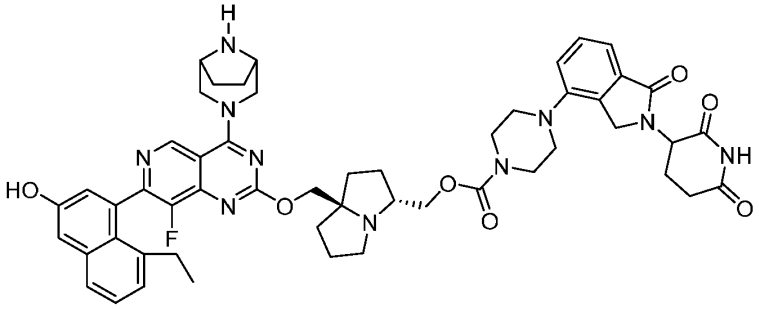
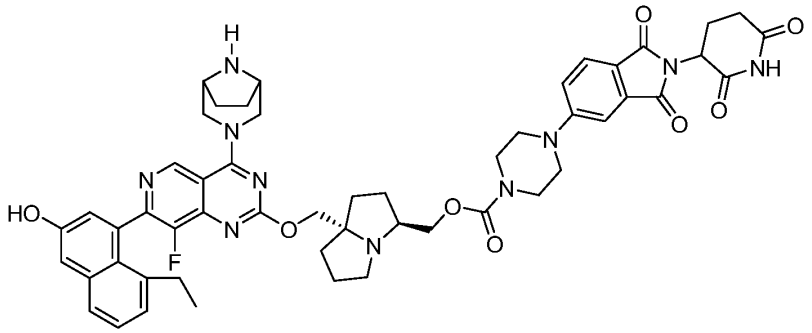
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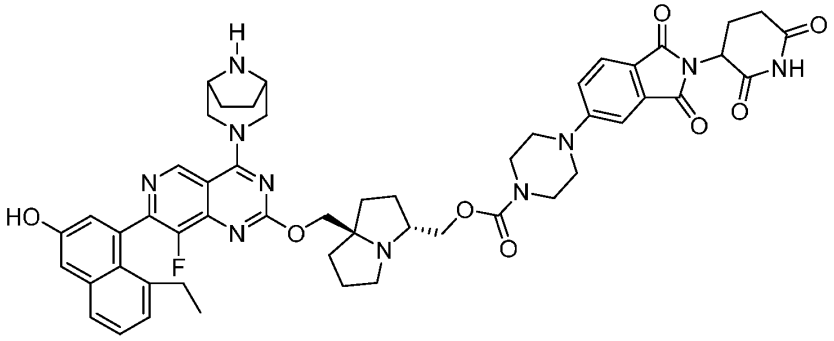
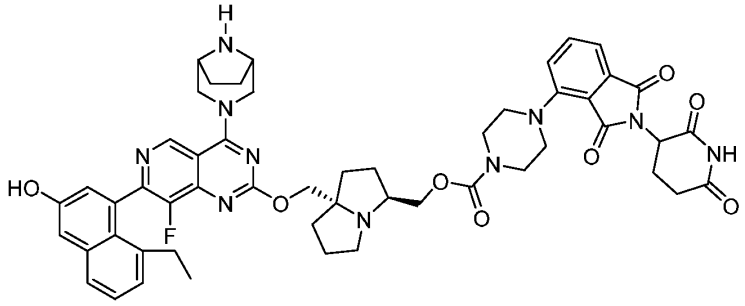
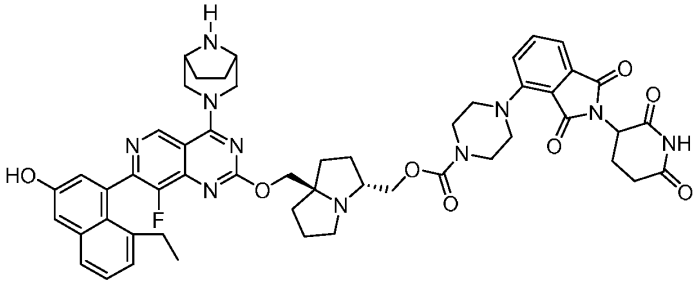
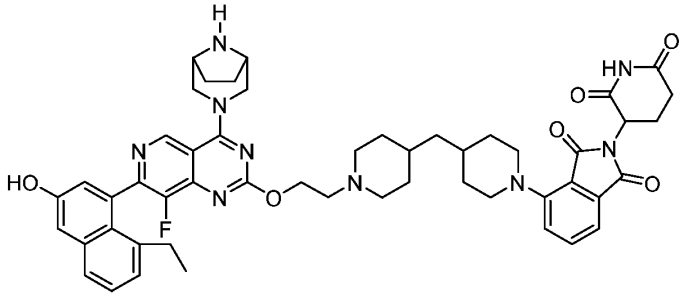
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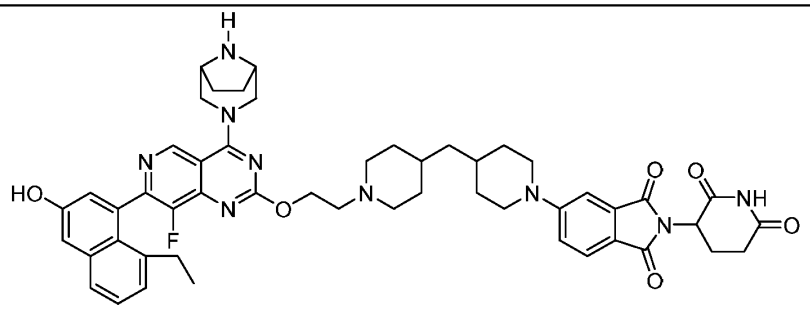
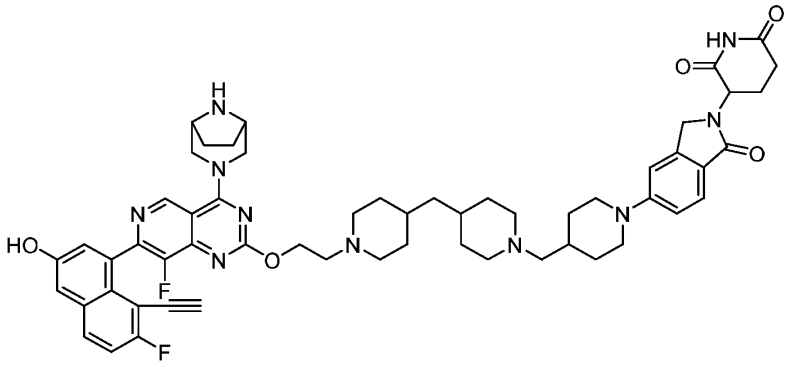
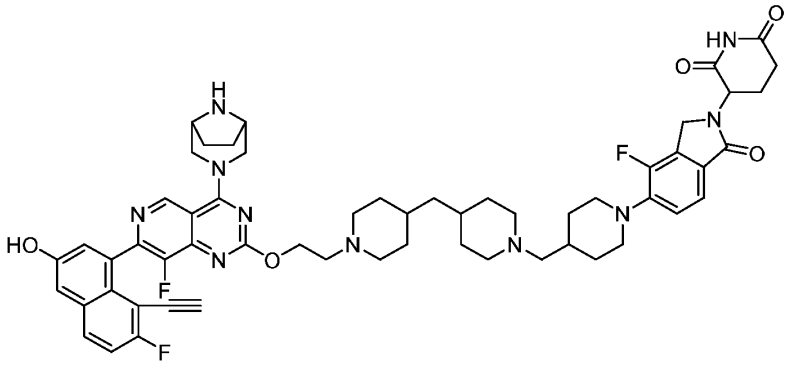
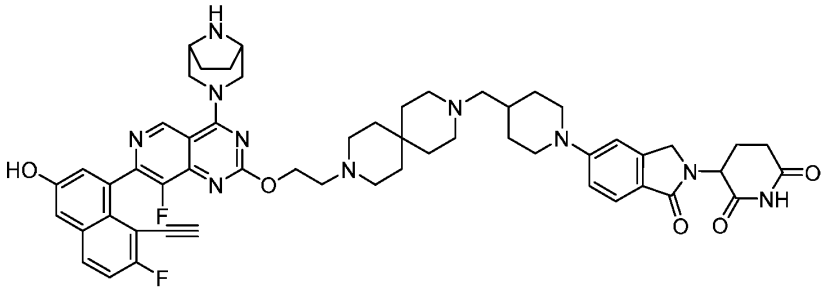
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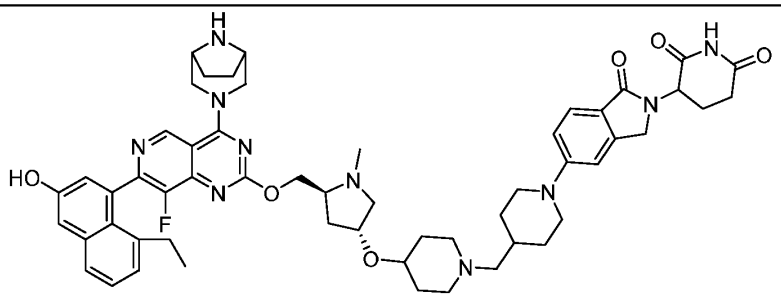
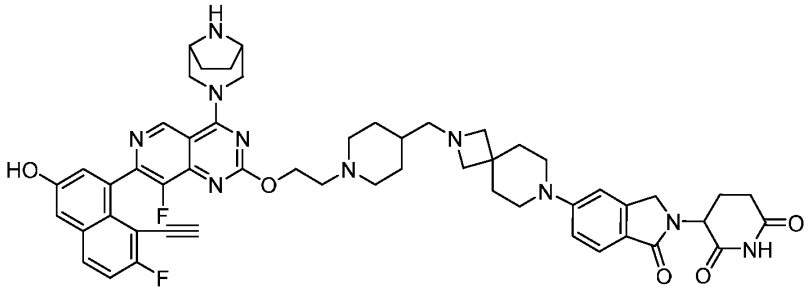
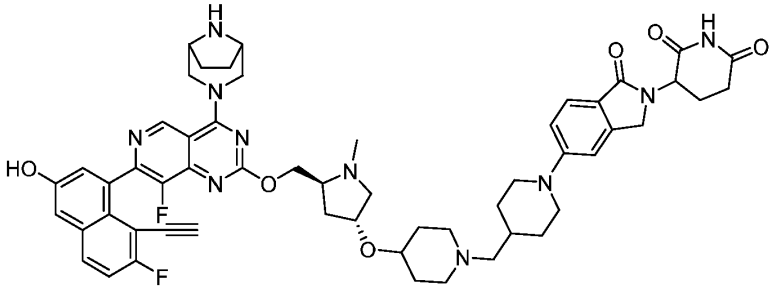
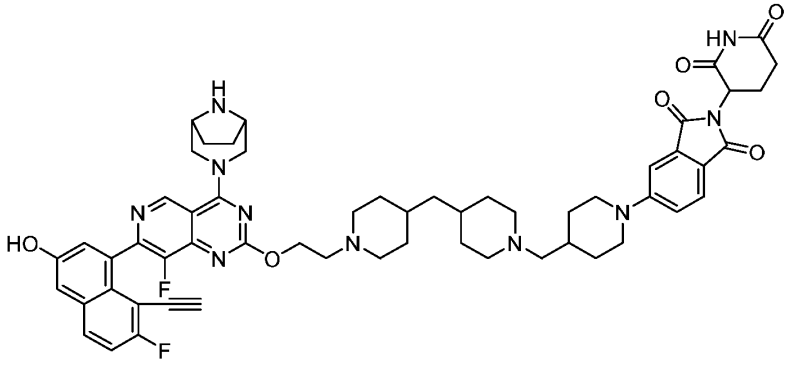
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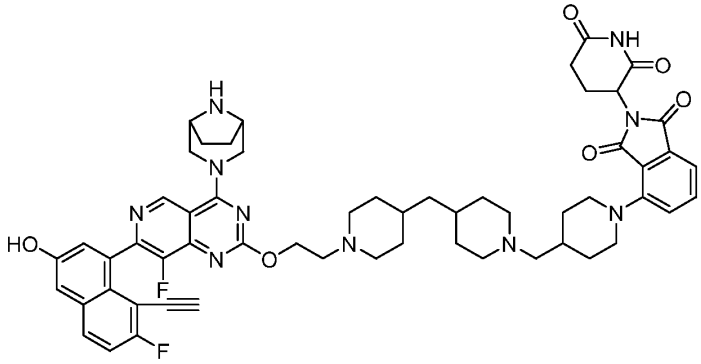
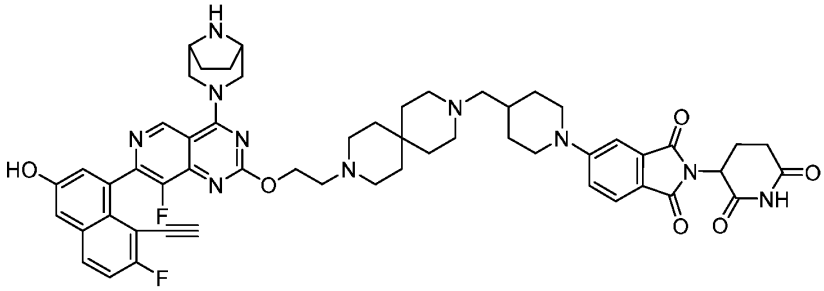
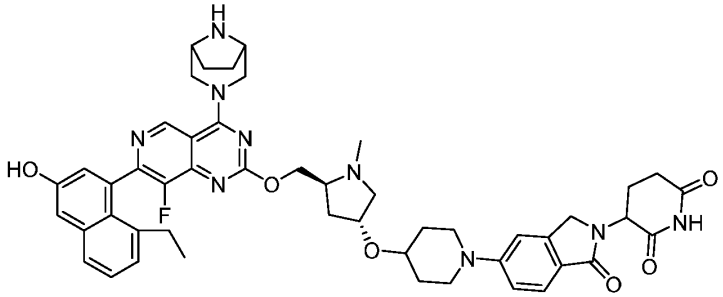
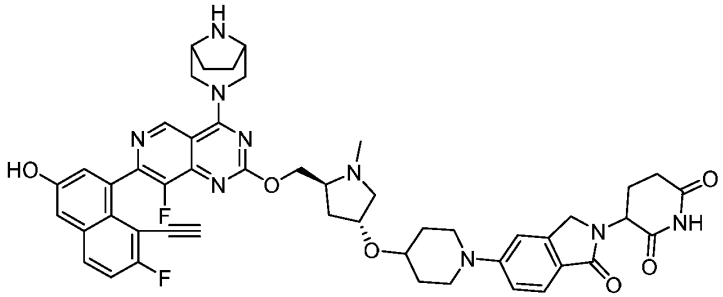
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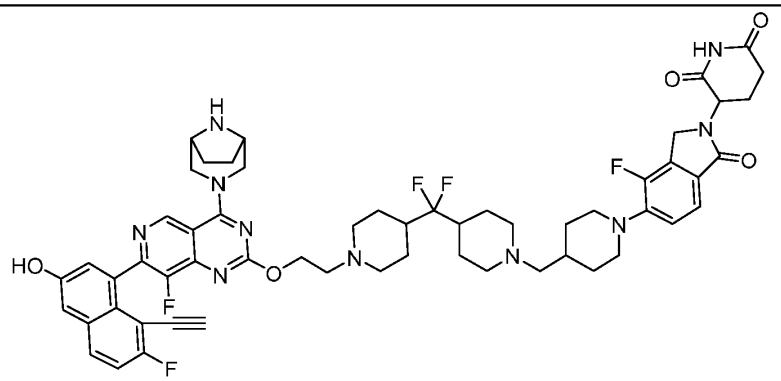
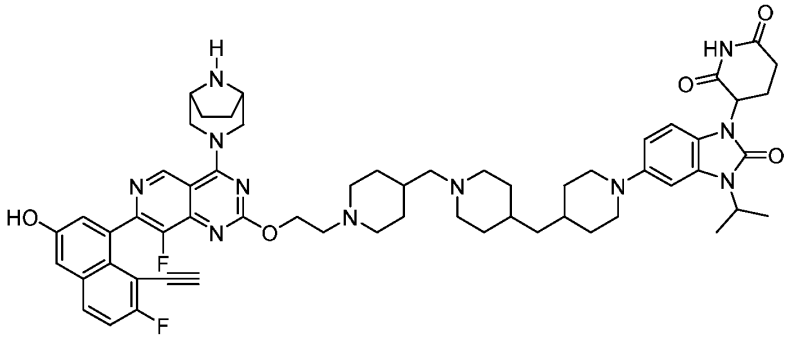
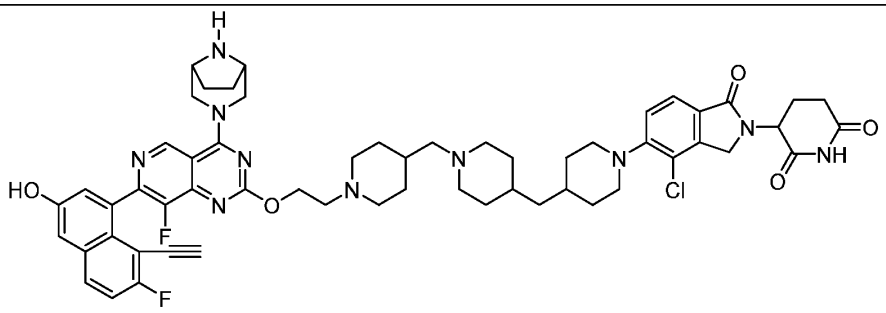
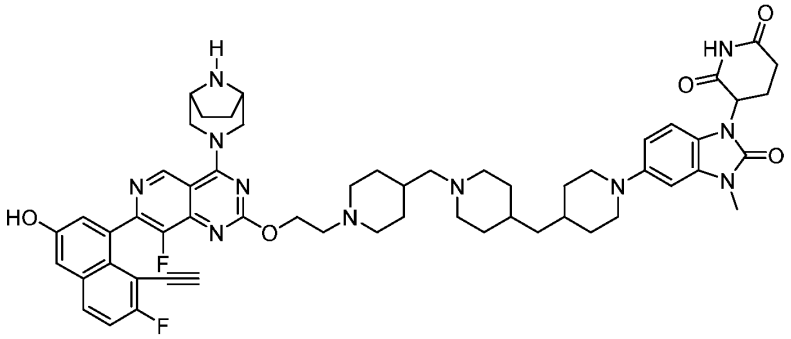
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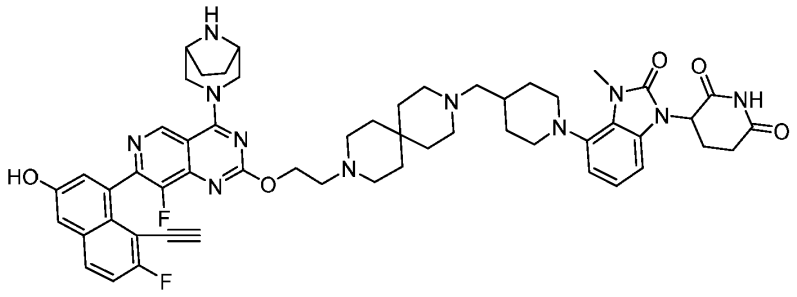
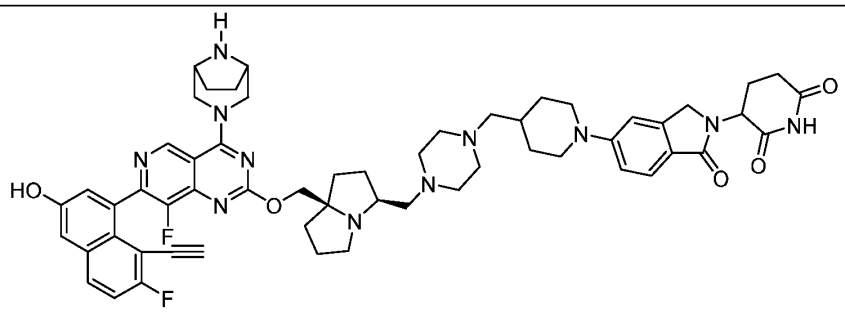
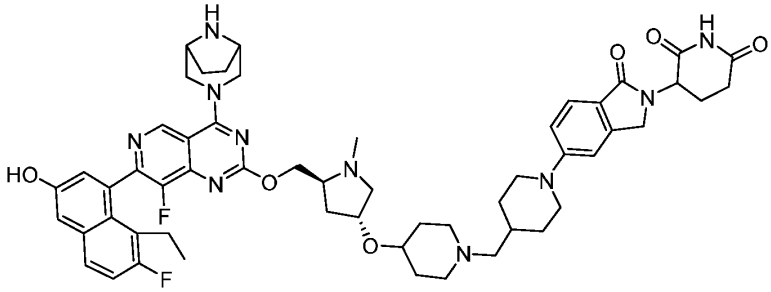
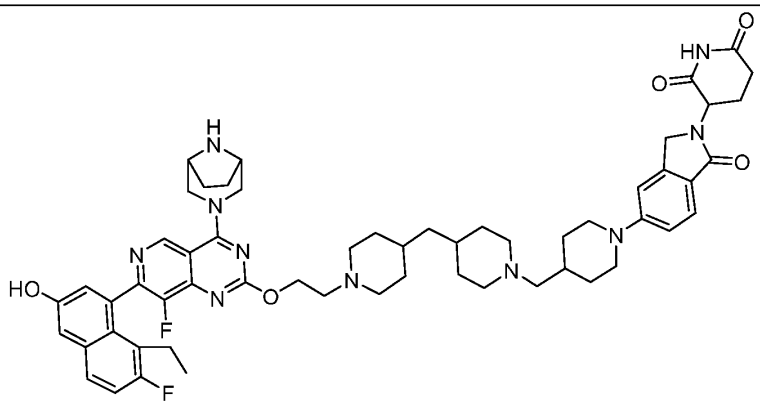
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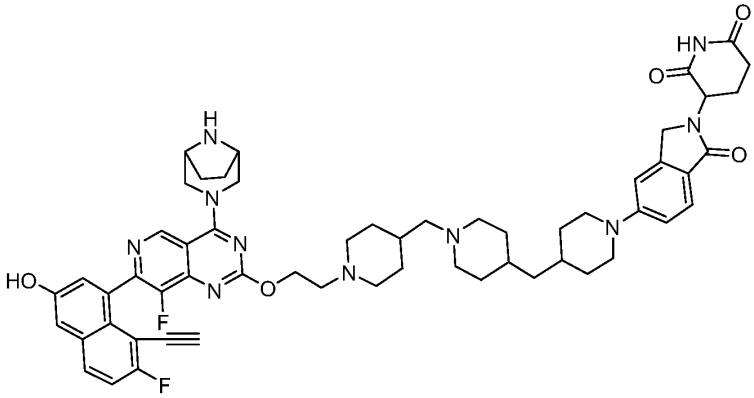
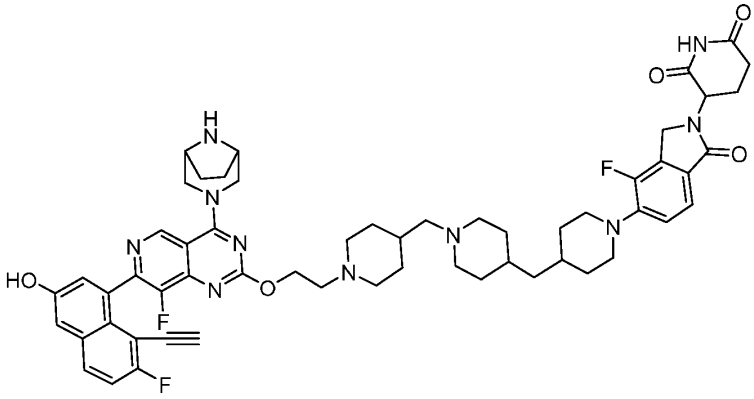
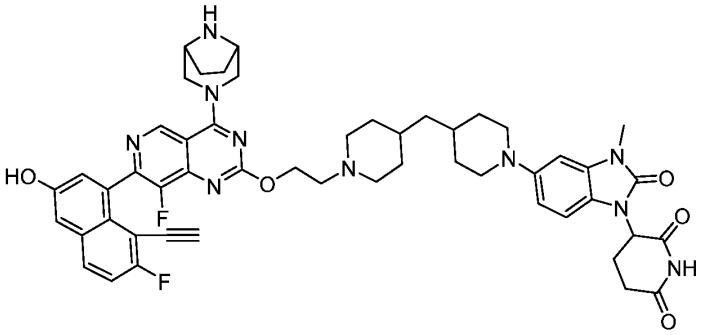
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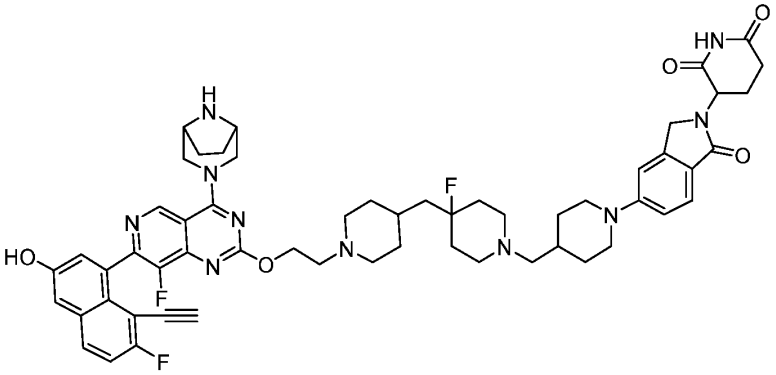
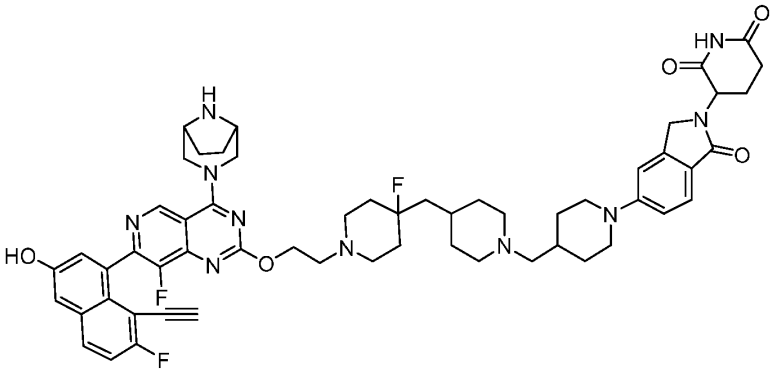
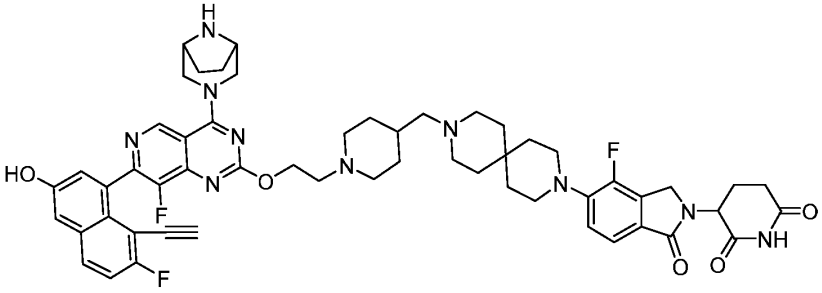
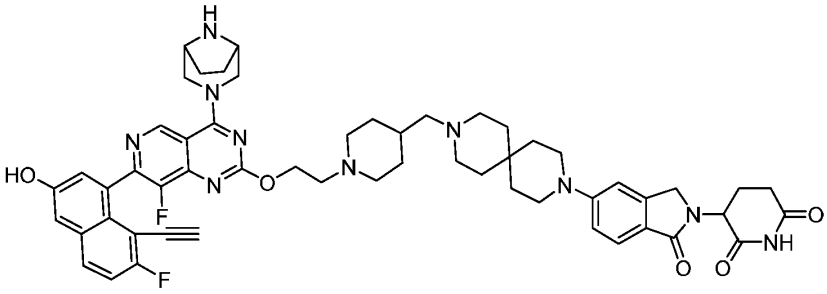
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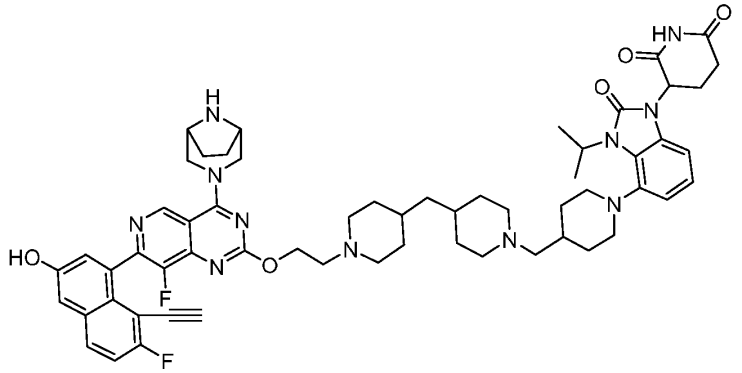
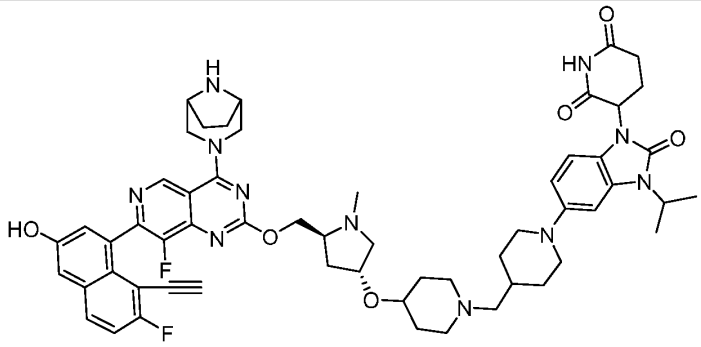
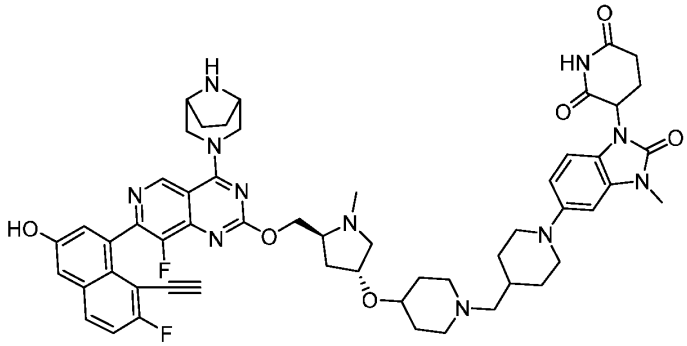
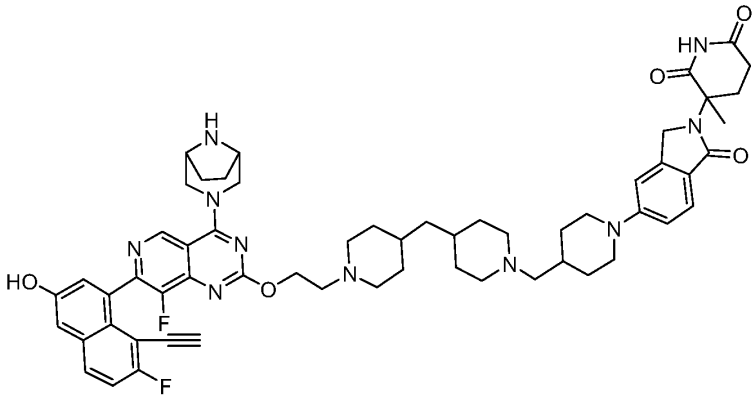
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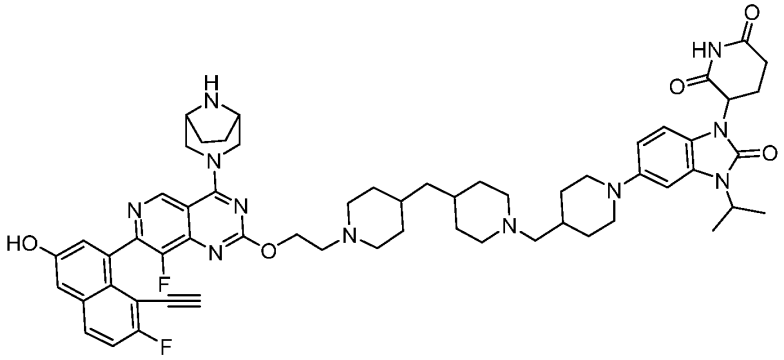
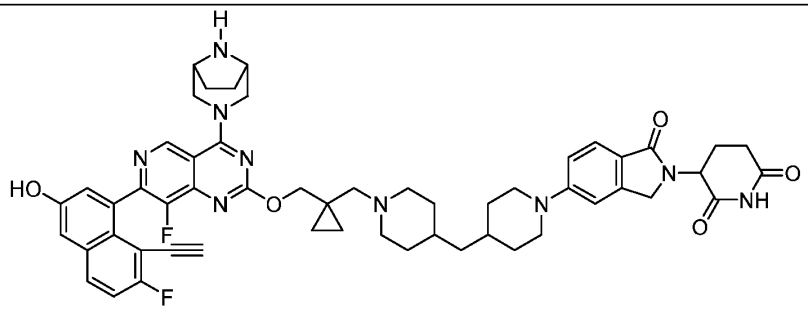
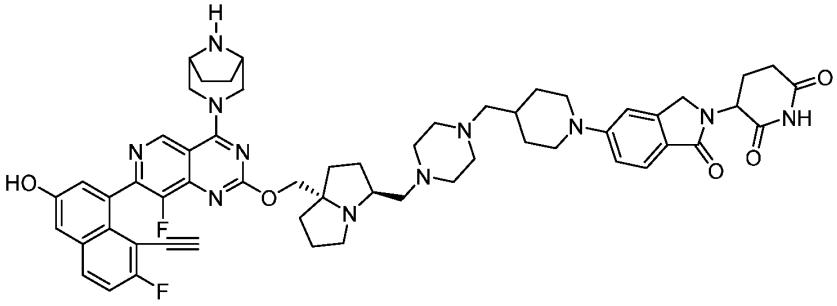
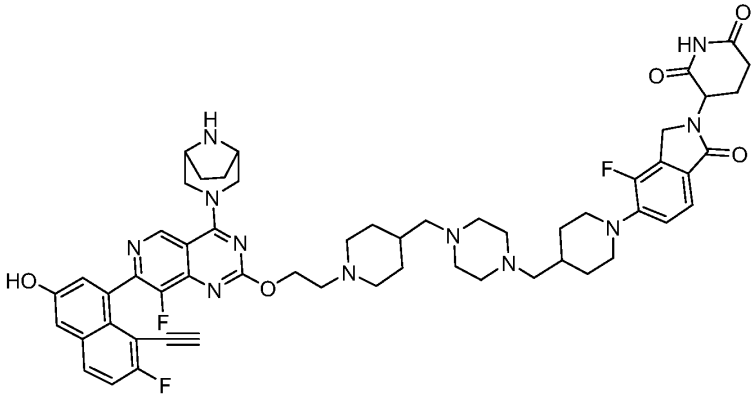
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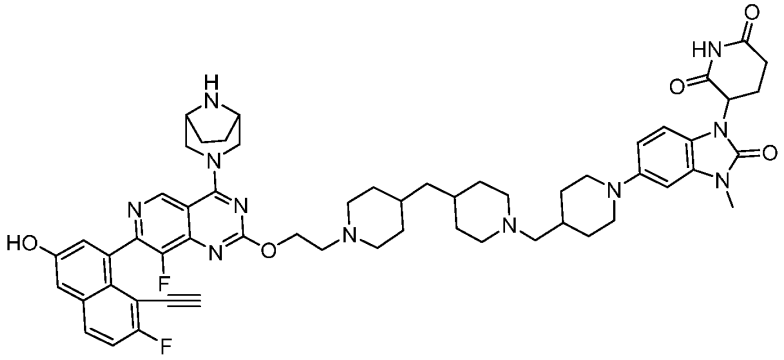
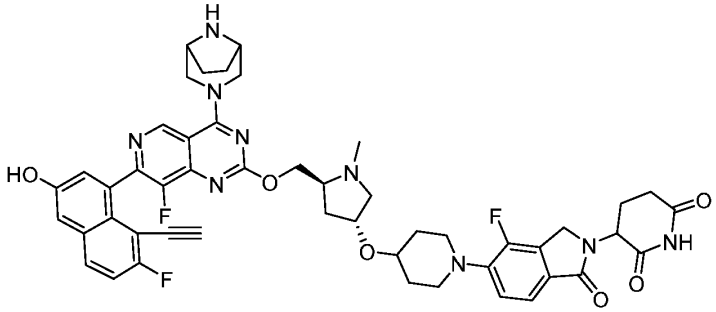
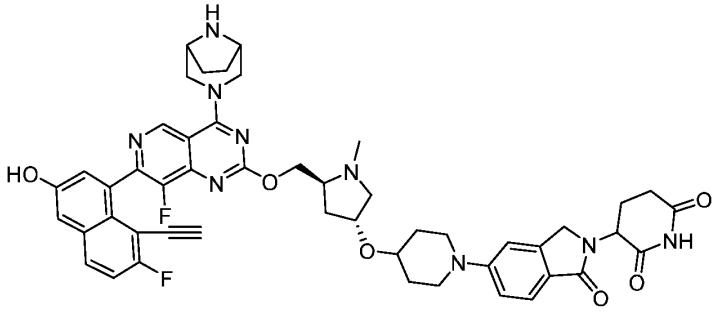
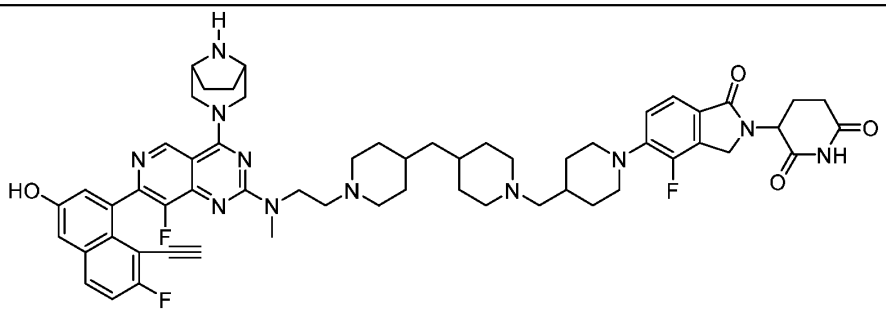
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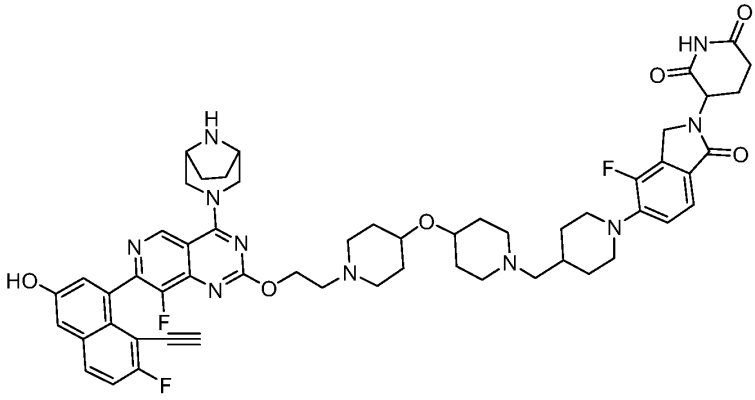
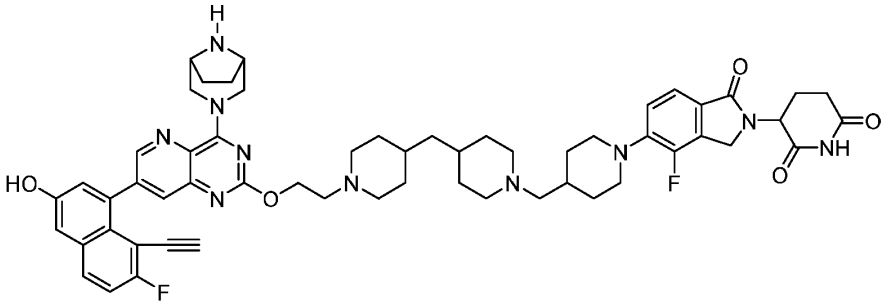
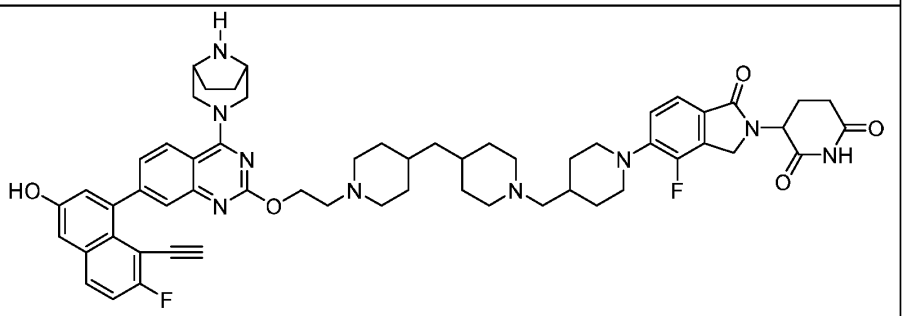
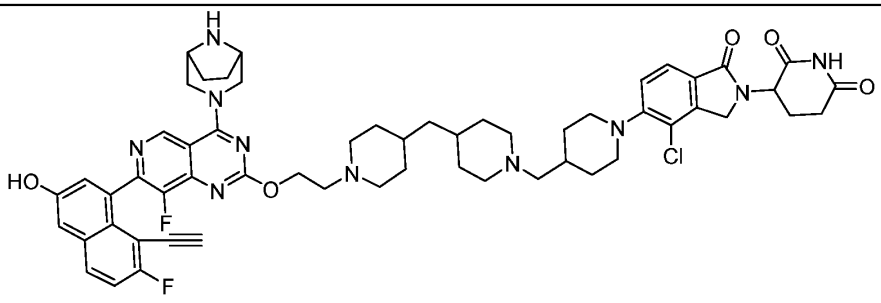
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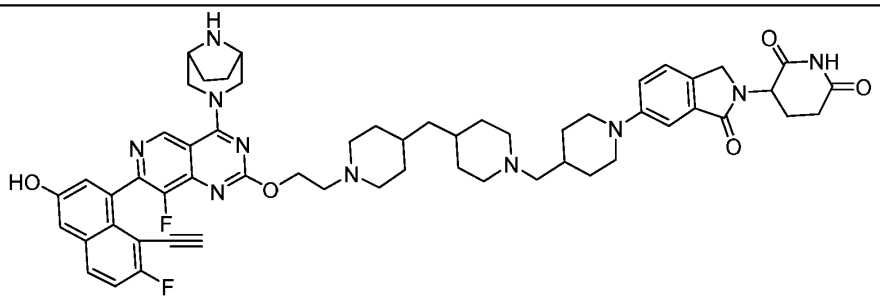
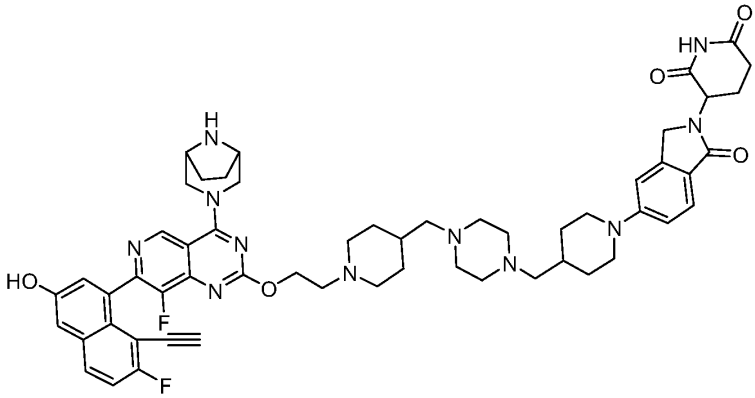
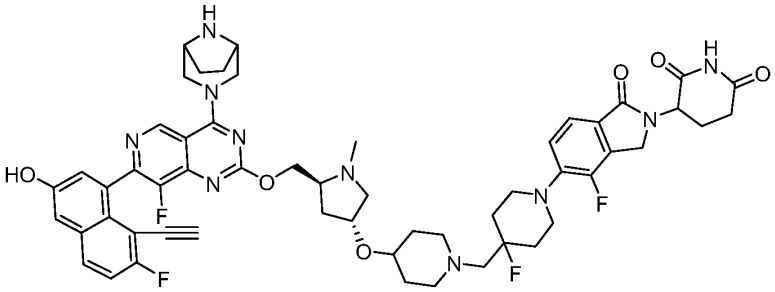
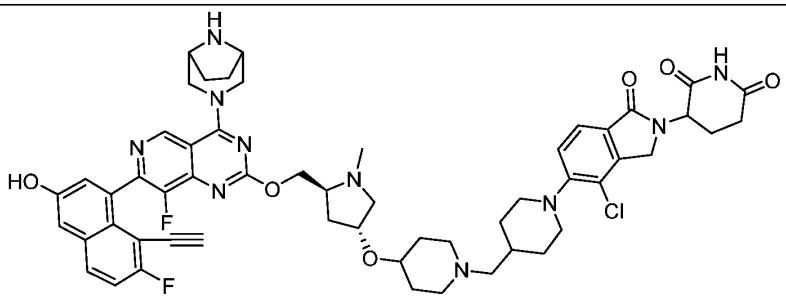
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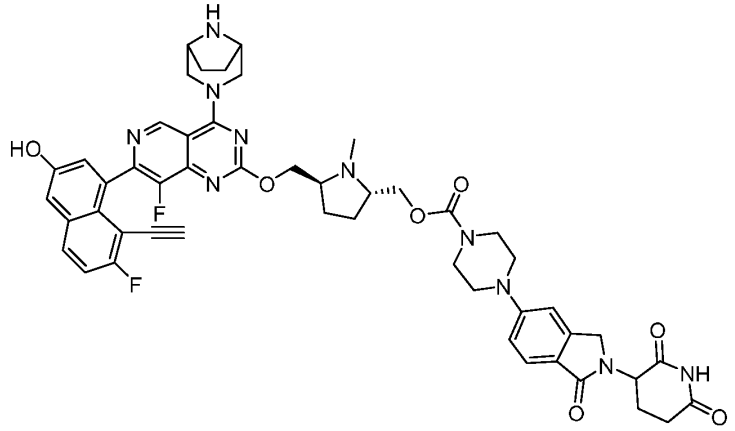
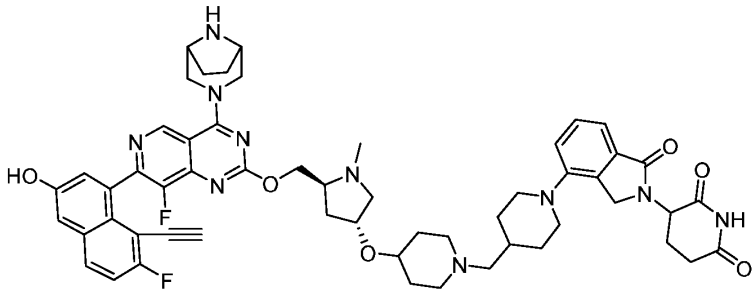
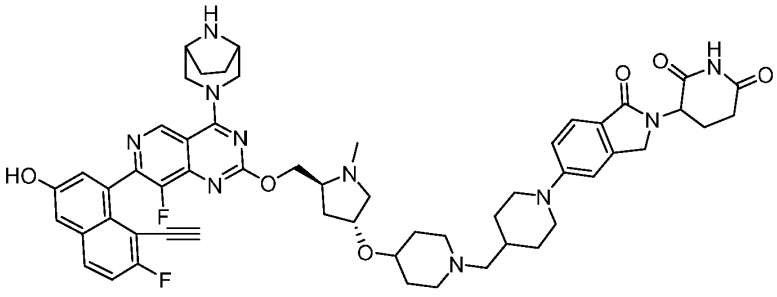
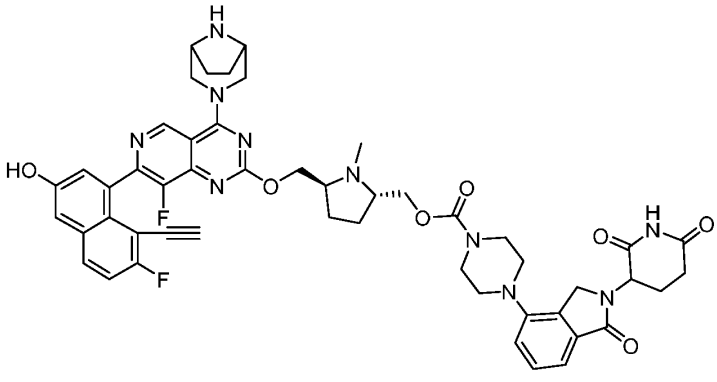
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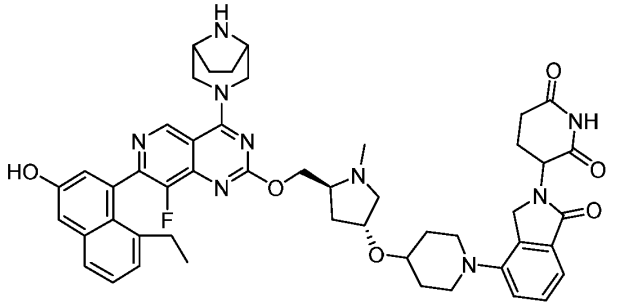
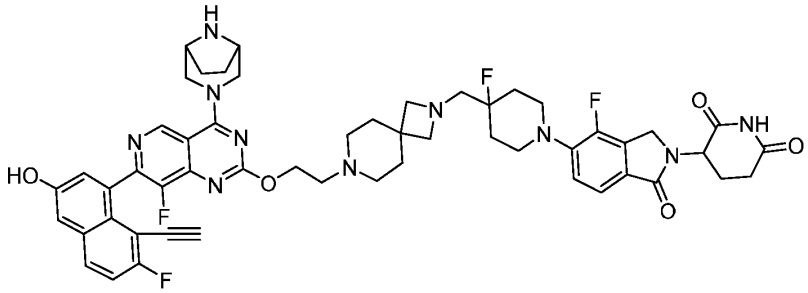
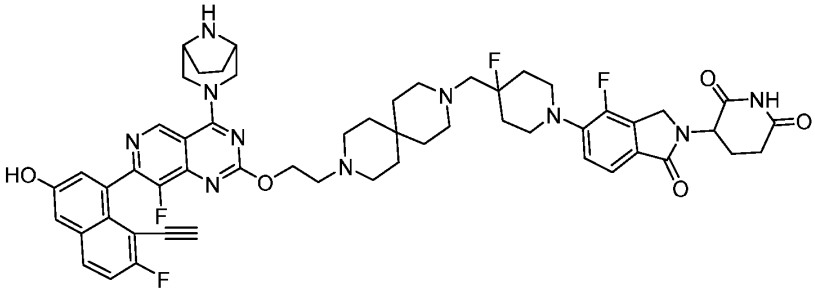
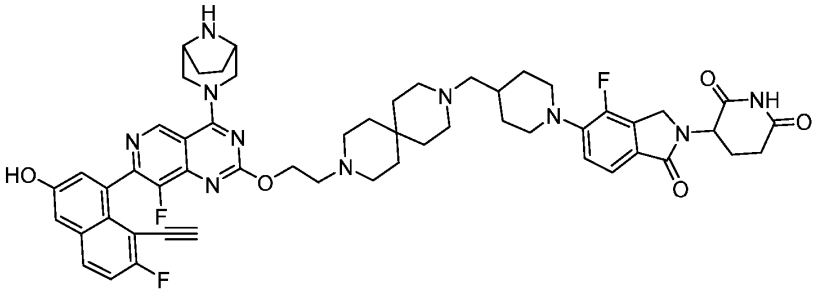
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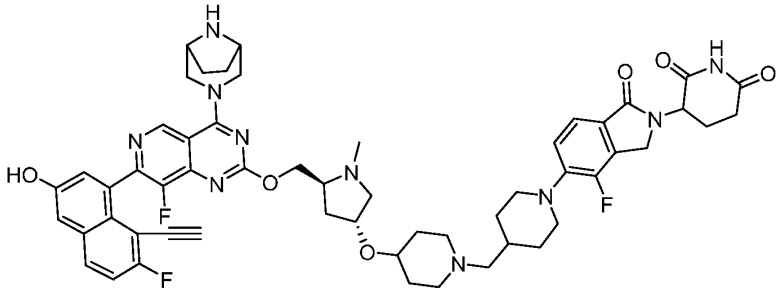
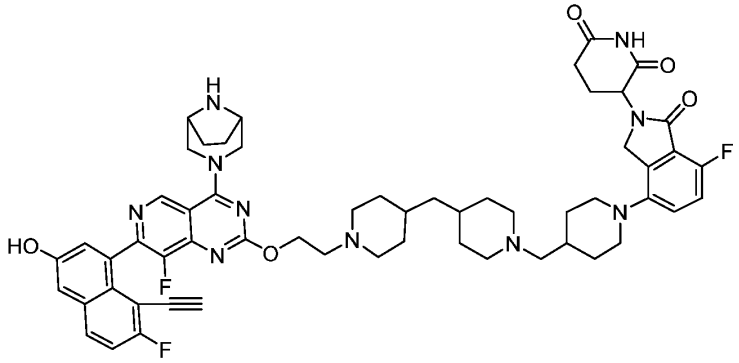
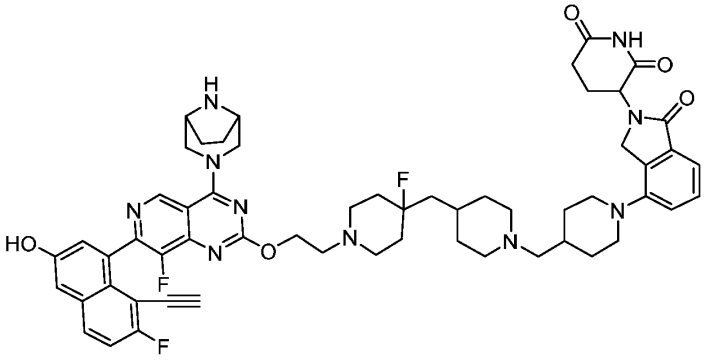
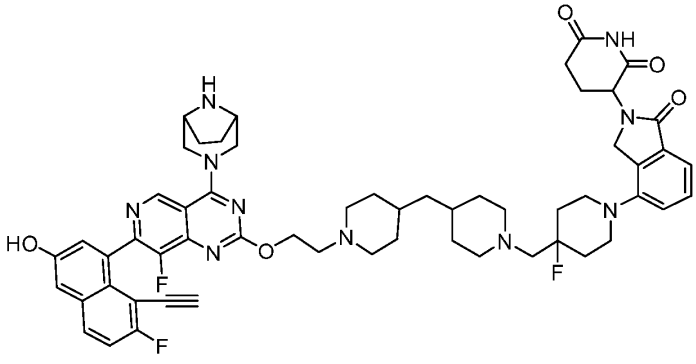
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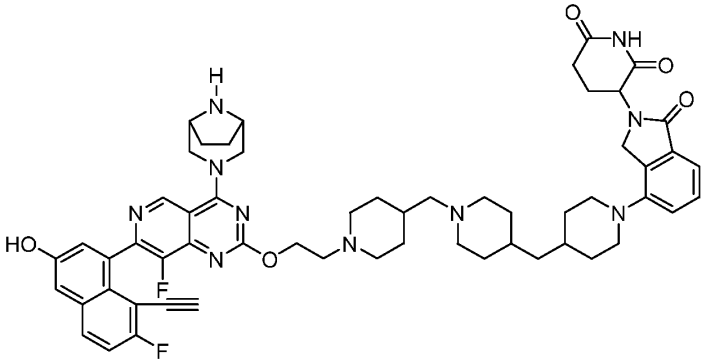
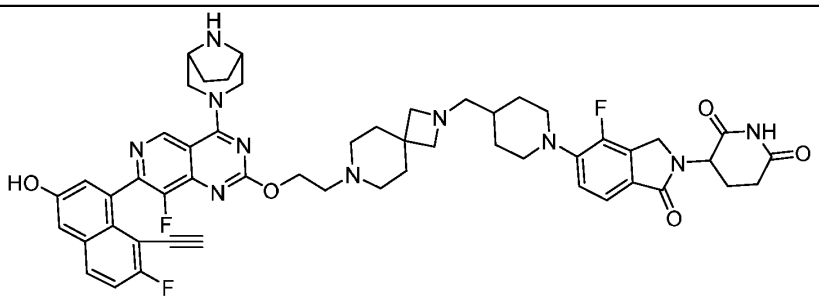
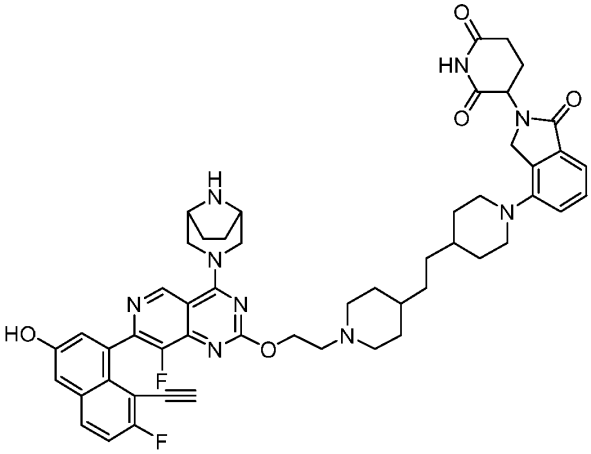
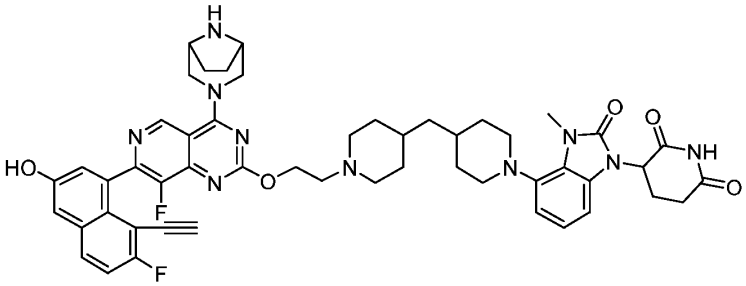
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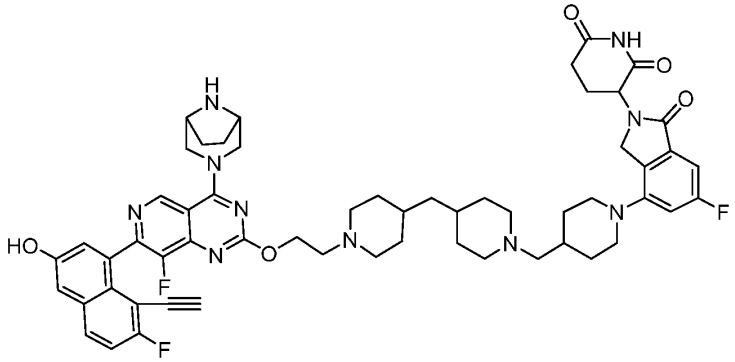
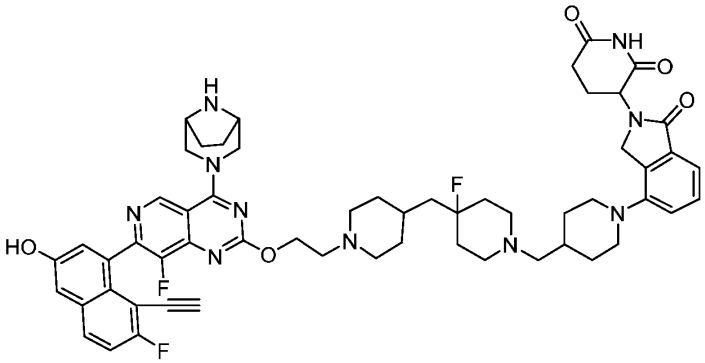
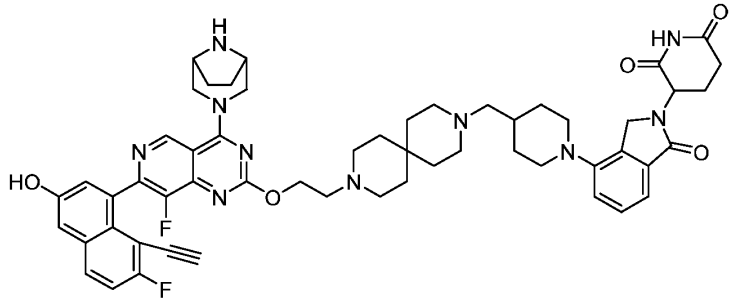
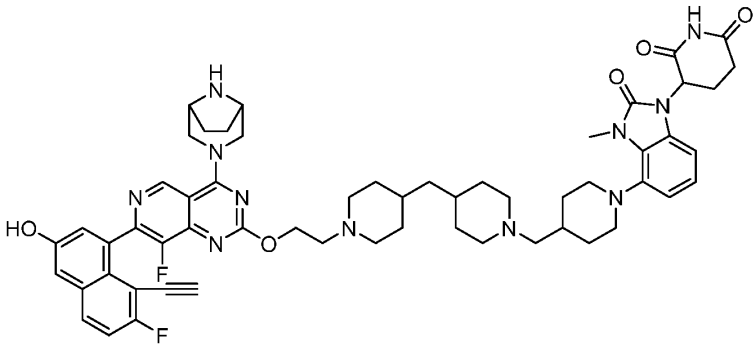
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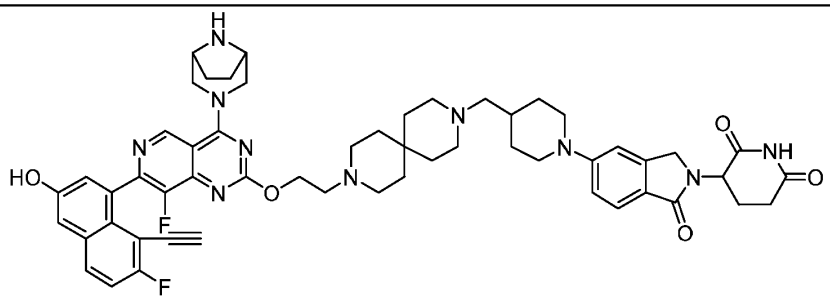
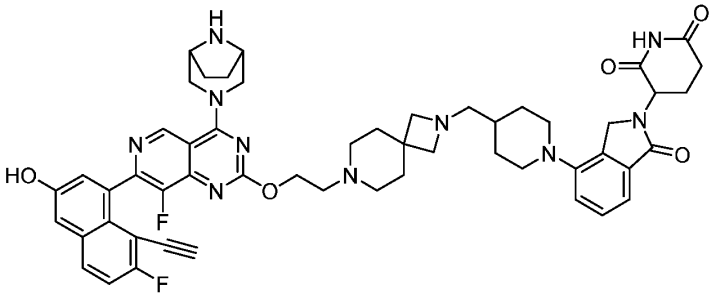
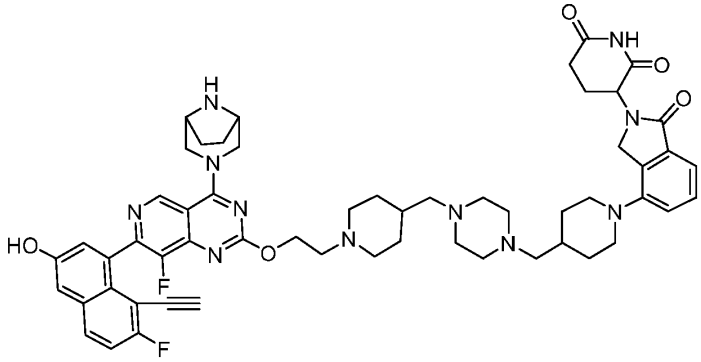
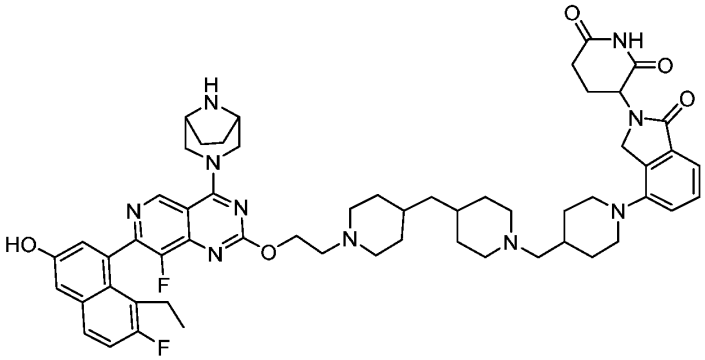
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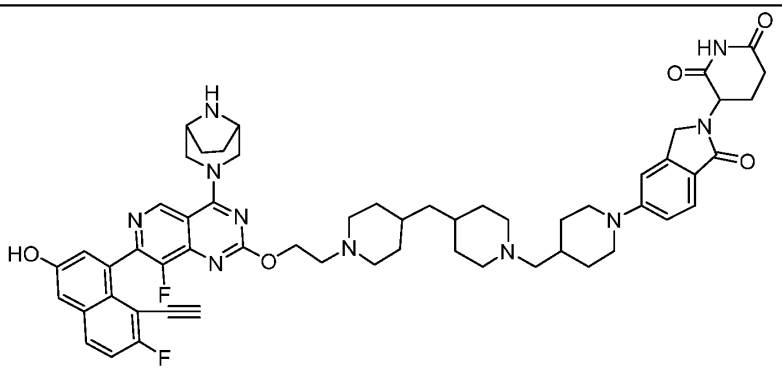
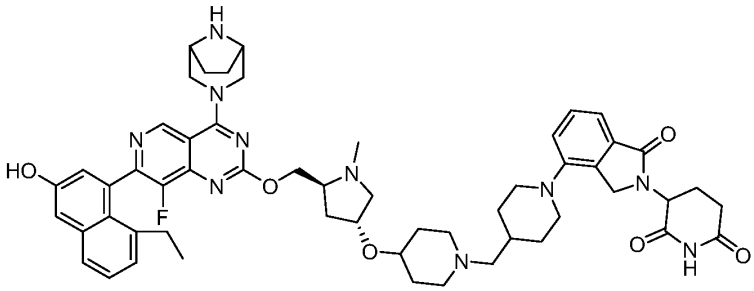
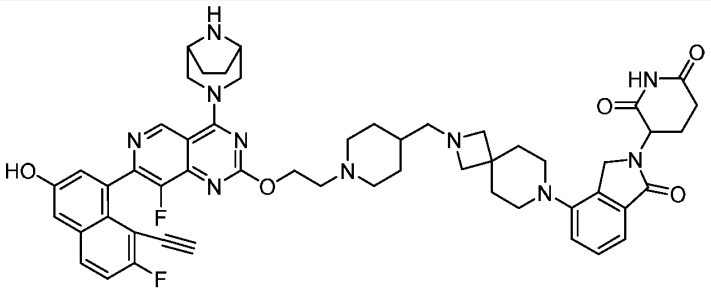
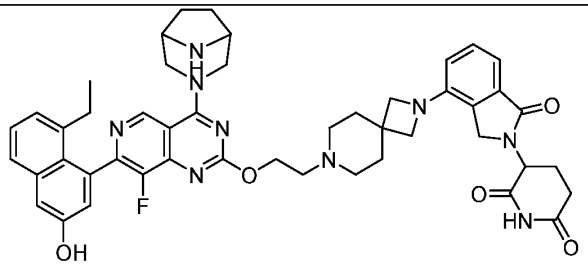
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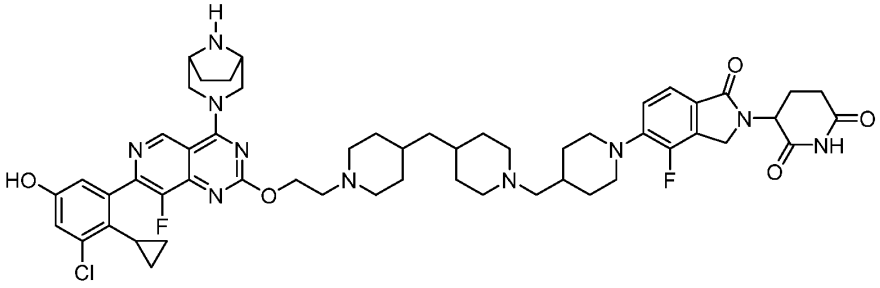
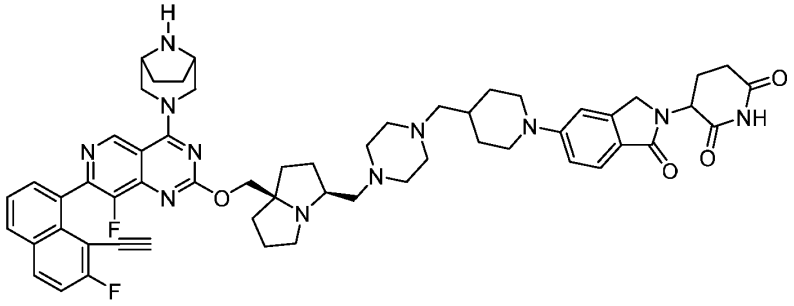
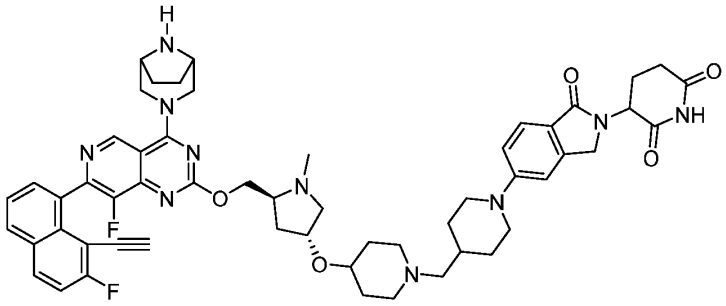
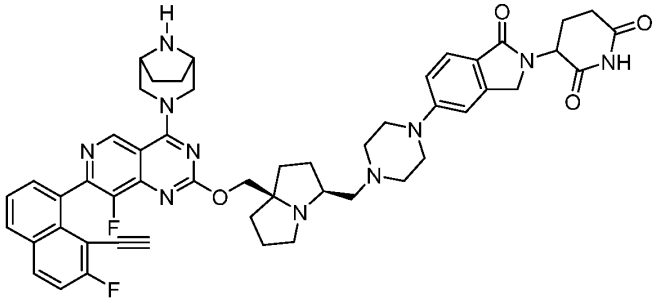
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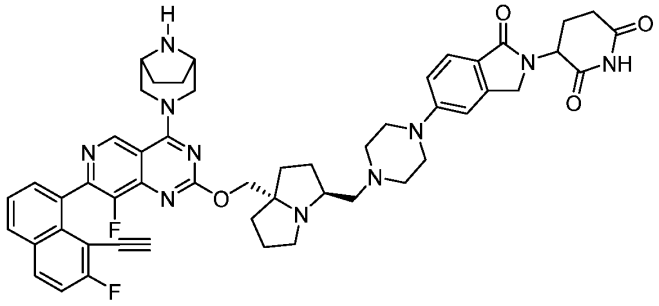
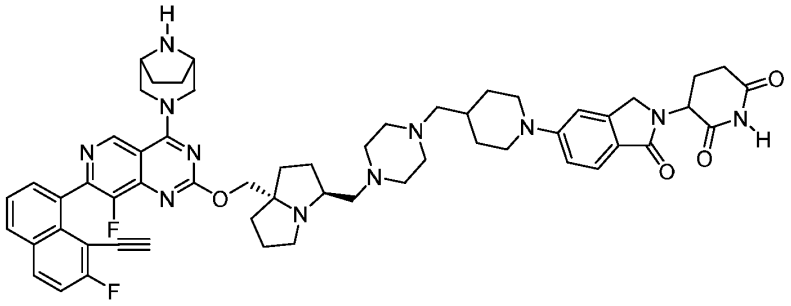
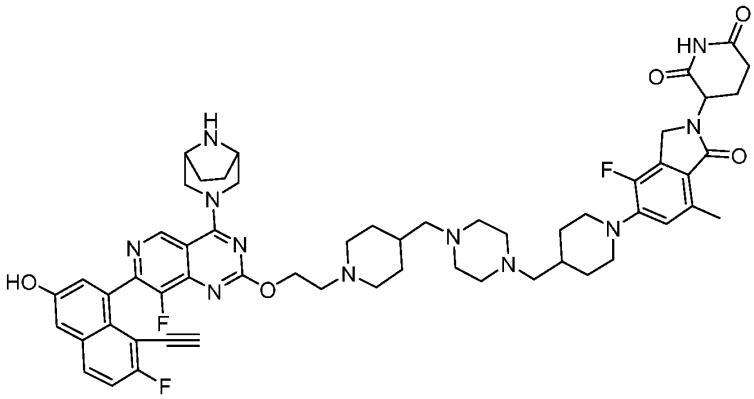
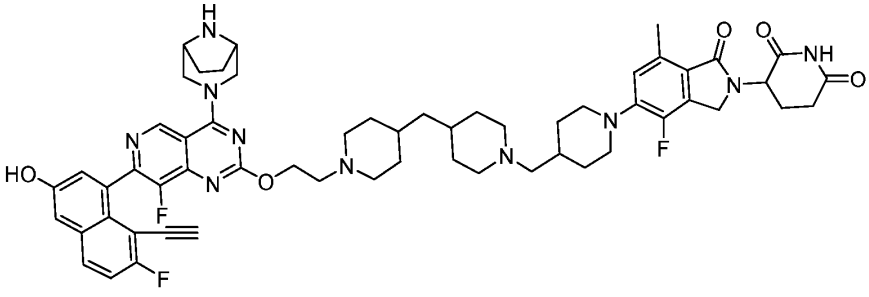
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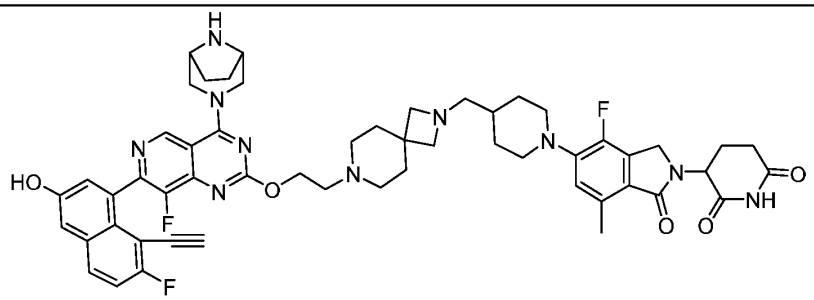
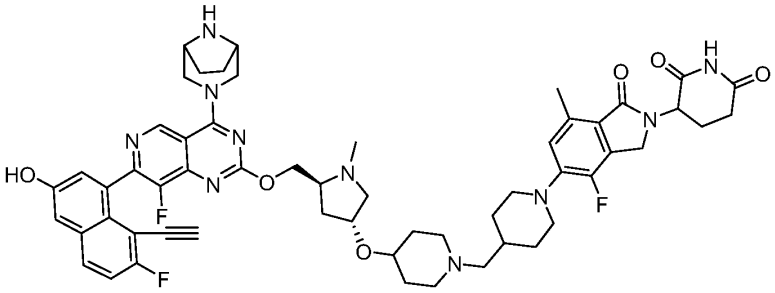
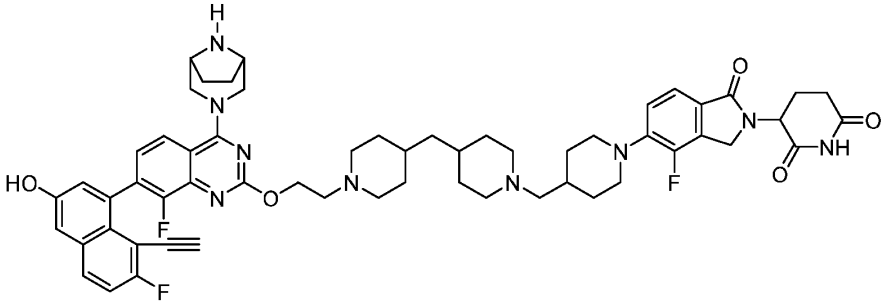
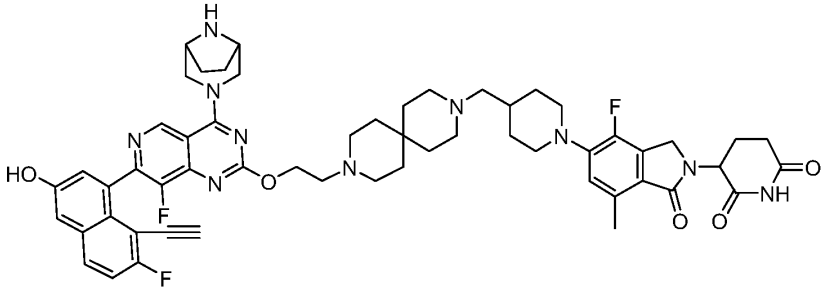
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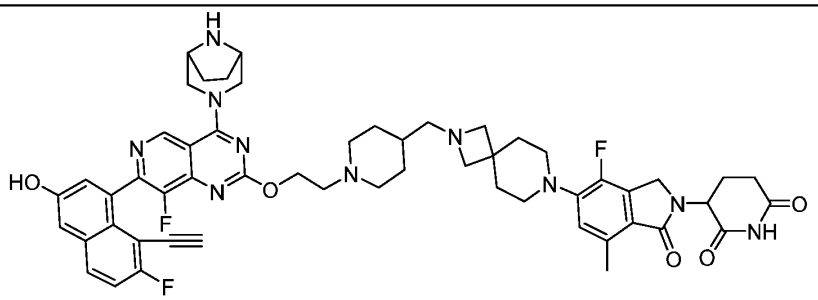
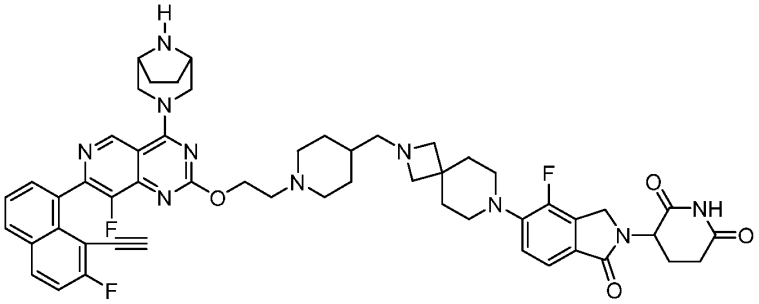
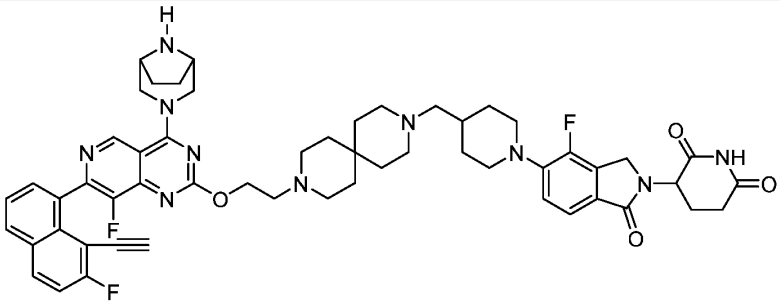
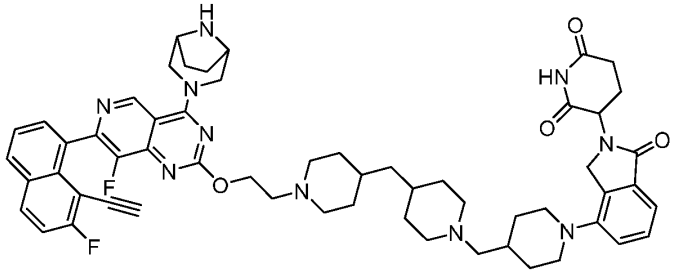
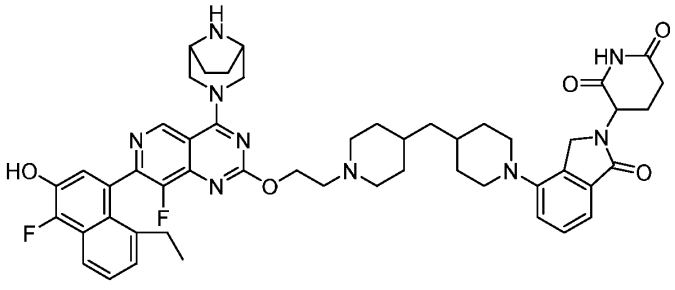
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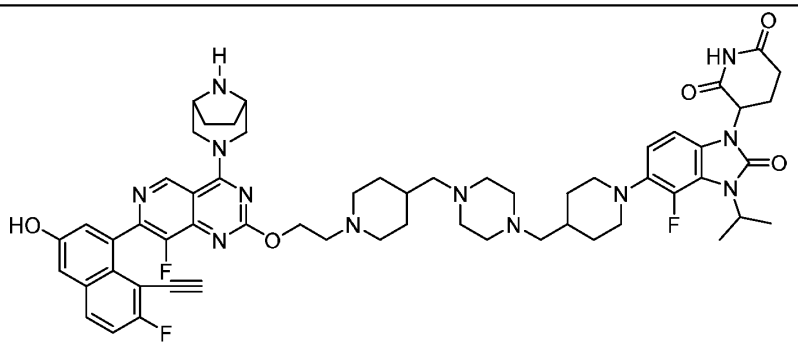
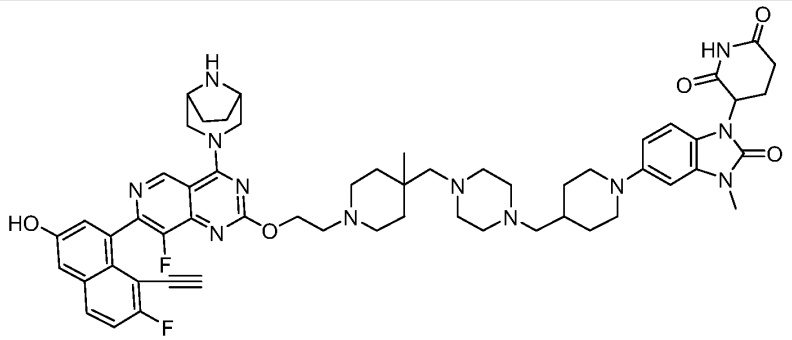
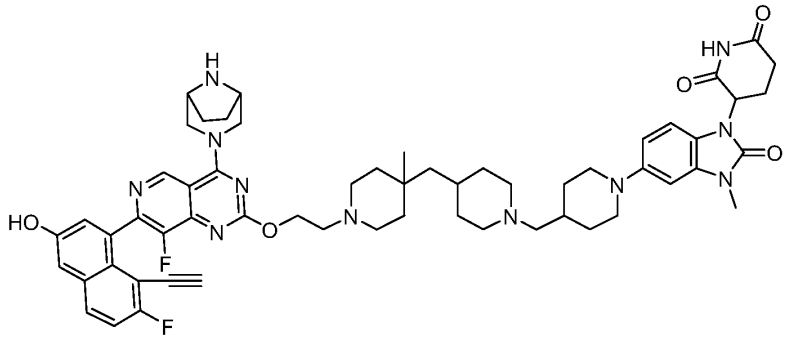
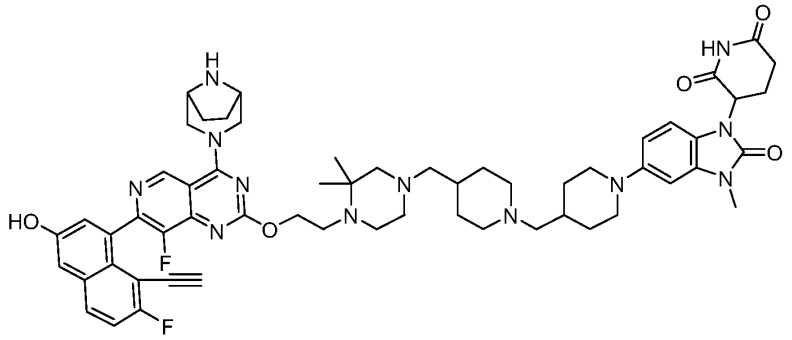
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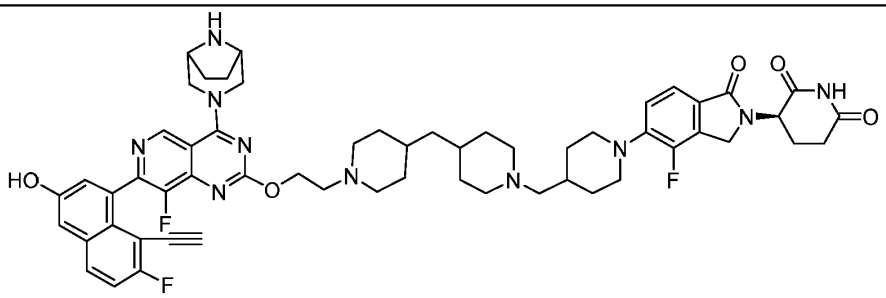
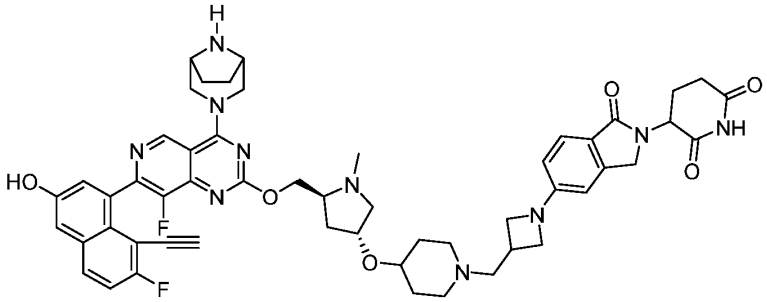
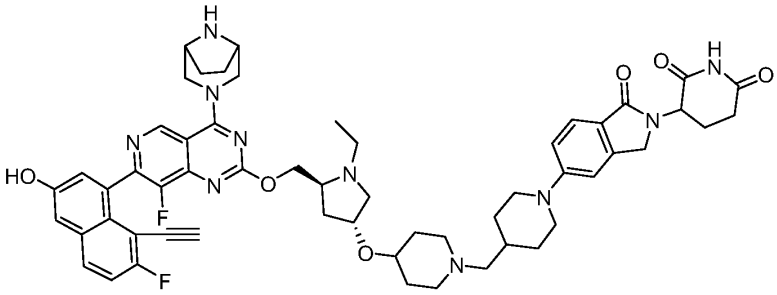
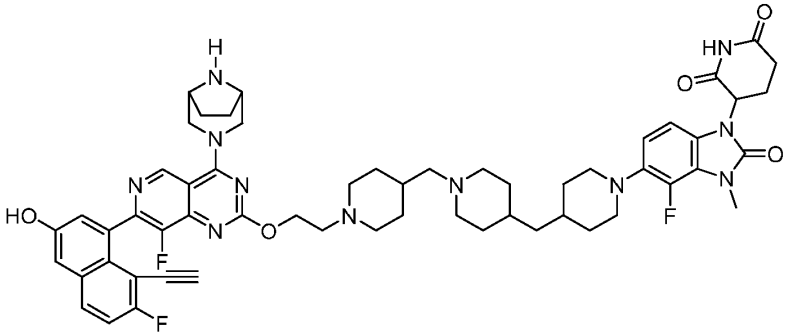
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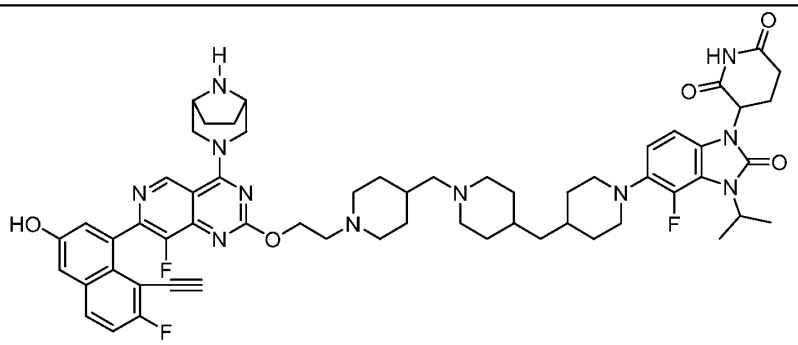
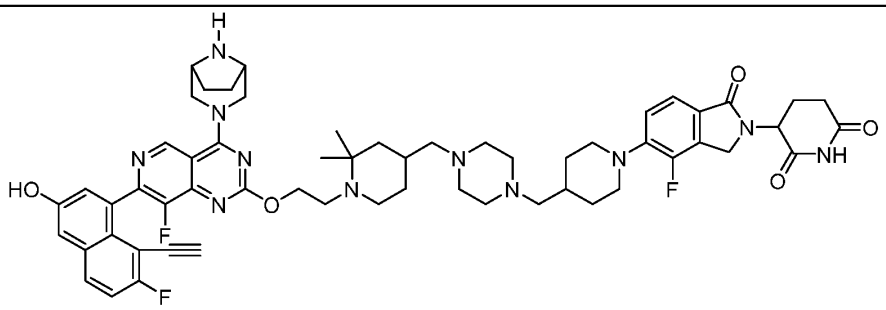
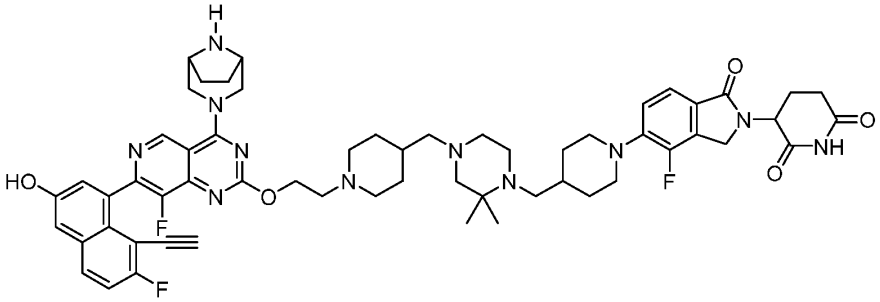
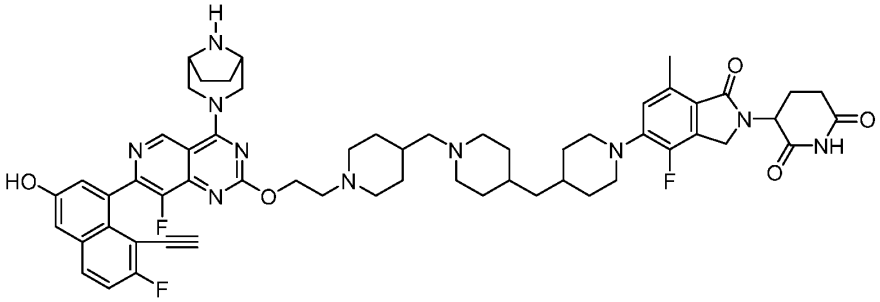
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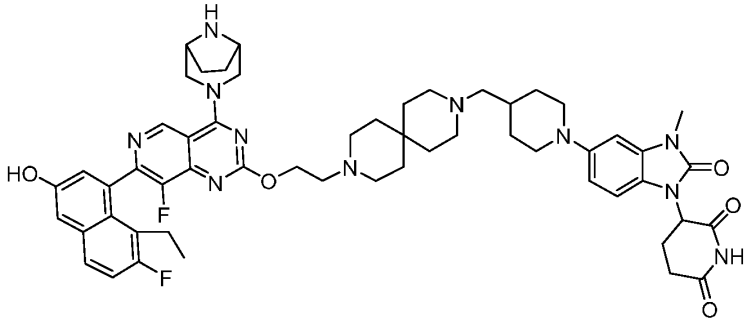
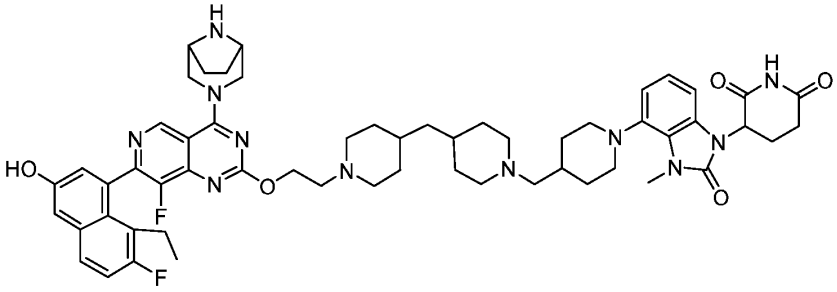
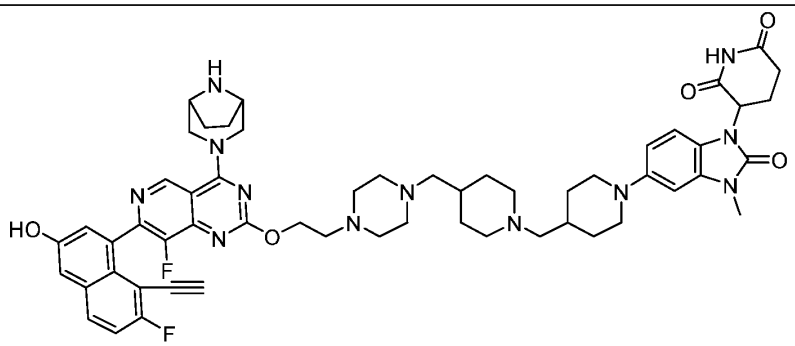
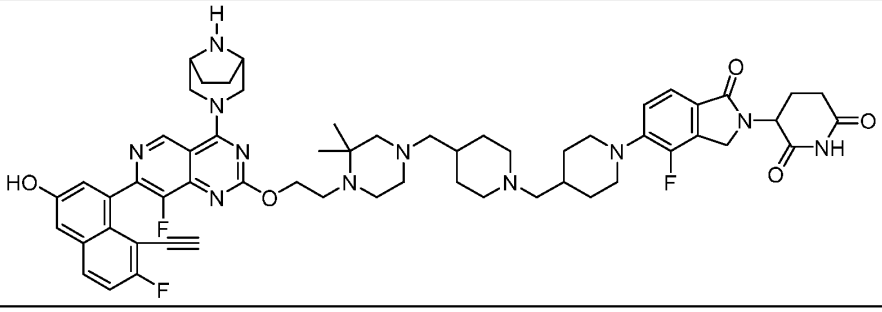
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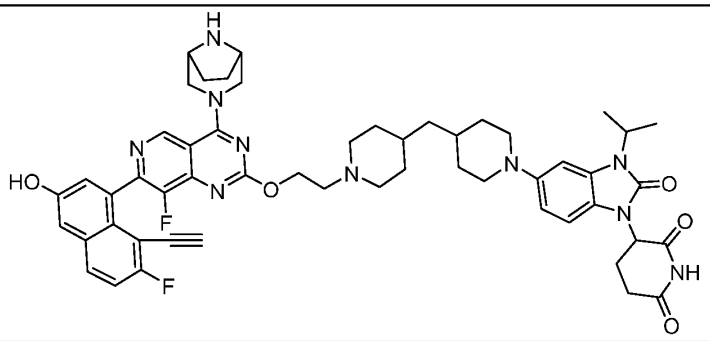
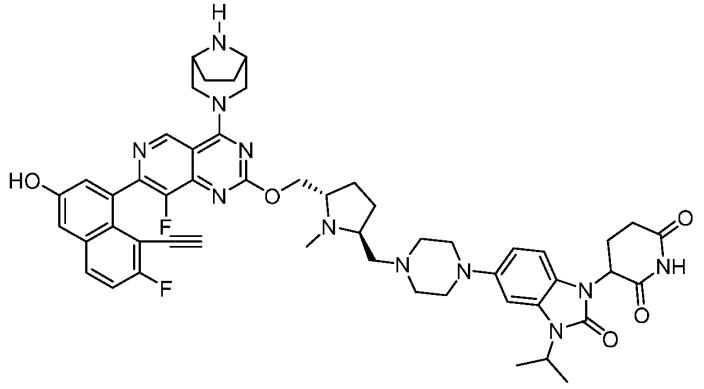
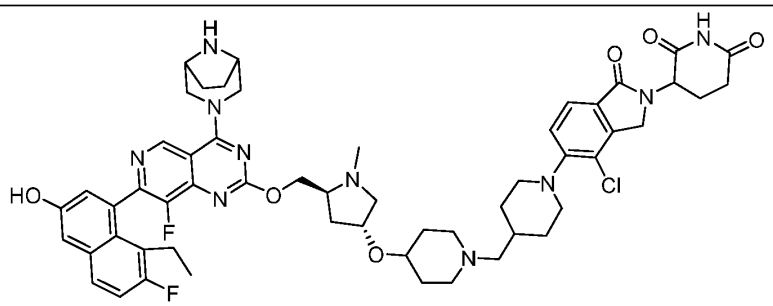
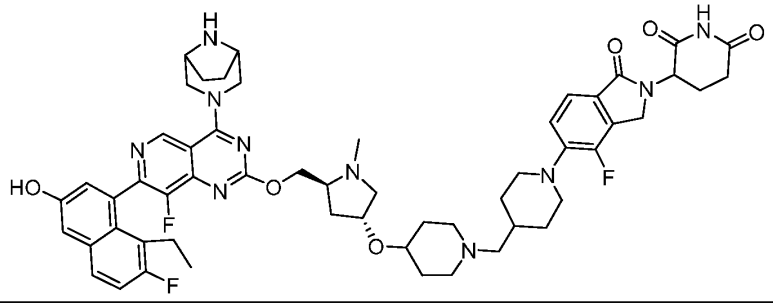
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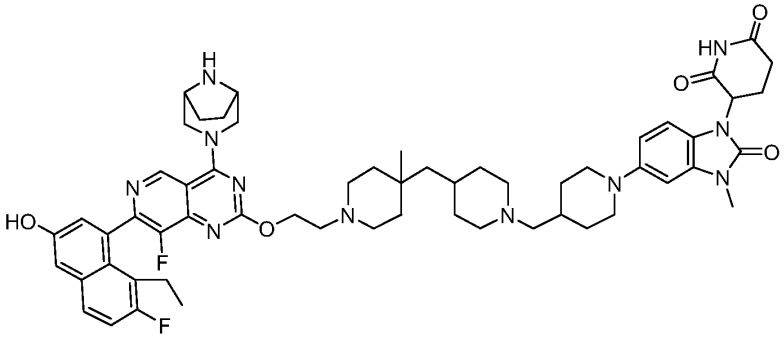
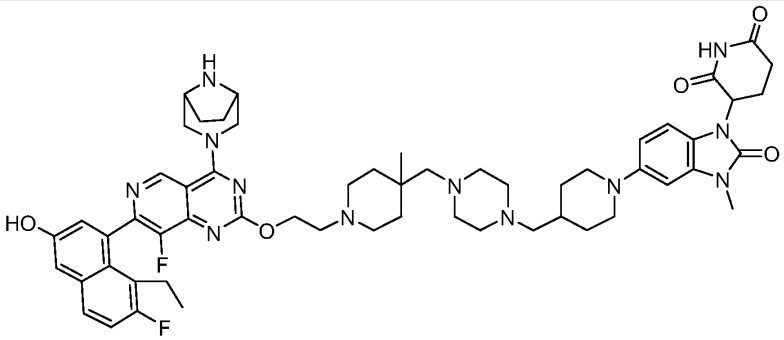
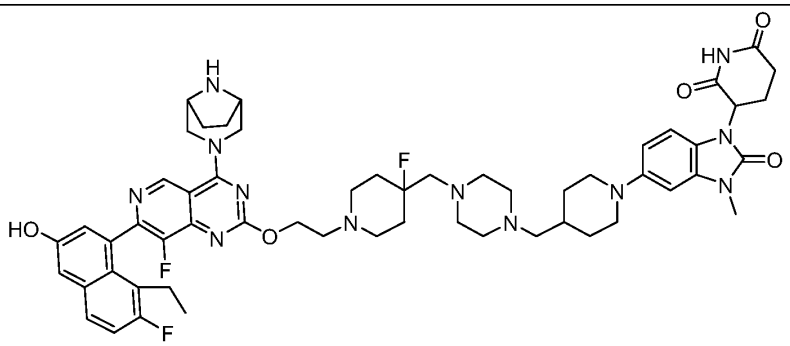
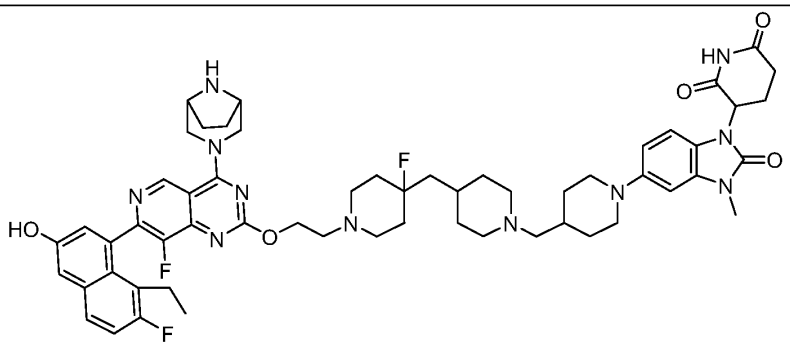
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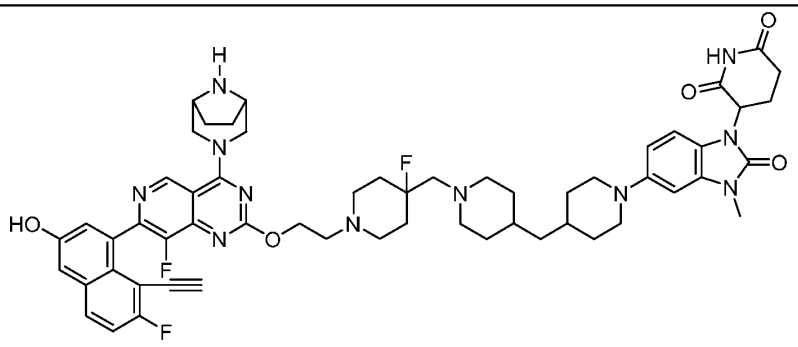
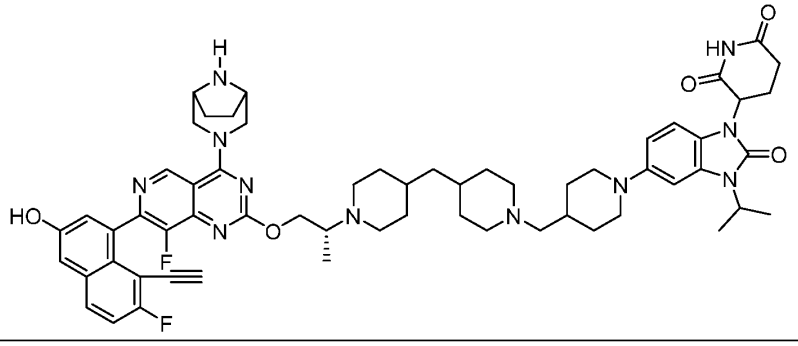
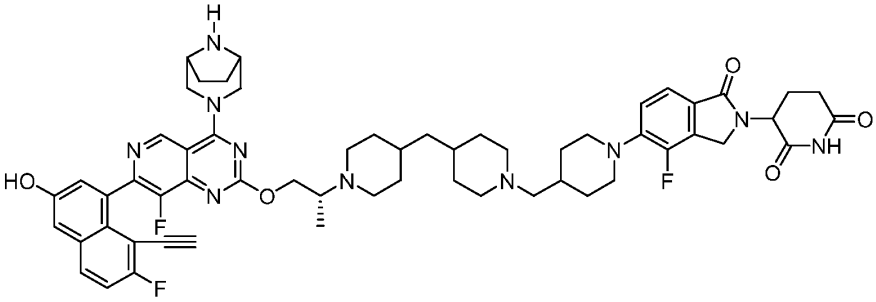
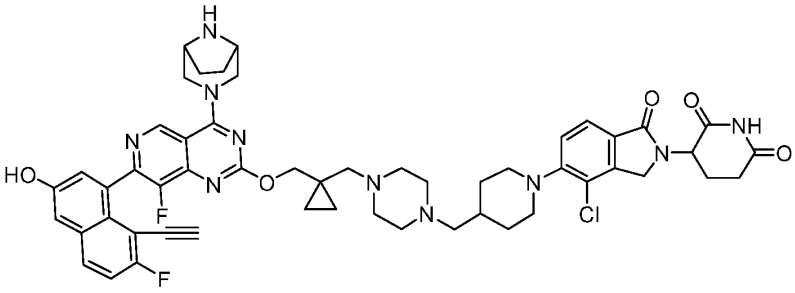
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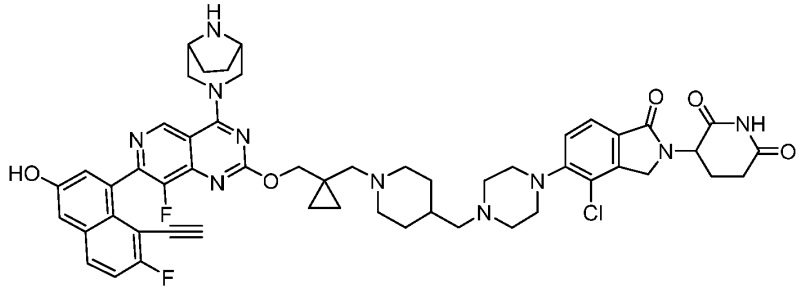
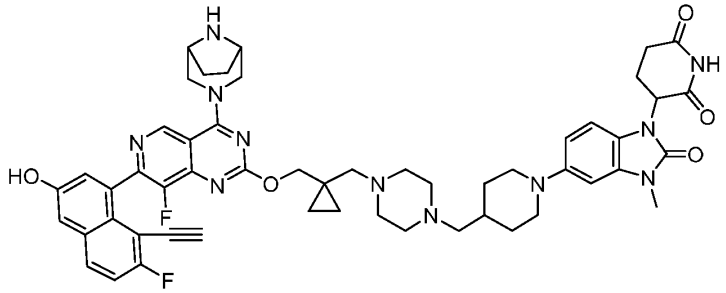
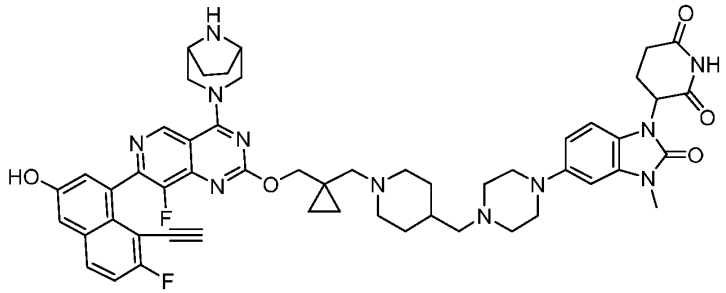
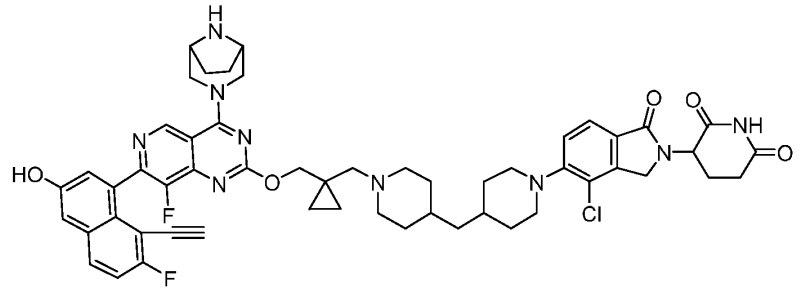
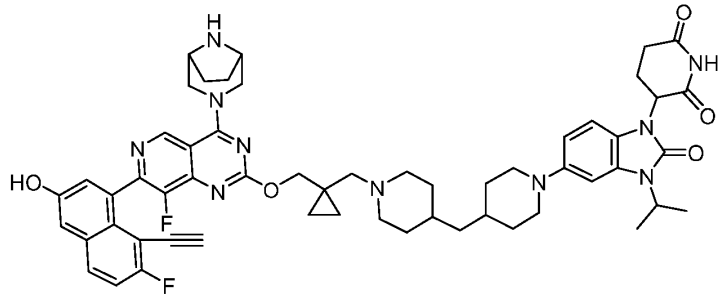
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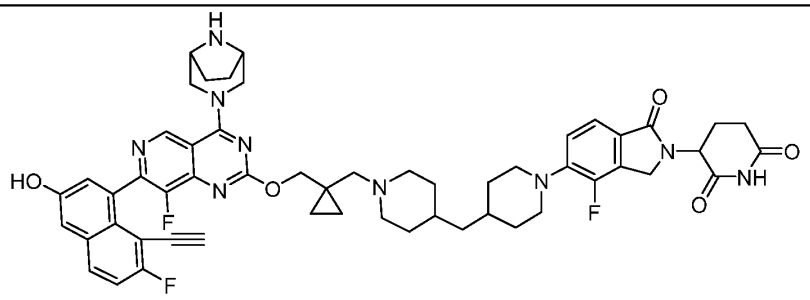
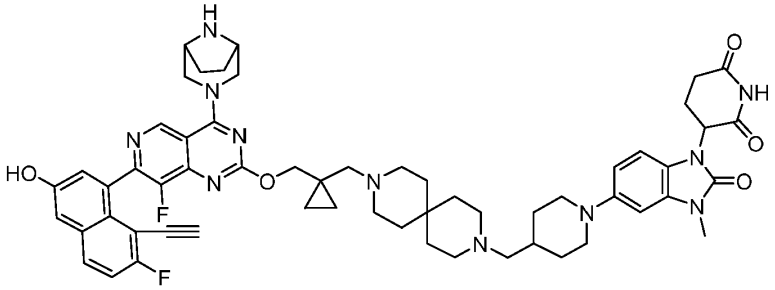
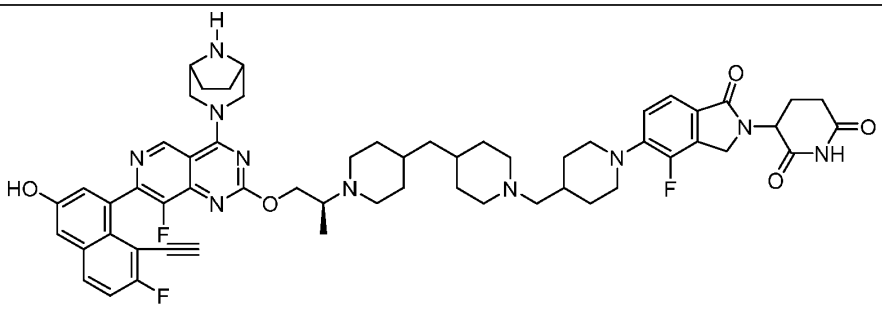
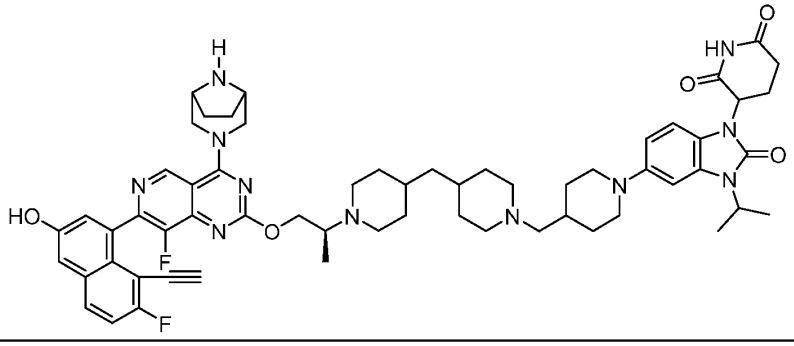
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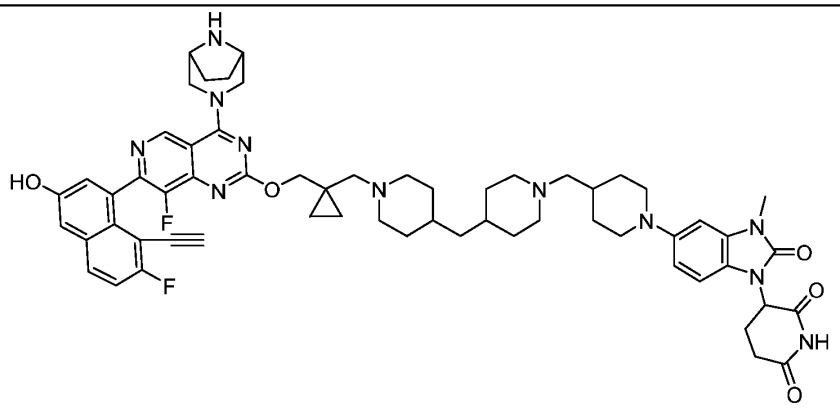
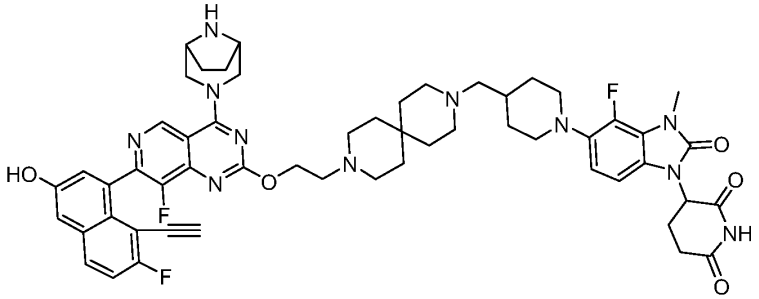
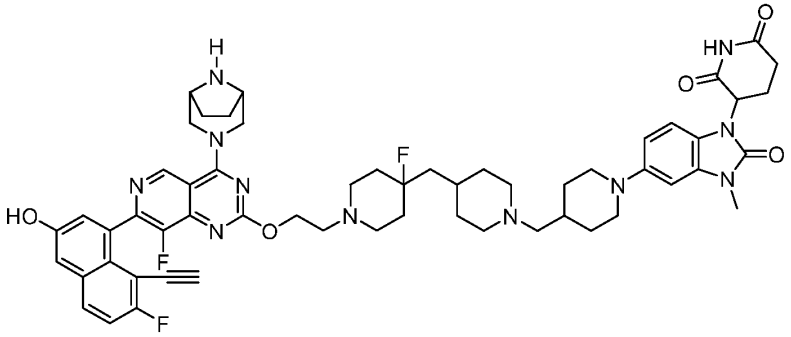
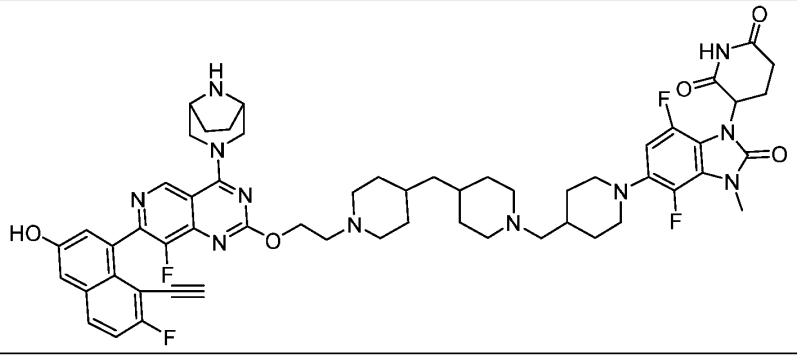
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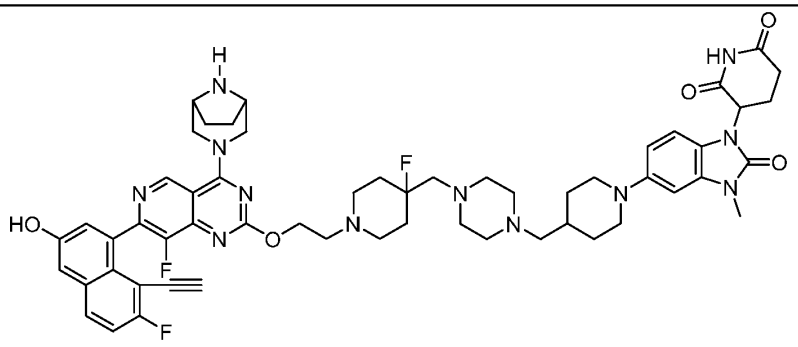
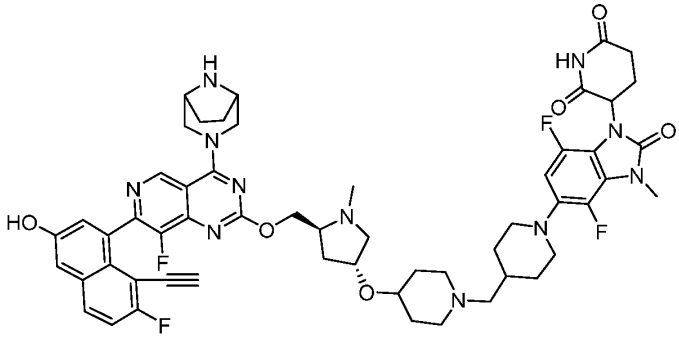
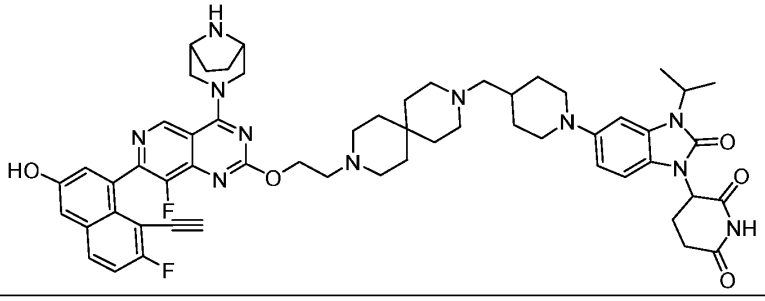
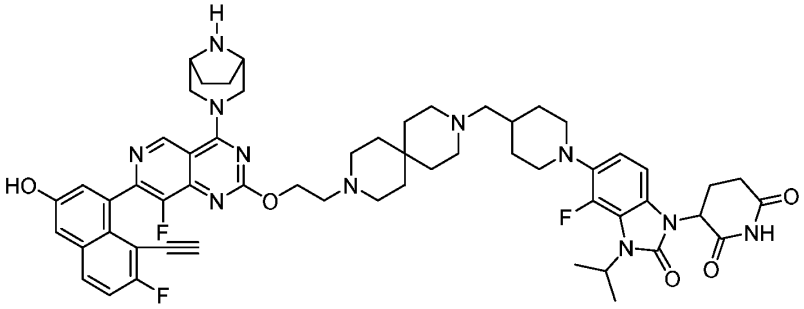
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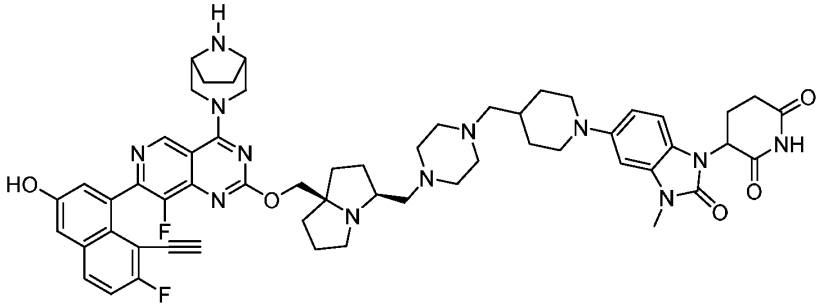
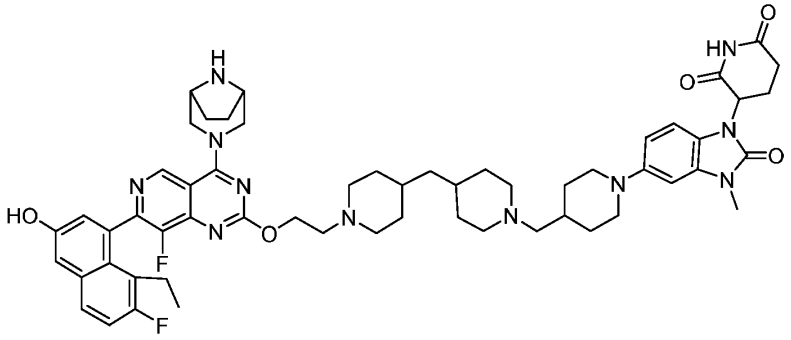
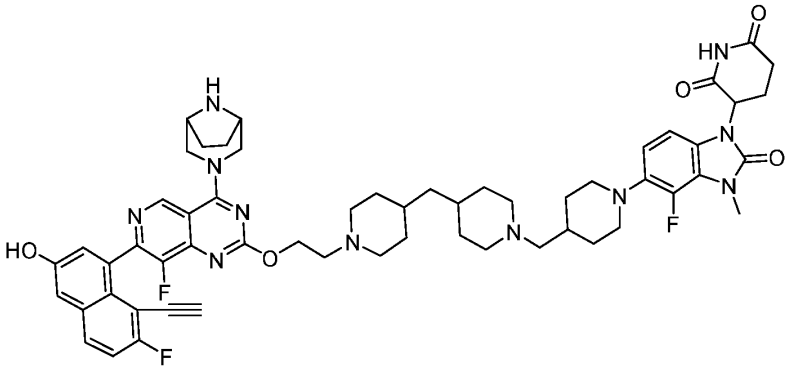
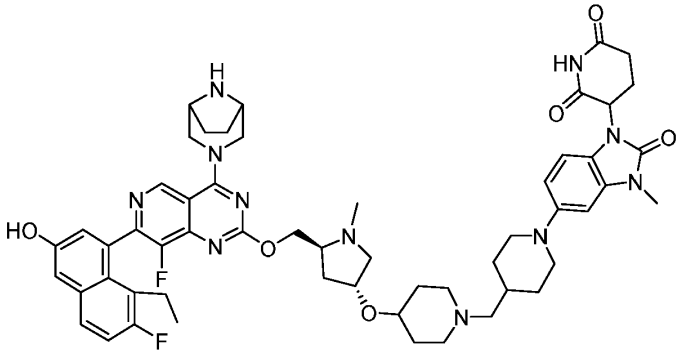
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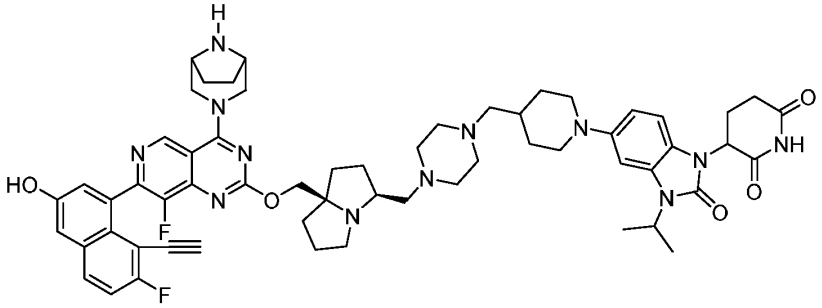
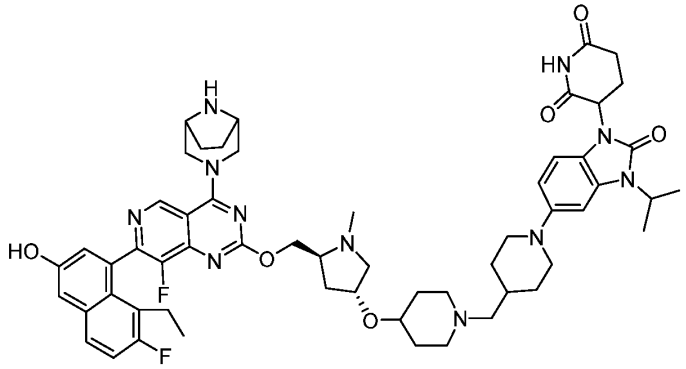
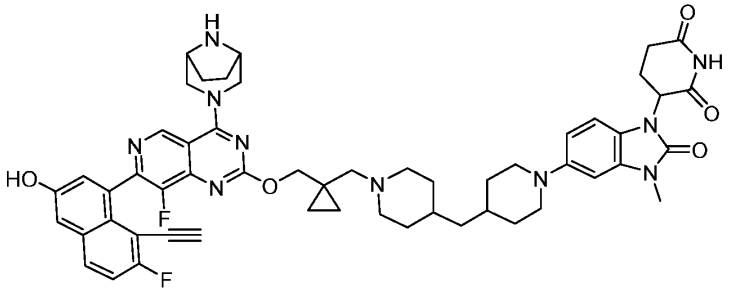
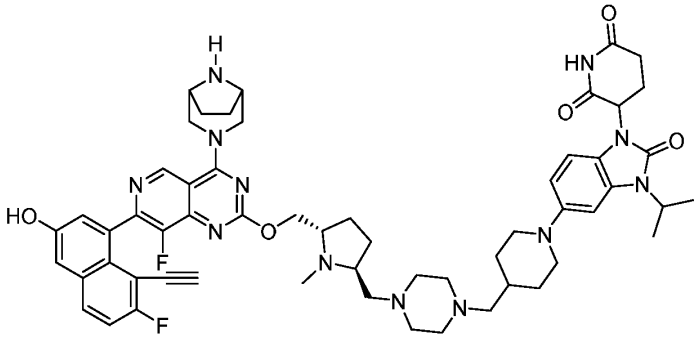
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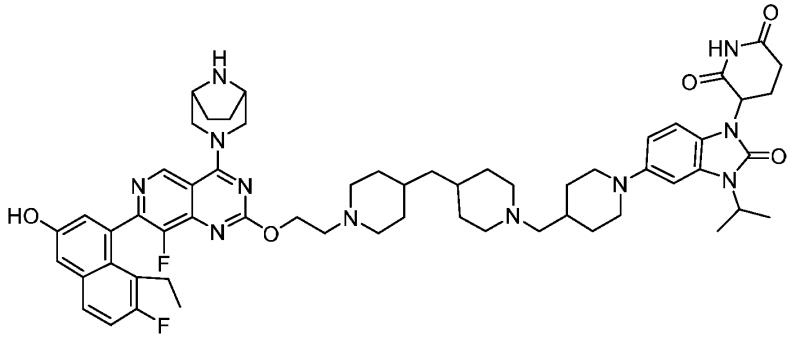
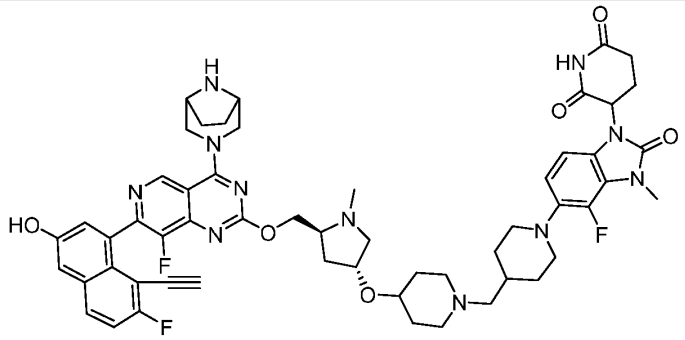
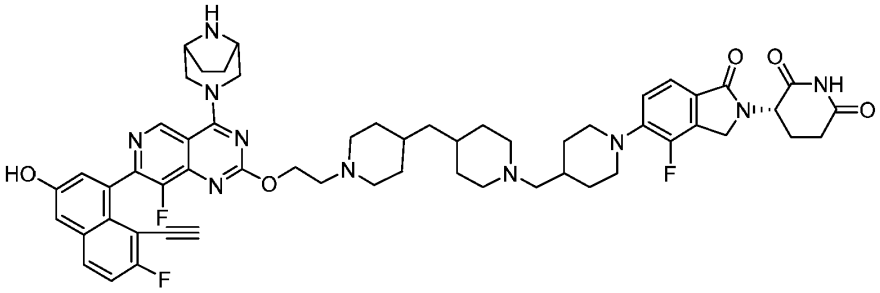
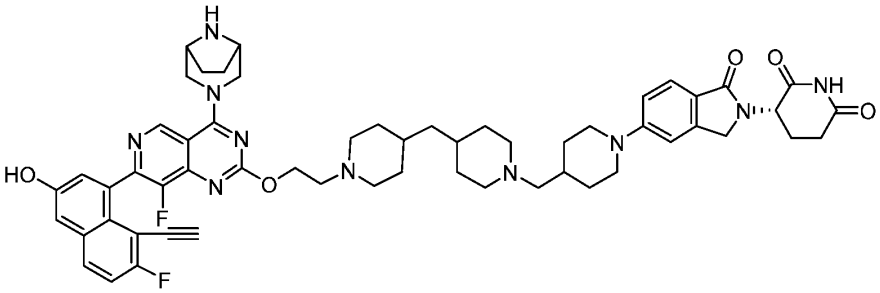
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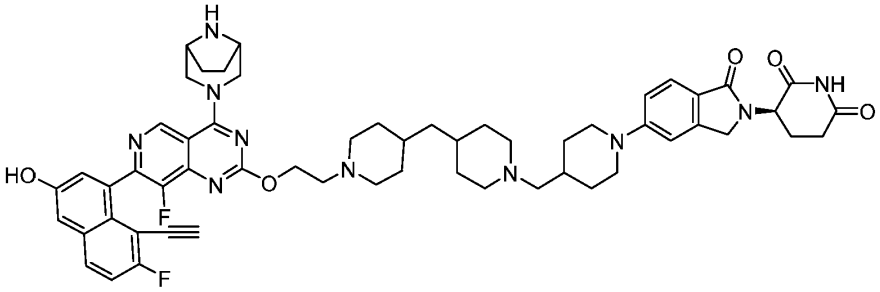
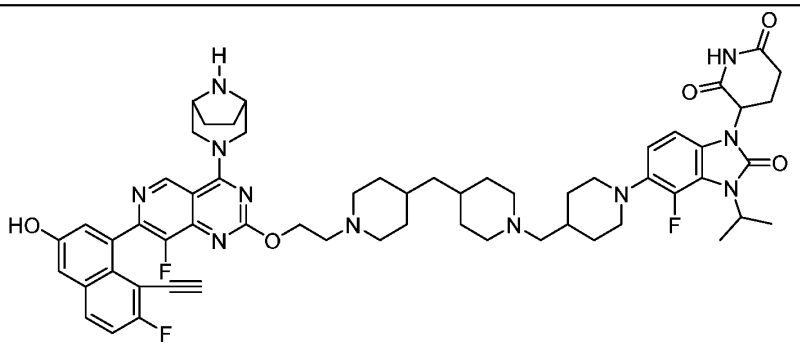
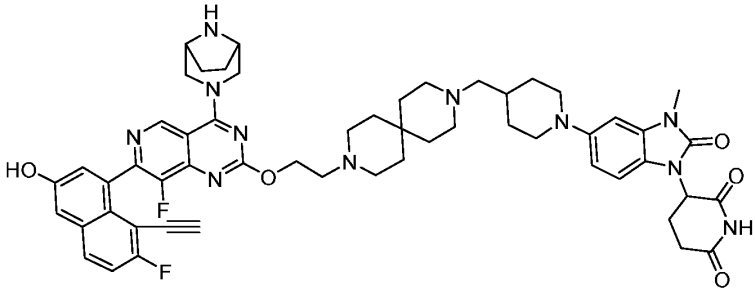
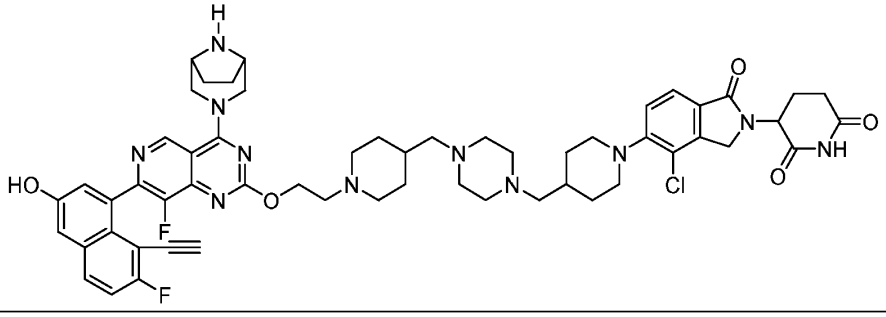
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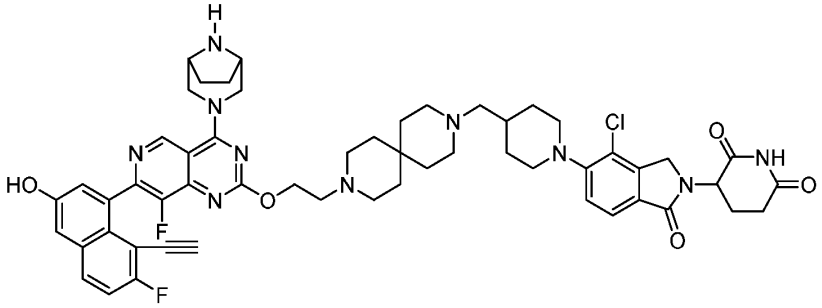
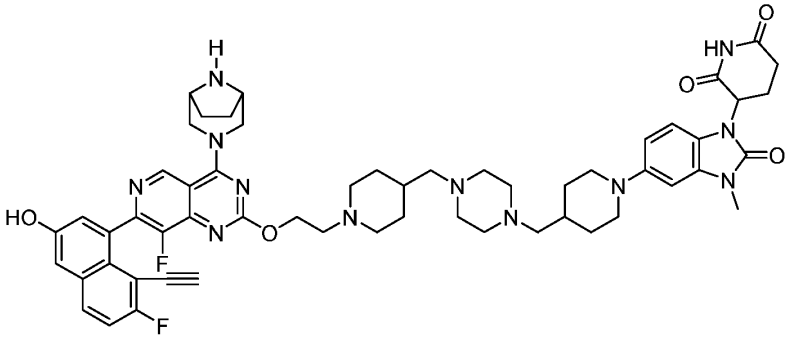
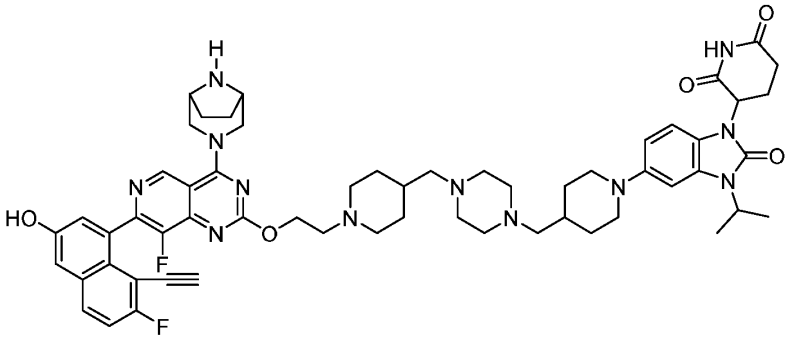
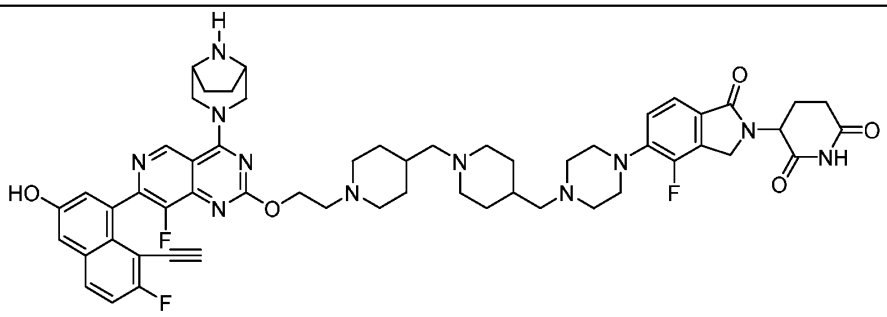
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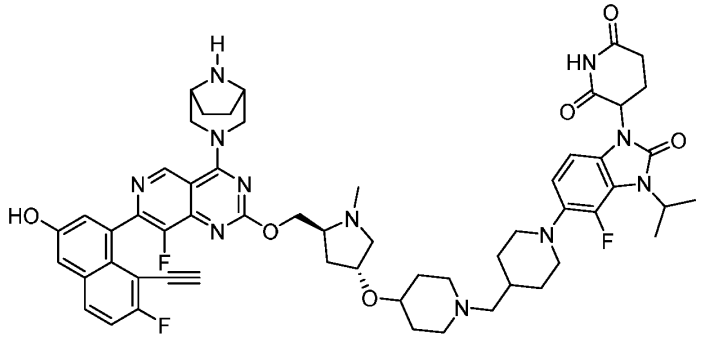
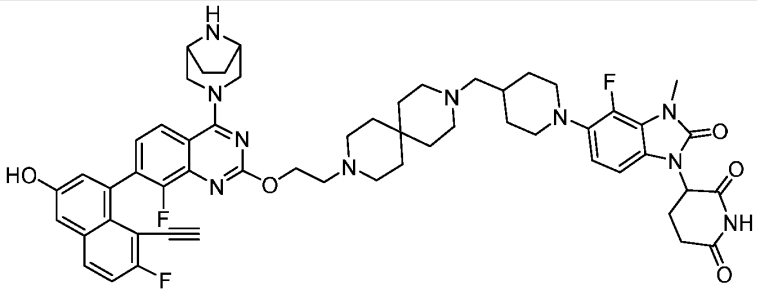
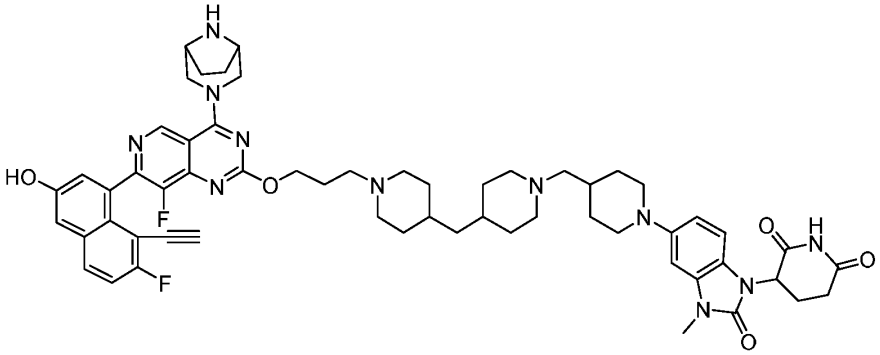
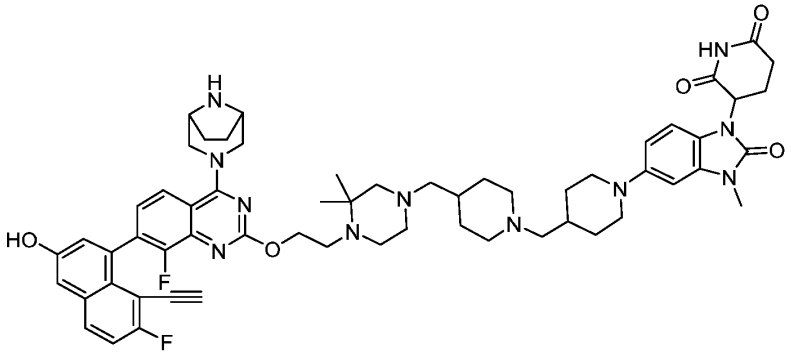
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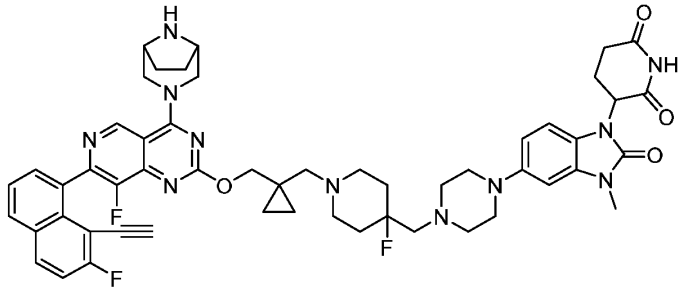
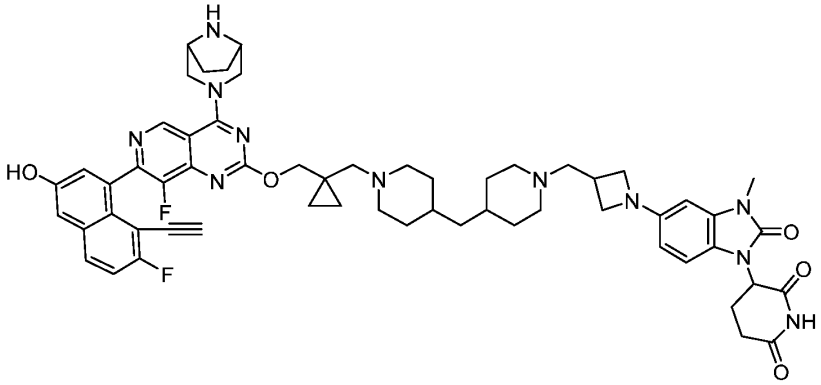
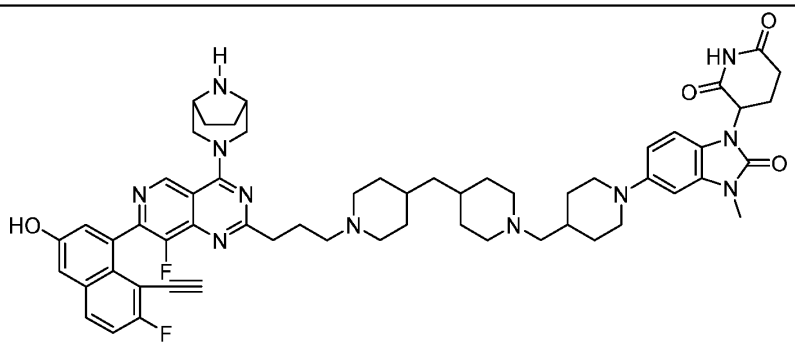
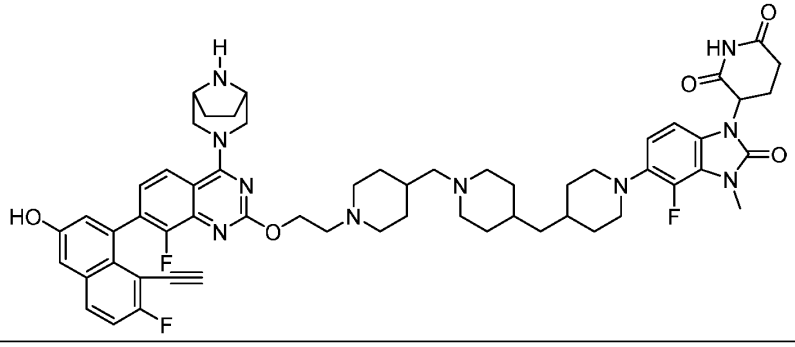
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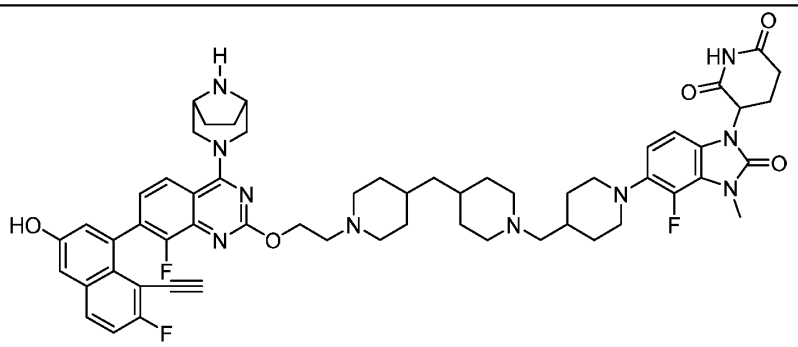
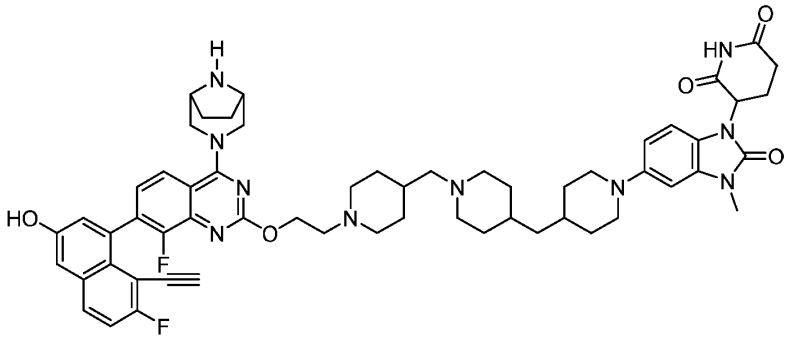
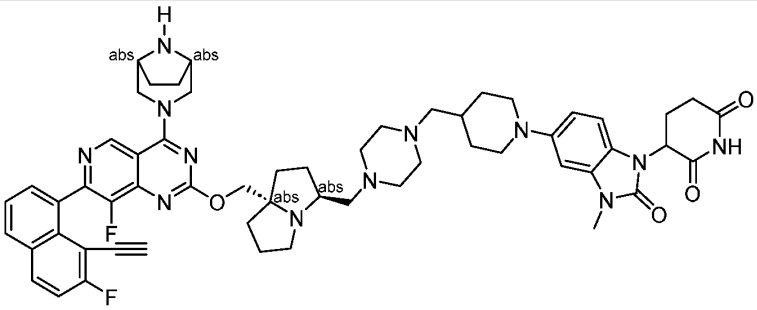
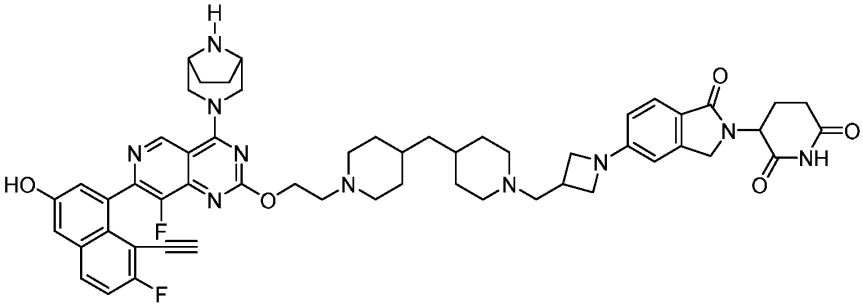
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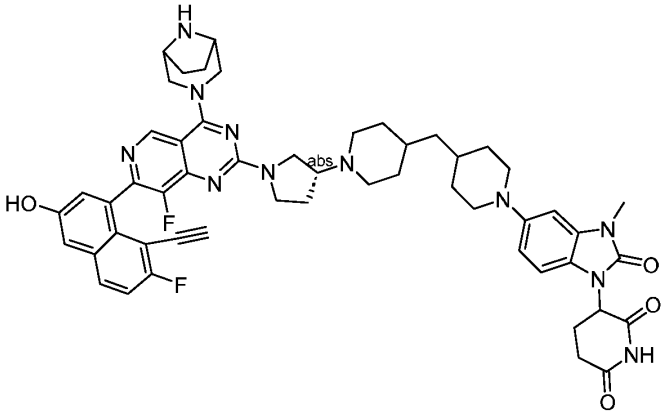
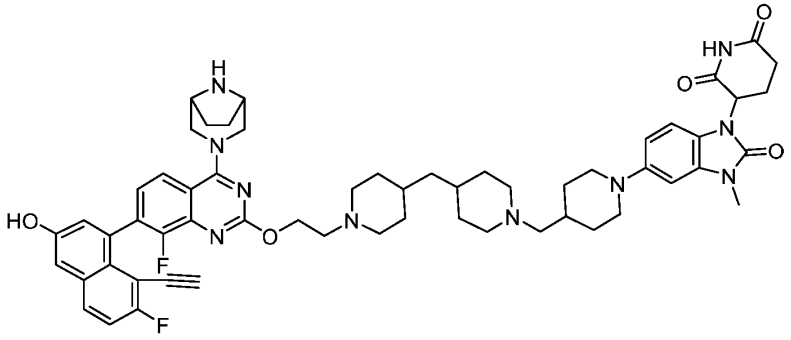
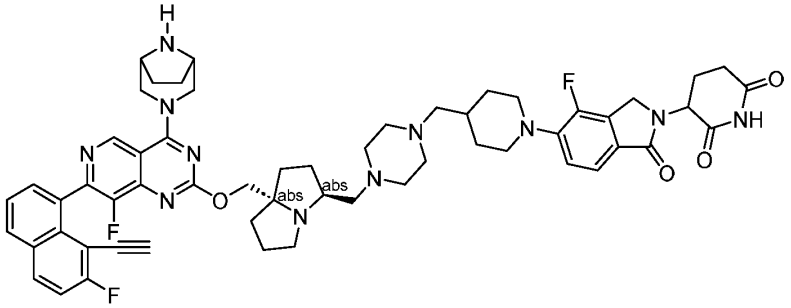
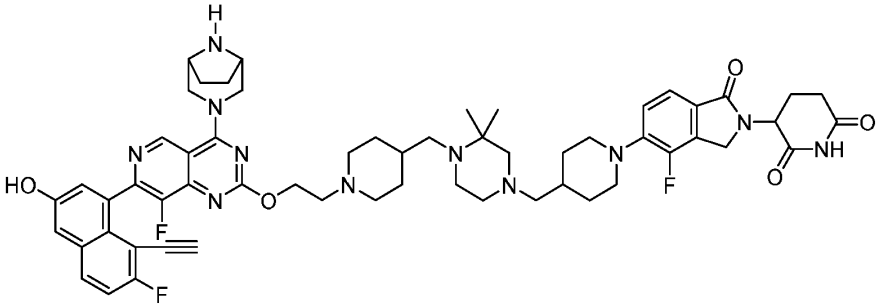
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Also provided herein are pharmaceutical compositions comprising any of the compounds described herein or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier.

The compounds disclosed herein may exist as tautomers and optical isomers (e.g., enantiomers, diastereomers, diastereomeric mixtures, racemic mixtures, and the like).

It is generally well known in the art that any compound that will be converted *in vivo* to provide a compound disclosed herein is a prodrug within the scope of the present disclosure.

Methods of Treatment

This application pertains to methods of treating or ameliorating a disease state or condition that is modulated through or causally related to the target protein, i.e., KRas.

Provided herein are methods of treating a disease or disorder comprising administering to a subject any of the compounds disclosed herein or pharmaceutically acceptable salts thereof, or a pharmaceutical composition disclosed herein.

In embodiments, the disease or disorder is cancer.

In embodiments, the cancer is bladder cancer, bowel cancer, breast cancer, cervical cancer, colon cancer, colorectal cancer, endometrial cancer, esophageal cancer, head cancer, kidney cancer, liver cancer, lung cancer, neck cancer, ovary cancer, pancreatic cancer, prostate cancer, stomach cancer, uterine cancer, ovarian cancer, testicular cancer, thyroid cancer, pineal cell tumor, carcinoma, cytoma, ependymoma, ganglioglioma, ganglioneuroma, gliobastoma, glioma, leukemia, lymphoma, medulloblastoma, melanoma, meningioma, myeloma, nephroblastoma, neuroblastoma, neurofibroma, oligodendroglioma peripheral neuroepithelioma, sarcoma, or schwannoma.

In embodiments, the carcinoma is teratocarcinoma. In embodiments, the cytoma is astrocytoma.

In embodiments, the carcinoma is squamous-cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinoma, and renal cell carcinoma. In embodiments, the leukemia is precursor B-lymphoblastic leukemia, T-cell acute lymphoblastic Leukemia, adult T-cell leukemia, Philadelphia chromosome positive acute lymphoblastic leukemia, Philadelphia chromosome positive chronic myeloid leukemia, or acute lymphoblastic leukemia.

In embodiments, the lymphoma is Burkitt lymphoma, non-Hodgkin's lymphoma, precursor T-lymphoblastic lymphoma, peripheral T-cell lymphoma, precursor lymphoblastic lymphoma, diffuse large B-cell lymphoma, or B-cell lymphoma.

In embodiments, the lymphoma is Hodgkin's lymphoma (HL).

In embodiments, the nephroblastoma is Wilms' tumor. In embodiments, the sarcoma is selected from carcinosarcoma, Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcoma, synovial sarcoma, and meningeal sarcoma.

Provided herein is a method for regulating KRas protein activity comprising administering to a subject any of the compounds disclosed herein or pharmaceutically acceptable salts thereof, or a pharmaceutical composition disclosed herein.

Also provided herein are methods for regulating cereblon protein activity comprising administering to a subject any of the compounds disclosed herein or pharmaceutically acceptable salts thereof, or a pharmaceutical composition disclosed herein.

Further provided herein are methods of degrading a target protein comprising contacting a cell with any of the compounds disclosed herein or pharmaceutically acceptable salts thereof, or a pharmaceutical composition disclosed herein.

Administration / Dosages / Formulations

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, 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, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, com, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations (for example, sterile injectable aqueous or oleaginous suspensions) may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension, or emulsion in a nontoxic 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 water, Ringer's solution, U.S.P., 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 can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

To prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished using a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Compositions for rectal or vaginal administration are preferably suppositories that can be prepared by mixing the compounds of this disclosure with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol, or a suppository wax that are solid at

ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings, and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Dosage forms for topical or transdermal administration of a compound of this disclosure include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this disclosure.

The ointments, pastes, creams, and gels may contain, in addition to an active compound of this disclosure, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this disclosure, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Compounds of the present disclosure may be administered intratympanically, wherein a long, narrow, bore needle is passed through the ear canal and through the eardrum to administer medications into the middle ear space where they are absorbed by the inner ear.

According to the methods of treatment of the present disclosure, disorders are treated or prevented in a subject, such as a human or other animal, by administering to the subject a

therapeutically effective amount of a compound of the disclosure, in such amounts and for such time as is necessary to achieve the desired result. The term “therapeutically effective amount” of a compound of the disclosure, as used herein, means enough of the compound to decrease the symptoms of a disorder in a subject. As is well understood in the medical arts a therapeutically effective amount of a compound of this disclosure will be at a reasonable benefit/risk ratio applicable to any medical treatment.

In general, compounds of the disclosure will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g., humans, is in the range from about 0.5 mg to about 100 mg, conveniently administered, e.g., in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50 mg active ingredient.

In embodiments, a therapeutic amount or dose of the compounds of the present disclosure may range from about 0.1 mg/Kg to about 500 mg/Kg, alternatively from about 1 to about 50 mg/Kg. In general, treatment regimens according to the present disclosure comprise administration to a subject in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this disclosure per day in single or multiple doses. Therapeutic amounts or doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

Upon improvement of a subject’s condition, a maintenance dose of a compound, composition or combination of this disclosure may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained; when the symptoms have been alleviated to the desired level, treatment should cease. The subject may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

It will be understood, however, that the total daily usage of the compounds and compositions of the present disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific inhibitory dose for any particular subject will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The disclosure also provides for a pharmaceutical combination, e.g., a kit, comprising a) a first agent which is a compound of the disclosure as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

Some examples of materials which can serve as pharmaceutically acceptable carriers 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, or 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; polyacrylates; waxes; polyethylenepolyoxypropylene-block polymers; wool fat; 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 a propylene glycol or 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; and phosphate buffer solutions. Further, non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. The protein kinase inhibitors or pharmaceutical salts thereof may be formulated into pharmaceutical compositions for administration to animals or humans. These pharmaceutical compositions, which comprise an amount of the protein inhibitor effective to treat or prevent a protein kinase-mediated condition and a pharmaceutically acceptable carrier, are other embodiments of the present disclosure.

Kits

Provided herein are kits comprising a compound capable of degrading KRas selected from one or more compounds disclosed herein, or pharmaceutically acceptable salts thereof, and instructions for use in treating a disorder associated with KRas.

The disclosure provides kits comprising a compound capable of degrading KRas selected from a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

Provided herein are kits comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for the treatment of any of the indications disclosed herein.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures, embodiments, claims, and

examples described herein. Such equivalents were within the scope of this disclosure and covered by the claims appended hereto. For example, it should be understood, that modifications in reaction conditions, including but not limited to reaction times, reaction size/volume, and experimental reagents, such as solvents, catalysts, pressures, atmospheric conditions, e.g., nitrogen atmosphere, and reducing/oxidizing agents, with art-recognized alternatives and using no more than routine experimentation, are within the scope of the present application.

It is to be understood that wherever values and ranges are provided herein, all values and ranges encompassed by these values and ranges, are meant to be encompassed within the scope of the present disclosure. Moreover, all values that fall within these ranges, as well as the upper or lower limits of a range of values, are also contemplated by the present application.

The following examples further illustrate aspects of the present disclosure. However, they are in no way a limitation of the teachings of the present disclosure as set forth.

EXAMPLES

The compounds and methods disclosed herein are further illustrated by the following examples, which should not be construed as further limiting. The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of organic synthesis, cell biology, cell culture, and molecular biology, which are within the skill of the art.

The following examples further illustrate aspects of the present disclosure. However, they are in no way a limitation of the teachings of the present disclosure as set forth.

Abbreviations

AcOH or HOAc	Acetic acid
CBz	Benzyl chloroformate
Boc	tert-butoxycarbonyl
$CDCl_3$	Chloroform-d
Cs_2CO_3	Cesium carbonate
DIEA	Diisopropylethylamine
D_{max}	Maximal degradation (%)
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide (C_2D_6SO)
DTT	Dithiothreitol
ESI	Electrospray ionization
EtOH	Ethanol
eq	Equivalent(s)
g	Gram(s)
h	Hour(s)
Hz	Hertz
HCl	Hydrochloric acid
HPLC	High performance liquid chromatography
DC_{50}	Half maximal degradation concentration

K_2CO_3	Potassium carbonate
K_3PO_4	Potassium phosphate
min	Minute(s)
m/z	Mass/charge
MS	Mass spectrometry
MHz	Megahertz
MeOH	Methanol
MOM	Methoxymethyl
µL	Microliter(s)
µm	Micrometer(s)
mg	Milligram(s)
mm	Millimeter(s)
mL	Milliliter(s)
mmol	Millimole(s)
NH_4Cl	Ammonium chloride
nM	Nanomolar
NMR	Nuclear magnetic resonance
$Pd(dppf)Cl_2$	[1,1-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
PMB	*para*-methoxybenzyl
psi	Pound(s) per square inch
TEA	Triethylamine
TFA	Trifluoroacetic acid
Tf	Trifluoromethanesulfonate
TIPS	Triisopropylsilyl ether
TBDPS	tert-butyldiphenylsilyl
THF	Tetrahydrofuran
TLC	Thin-layer chromatography

Synthetic Procedures

Example 1: Synthesis of 3-[4-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl] oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl] piperidine-2,6-dione (**Compound 43**)

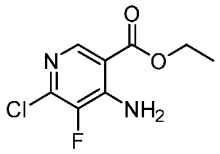
Step 1: Preparation of 2-chloro-3-fluoro-5-iodo-pyridin-4-amine



To a solution of 2-chloro-3-fluoro-pyridin-4-amine (2.00 g, 13.7 mmol, 1 *eq*) and NIS (3.68 g, 16.4 mmol, 1.2 *eq*) in CH_3CN (15 mL) was added p-TsOH (118 mg, 0.682 mmol, 0.05 *eq*), and the reaction mixture was stirred at 70 °C for 16 hours. The reaction mixture was diluted with EtOAc (40 mL), and the resulting mixture was washed with saturated aqueous Na_2CO_3 (2 x 30 mL), saturated aqueous Na_2SO_3 (40 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (3.63 g, 13.3

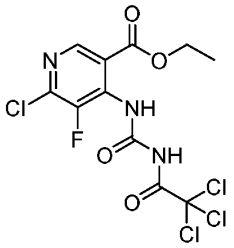
mmol, 98% yield) as a yellow solid. LC/MS (ESI) *m/z*: 272.8 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 6.67 (br s, 2H).

Step 2: Preparation of ethyl 4-amino-6-chloro-5-fluoro-pyridine-3-carboxylate



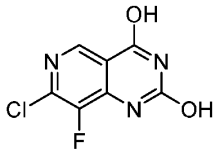
To a solution of 2-chloro-3-fluoro-5-iodo-pyridin-4-amine (3.63 g, 13.3 mmol, 1 *eq*) in EtOH (70 mL) were added triethylamine (4.85 g, 48.0 mmol, 6.68 mL, 3.6 *eq*) and $Pd(PPh_3)_2Cl_2$ (935 mg, 1.33 mmol, 0.1 *eq*), and the reaction mixture was stirred at 80 °C under CO (15 psi) (degassed under vacuum and purged with CO several times) for 16 hours. The reaction mixture was concentrated under reduced pressure to remove ~ 70% of EtOH and then filtered. The filter cake was washed with TBME (2 x 30 mL) and then dried under reduced pressure to give the title compound (3.40 g, crude) as a yellow solid. LC/MS (ESI) *m/z*: 219.0 $[M+H]^+$.

Step 3: Preparation of ethyl 6-chloro-5-fluoro-4-[(2,2,2-trichloroacetyl)carbamoylamino]pyridine-3-carboxylate



To a solution of ethyl 4-amino-6-chloro-5-fluoro-pyridine-3-carboxylate (3.40 g, 15.6 mmol, 1 *eq*) in THF (10 mL) was added 2,2,2-trichloroacetyl isocyanate (3.22 g, 17.1 mmol, 2.03 mL, 1.1 *eq*), and the reaction mixture was stirred at 20 °C under N_2 for 1 hour. The reaction mixture was concentrated under reduced pressure to give the title compound (6.10 g, crude) as a brown solid. LC/MS (ESI) *m/z*: 408.1 $[M+H]^+$.

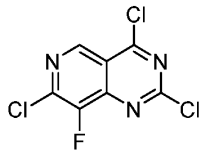
Step 4: Preparation of 7-chloro-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol



To a solution of ethyl 6-chloro-5-fluoro-4-[(2,2,2-trichloroacetyl)carbamoylamino]pyridine-3-carboxylate (6.10 g, 15.0 mmol, 1 *eq*) in CH_3OH (55

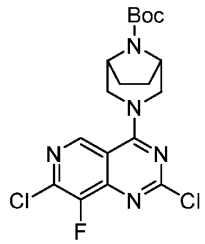
mL) was added ammonia (7 M, 10.7 mL, 5 *eq*), and the reaction mixture was stirred at 20 °C for 1 hour. The reaction mixture was filtered, and the filter cake was washed with TBME (3 x 20 mL), then dried under reduced pressure to give the title compound (3.03 g, 14.06 mmol, 94% yield) as a white solid. LC/MS (ESI) *m/z*: 216.1 $[M+H]^+$.

Step 5: Preparation of 2,4,7-trichloro-8-fluoro-pyrido[4,3-d]pyrimidine



To a solution of 7-chloro-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol (2.50 g, 11.6 mmol, 1 *eq*) in toluene (30 mL) were added DIEA (4.50 g, 34.8 mmol, 6.06 mL, 3 *eq*) and $POCl_3$ (8.89 g, 58.0 mmol, 5.39 mL, 5 *eq*), and the reaction mixture was stirred at 100 °C under N_2 for 1 hour. The reaction mixture was concentrated under reduced pressure to give the title compound (2.9 g, crude) as a yellow oil. LC/MS (ESI) *m/z*: 253.7 $[M+H]^+$.

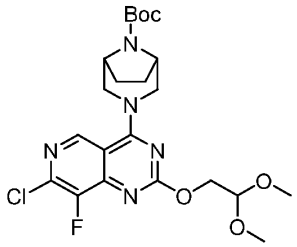
Step 6: Preparation of *tert*-butyl 3-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 2,4,7-trichloro-8-fluoro-pyrido[4,3-d]pyrimidine (2.90 g, 11.5 mmol, 1 *eq*) in CH_2Cl_2 (50 mL) were added DIEA (7.42 g, 57.4 mmol, 5 *eq*) and *tert*-butyl (1S,5R)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.44 g, 11.5 mmol, 1 *eq*) at -40 °C, and the reaction mixture was stirred at -40 °C under N_2 for 0.5 hour. The reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with brine (2 x 60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude product. The crude product was purified by flash silica gel chromatography (eluent: 0~25% EtOAc/petroleum ether) to give the title compound (2.47 g, 5.77 mmol, 50% yield) as a yellow solid. LC/MS (ESI) *m/z*: 428.2 $[M+H]^+$. ^{1}H-NMR (400 MHz,

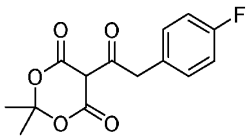
DMSO-d_6) δ 9.06 (s, 1H), 4.60-4.40 (m, 2H), 4.31-4.22 (m, 2H), 3.80-3.59 (m, 2H), 1.85-1.74 (m, 2H), 1.66-1.57 (m, 2H), 1.46 (s, 9H).

Step 7: Preparation of *tert*-butyl 3-[7-chloro-2-(2,2-dimethoxyethoxy)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



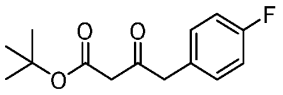
To a solution of *tert*-butyl 3-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 1.17 mmol, 1 *eq*) and 2,2-dimethoxyethanol (186 mg, 1.75 mmol, 1.5 *eq*) in CH_3CN (10 mL) were added Cs_2CO_3 (456 mg, 1.40 mmol, 1.2 *eq*) and DABCO (13 mg, 0.17 mmol, 0.1 *eq*), and the reaction mixture was stirred at 20 °C under N_2 for 16 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give crude product. The crude product was purified by flash silica gel chromatography (eluent: 0~15% THF/petroleum ether) to give the title compound. LC/MS (ESI) *m/z*: 498.3 $[M+H]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 4.81 (t, *J* = 5.6 Hz, 1H), 4.54-4.45 (m, 4H), 4.43-4.27 (m, 2H), 3.74-3.55 (m, 2H), 3.48 (s, 6H), 2.02-1.90 (m, 2H), 1.75-1.65 (m, 2H), 1.52 (s, 9H).

Step 8: Preparation of 5-[2-(4-fluorophenyl)acetyl]-2,2-dimethyl-1,3-dioxane-4,6-dione



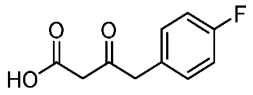
To a solution of 2-(4-fluorophenyl)acetic acid (50 g, 324.38 mmol, 1.0 *eq*), 2,2-dimethyl-1,3-dioxane-4,6-dione (51.4 g, 356.82 mmol, 1.1 *eq*), and DMAP (3.4 g, 27.57 mmol, 0.085 *eq*) in CH_3CN (150 mL) was added DIEA (121 mL, 697.43 mmol, 2.2 *eq*) followed by 2,2-dimethylpropanoyl chloride (44 mL, 356.82 mmol, 1.1 *eq*) slowly over 3 hours while maintaining the temperature below 45 °C. The reaction mixture was stirred at 45 °C for 3 hours. The reaction was cooled to 0 °C. HCl (500 mL, 1 M, 1.54 *eq*) was then added, and the mixture was stirred at 0 °C for 30 minutes. The mixture was filtered, and the filter cake was washed with water (CH_3CN: Water =1: 4, 500 mL). The filter cake was dissolved with CH_2Cl_2 (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum to give the title compound (84.5 g, 301.52 mmol, 93% yield) as a white solid.

Step 9: Preparation of tert-butyl 4-(4-fluorophenyl)-3-oxo-butanoate



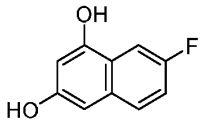
A solution of 5-[2-(4-fluorophenyl)acetyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (168 g, 601.25 mmol, 1.0 eq) in *t*-BuOH (500 mL) was stirred at 90 °C for 2.5 hours. The reaction mixture was concentrated in vacuum to give the title compound (151 g, 598.54 mmol, 100% yield) as a yellow oil. LC/MS (ESI) *m/z*: 197.1 $[M-56]^+$.

Step 10: Preparation of 4-(4-fluorophenyl)-3-oxo-butanoic acid



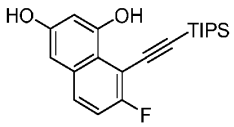
To a solution of tert-butyl 4-(4-fluorophenyl)-3-oxo-butanoate (151 g, 598.54 mmol, 1.0 eq) in CH_2Cl_2 (300 mL) was added TFA (293 mL, 3.95 mol, 6.60 eq), and the reaction mixture was stirred at 20 °C for 1 hour. The mixture was concentrated in vacuum to give the title compound (115 g, 532.28 mmol, 89% yield) as a yellow solid. LC/MS (ESI) m/z: 197.1 $[M+H]^+$.

Step 11: Preparation of 7-fluoronaphthalene-1,3-diol



A solution of 4-(4-fluorophenyl)-3-oxo-butanoic acid (115 g, 586.21 mmol, 1.0 eq) in CF_3SO_3H (1200 mL) was stirred at 20 °C for 16 hours. The reaction was cooled to 0 °C, and slowly poured onto ice-water (3.0 L). The resulting precipitate was filtered, and the filter cake was dissolved with ethyl acetate (200 mL × 3). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (40 mL × 2) and brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum to give the title compound (54.4 g, 267.18 mmol, 46% yield) as a red solid. LC/MS (ESI) *m/z*: 179.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 9.49 (s, 1H), 7.67 - 7.53 (m, 2H), 7.25-7.20 (m, 1H), 6.64 (s, 1H), 6.56 (s, 1H).

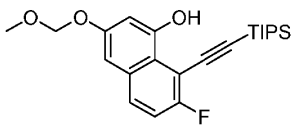
Step 12: Preparation of 7-fluoro-8-(2-triisopropylsilylethynyl)naphthalene-1,3-diol



To a solution of 7-fluoronaphthalene-1,3-diol (43.5 g, 244.23 mmol, 1.0 eq), 2-bromoethynyl(triisopropyl)silane (67 g, 256.44 mmol, 1.05 eq), and KOAc (48 g, 488.45 mmol, 2.0 eq) in dioxane (300 mL) was added dichlororuthenium;1-isopropyl-4-methyl-benzene (9.0 g,

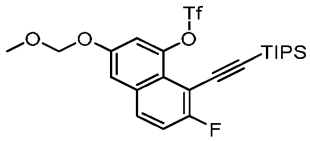
14.65 mmol, 0.06 eq) under N_2, and the reaction mixture was stirred at 110 °C for 16 hours. The mixture was filtered and concentrated in vacuum, and the resulting residue was purified by flash chromatography on SiO_2 (gradient: 0-20% ethyl acetate in petroleum ether) to afford the title compound (46.3 g, 124.11 mmol, 51% yield) as a black oil. LC/MS (ESI) *m/z*: 359.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.61-7.57 (m, 1H), 7.17 (t, *J*=8.8 Hz, 1H), 6.74 (d, *J*=2.4 Hz, 1H), 6.66 (d, *J*=2.0 Hz, 1H), 1.22 - 1.16 (m, 21H).

Step 13: Preparation of 7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)naphthalen-1-ol



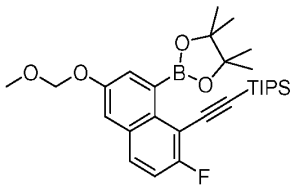
To a solution of 7-fluoro-8-(2-triisopropylsilylethynyl)naphthalene-1,3-diol (46.3 g, 129.14 mmol, 1.0 eq) in CH_2Cl_2 (450 mL) at 0 °C were added DIEA (67.5 mL, 387.43 mmol, 3.0 eq) and MOMCl (14.7 mL, 193.71 mmol, 1.5 eq), and the reaction mixture was stirred at 0 °C for 40 minutes. The reaction was quenched by addition of water (50 mL) at 0 °C, then extracted with dichloromethane (50 mL × 3). The combined organic extract was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The resulting residue was purified by flash chromatography on SiO_2 (gradient: 0-15% dichloromethane in petroleum ether) to afford the title compound (26.8 g, 62.51 mmol, 48% yield) as a yellow oil. LC/MS (ESI) *m/z*: 403.1 $[M+H]^+$.

Step 14: Preparation of [7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl] trifluoromethanesulfonate



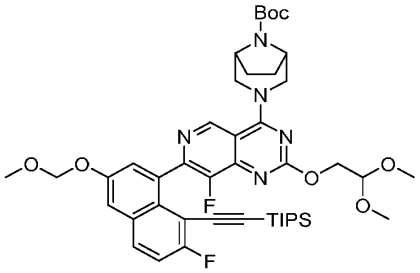
To a solution of 7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)naphthalen-1-ol (21.8 g, 54.15 mmol, 1.0 eq) and DIEA (28.3 mL, 162.45 mmol, 3.0 eq) in CH_2Cl_2 (300 mL) at -40 °C was added Tf_2O (13.4 mL, 81.23 mmol, 1.5 eq), and the reaction mixture was stirred at -40 °C for 40 minutes. The reaction was quenched by addition of water (150 mL) at -40 °C, warmed to 25 °C, and then extracted with dichloromethane (100 mL × 3). The combined organic extract was washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated in vacuum. The resulting residue was purified by flash chromatography on SiO_2 (gradient: 0-15% dichloromethane in petroleum ether) to the title compound (28 g, 51.95 mmol, 96% yield) as a yellow oil.

Step 15: Preparation of 2-[2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl-triisopropyl-silane



To a solution of [7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl] trifluoromethanesulfonate (23.8 g, 44.52 mmol, 1.0 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (22.6 g, 89.03 mmol, 2.0 eq), and KOAc (13.1 g, 133.55 mmol, 3.0 eq) in toluene (350 mL) was added $Pd(dppf)Cl_2$ (3.26 g, 4.45 mmol, 0.1 eq) under N_2, and the reaction mixture was stirred at 110 °C for 16 hours under N_2. The mixture was filtered through a pad of Celite® under vacuum and rinsed with ethyl acetate (80 mL × 2). The filtrate was evaporated to dryness, and the resulting residue was purified by flash chromatography on SiO_2 (gradient: 0~3% ethyl acetate in petroleum ether) to afford the title compound (21.4 g, 27.97 mmol, 63% yield) as a yellow solid. LC/MS (ESI) *m/z*: 513.0 $[M+H]^+$.

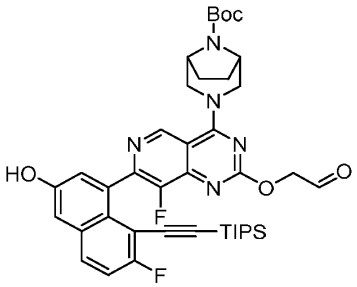
Step 16: Preparation of tert-butyl 3-[2-(2,2-dimethoxyethoxy)-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of tert-butyl 3-[7-chloro-2-(2,2-dimethoxyethoxy)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg, 0.803 mmol, 1.0 eq) and 2-[2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl-triisopropyl-silane (494 mg, 0.964 mmol, 1.2 eq) in dioxane (10 mL) and H_2O (2 mL) were added K_3PO_4 (512 mg, 2.41 mmol, 3.0 eq) and [2-(2-aminophenyl)phenyl]palladium(1+);bis(1-adamantyl)-butyl-phosphane;methanesulfonate (117 mg, 0.161 mmol, 0.2 eq) under N_2, and the reaction mixture was stirred at 85 °C for 15 hours under N_2. The mixture was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The resulting residue was purified by flash chromatography on SiO_2 (gradient: 0~27%

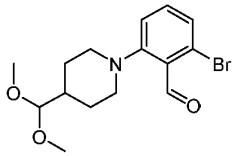
ethyl acetate in petroleum ether) to afford the title compound (590 mg, 0.684 mmol, 85% yield) as a yellow solid. LC/MS (ESI) *m/z*: 848.4 $[M+H]^+$.

Step 17: Preparation of tert-butyl 3-[8-fluoro-7-[7-fluoro-3-hydroxy-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of tert-butyl 3-[2-(2,2-dimethoxyethoxy)-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (630 mg, 0.743 mmol, 1.0 eq) in acetone (1.6 mL) was added aqueous HCl (1.58 mL, 12 M, 25.51 eq), and the reaction mixture was stirred at 20 °C for 15 minutes. A solution of $NaHCO_3$ (867 µL, 22.29 mmol, 30.0 eq) in water (3 mL), Boc_2O (341 µL, 1.49 mmol, 2.0 eq), and THF (3 mL) were added, and the reaction mixture was stirred at 20 °C for 1 hour. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (40 mL x 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The resulting residue was purified by flash chromatography on SiO_2 (gradient: 0~50% ethyl acetate in petroleum ether) to afford the title compound (420 mg, 386.23 µmol, 52% yield) as a yellow solid. LC/MS (ESI) *m/z*: 758.4 $[M+H]^+$.

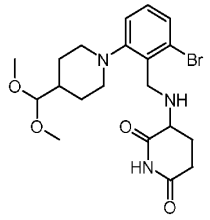
Step 18: Preparation of 2-bromo-6-[4-(dimethoxymethyl)-1-piperidyl]benzaldehyde



To a solution of 4-(dimethoxymethyl)piperidine (8.47 g, 53.20 mmol, 1.20 eq) and 2-bromo-6-fluoro-benzaldehyde (9.00 g, 44.33 mmol, 1 eq) in DMSO (90 mL) was added *N*,*N*-diisopropylethylamine (22.92 g, 177.33 mmol, 4.00 eq), and the reaction mixture was stirred at 100 °C for 12 hours. The residue was diluted with water (100 mL) and extracted with ethyl acetate (100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was

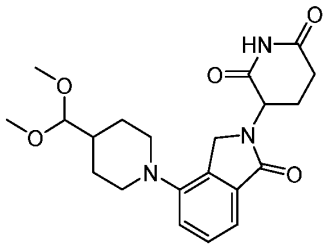
purified by flash silica gel chromatography (gradient: 0~7% ethyl acetate/petroleum ether) to give the title compound (11.10 g, 32.43 mmol, 73% yield) as a yellow solid.LC/MS (ESI) *m/z*: 344.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 7.31 - 7.28 (m, 2H), 7.14 - 7.04 (m, 1H), 4.19 - 4.13 (m, 1H), 3.42 (s, 6H), 3.36 - 3.28 (m, 2H), 2.86 (dd, *J* = 2.0, 12.0 Hz, 2H), 1.93 - 1.84 (m, 2H), 1.78 (dd, *J* = 4.0, 7.2, 15.2 Hz, 1H), 1.65 - 1.54 (m, 2H).

Step 19: Preparation of 3-[[2-bromo-6-[4-(dimethoxymethyl)-1-piperidyl]phenyl]methylamino]piperidine-2,6-dione



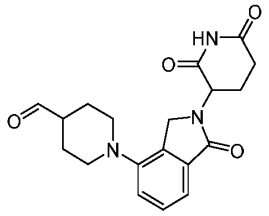
To a solution of 3-aminopiperidine-2,6-dione (5.05 g, 30.68 mmol, 1.00 eq, hydrochloride) in methanol (100 mL) and dichloromethane (100 mL) was added sodium acetate (7.55 g, 92.04 mmol, 3.00 eq), and the resulting mixture was stirred at 25 °C for 1 hour. 2-Bromo-6-[4-(dimethoxymethyl)-1-piperidyl]benzaldehyde (10.50 g, 30.68 mmol, 1.00 eq) and 2-methylpyridine borane (6.56 g, 61.36 mmol, 2.00 eq) were then added, and the reaction mixture was stirred at 25 °C for 12 hours. The reaction mixture was filtered. and the filtrate was diluted with water (100 mL), then extracted with ethyl acetate (100 mL). The organic extract was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was triturated with ethyl acetate/petroleum (3:1) to give the title compound (10.70 g, 23.55 mmol, 77% yield) as a purple solid. LC/MS (ESI) *m/z*: 456.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 7.36 - 7.29 (m, 1H), 7.21 - 7.11 (m, 2H), 4.12 (d, *J* = 6.8 Hz, 1H), 3.99 - 3.82 (m, 2H), 3.30 - 3.27 (m, 6H), 3.23 (dd, *J* = 4.8, 11.2 Hz, 1H), 3.09 (d, *J* = 10.8 Hz, 1H), 3.01 - 2.81 (m, 1H), 2.77 - 2.65 (m, 1H), 2.60 - 2.53 (m, 2H), 2.48 - 2.41 (m, 1H), 2.35 - 2.22 (m, 1H), 1.80 - 1.61 (m, 4H), 1.51 - 1.30 (m, 2H).

Step 20: Preparation of 3-[4-[4-(dimethoxymethyl)-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione



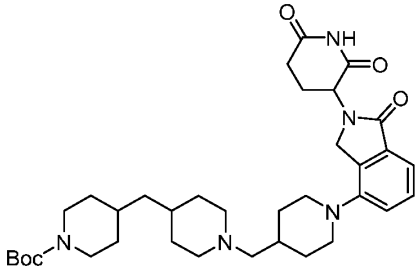
To a solution of 3-[[2-bromo-6-[4-(dimethoxymethyl)-1-piperidyl]phenyl]methylamino]piperidine-2,6-dione (10.70 g, 23.55 mmol, 1.00 eq) in DMF (150 mL) were added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii) (3.45 g, 4.71 mmol, 0.20 eq) and diisopropylethylamine (9.13 g, 70.65 mmol, 3.00 eq), and the reaction mixture was degassed and purged with carbon dioxide (3X), then stirred at 80 °C for 12 hours under carbon dioxide (50 Psi) atmosphere. The reaction mixture was filtered, and the filtrate was diluted with water (200 mL), then extracted with ethyl acetate (150 mL). The organic extract was washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 (250*80mm*15μm);mobile phase: [20-50% CH_3CN in water (trifluoroacetic acid)]) to give the title compound (2.60 g, 6.48 mmol, 27% yield) as a white solid. LC/MS (ESI) *m/z*: 402.2 $[M+H]^+$.

Step 21: Preparation of 1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperidine-4-carbaldehyde



To a solution of 3-[4-[4-(dimethoxymethyl)-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (70 mg, 0.17 mmol, 1.00 *eq*) in dichloromethane (2 mL) was added trifluoroacetic acid (60 mg, 0.52 mmol, 3.00 *eq*), and the reaction mixture was stirred at 25 °C for 1 hour. The mixture was concentrated under reduced pressure to give the title compound (80 mg, crude) as a colorless oil. LC/MS (ESI) *m/z*: 356.2 $[M+H]^+$.

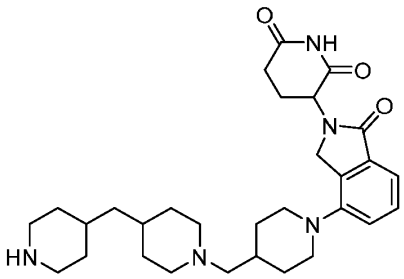
Step 22: Preparation of *tert*-butyl 4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate



To a solution of 1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperidine-4-carbaldehyde (340 mg, 0.95 mmol, 1 eq) in dimethyl sulfoxide (3 mL) and dichloromethane (3 mL) were added *N*-methylmorpholine (484 mg, 4.78 mmol, 0.5 mL, 5 eq), *tert*-butyl 4-(4-

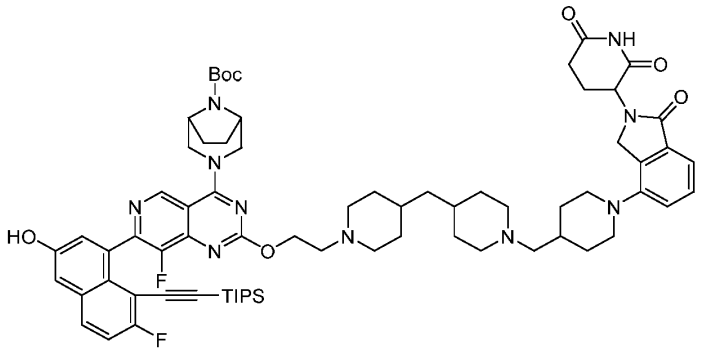
piperidylmethyl) piperidine-1-carboxylate (324 mg, 1.15 mmol, 1.2 eq), and acetic acid (57 mg, 0.95 mmol, 0.1 mL, 1 eq), and the resulting mixture was stirred at 25 °C for 1 hour. Sodium triacetoxyborohydride (406 mg, 1.91 mmol, 2 eq) was then added, and the reaction mixture was stirred at 25 °C for 15 hours. The mixture was diluted with water (15 mL) and extracted with 5:1 dichloromethane/isopropanol (10 × 3 mL). The organic extract was washed with brine (10 × 3 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The resulting residue was purified by flash silica gel chromatography (gradient: 0-100% ethyl acetate in petroleum ether gradient) to afford the title compound (312 mg, 0.50 mmol, 52% yield) as a yellow oil. LC/MS (ESI) *m/z*: 622.5 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.46 - 7.40 (m, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 5.14 - 5.08 (m, 1H), 4.43 (d, *J* = 17.2 Hz, 1H), 4.29 (d, *J* = 17.2 Hz, 1H), 4.13 (s, 1H), 3.92 (s, 2H), 3.34 (d, *J* = 0.8 Hz, 4H), 3.16 (s, 4H), 2.77 (d, *J* = 10.8 Hz, 5H), 1.99 - 1.89 (m, 6H), 1.76 - 1.71 (m, 4H), 1.60 (d, *J* = 12.4 Hz, 4H), 1.38 (s, 9H), 1.12 (s, 2H), 1.03 (d, *J* = 6.0 Hz, 1H), 0.95 - 0.90 (m, 2H).

Step 23: Preparation 3-[1-oxo-4-[4-[[4-(4-piperidylmethyl)-1-piperidyl] methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione



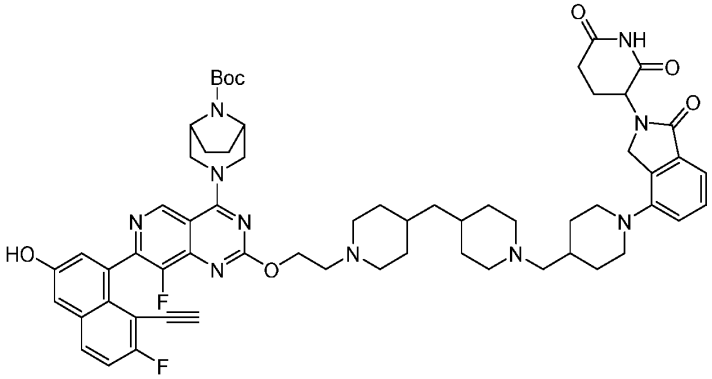
To a solution of *tert*-butyl 4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate (412 mg, 0.66 mmol, 1 eq) in dichloromethane (3 mL) was added trifluoroacetic acid (1.54 g, 13.51 mmol, 1 mL, 20.38 eq), and the reaction mixture was stirred at 25 °C for 2 hours. The mixture was concentrated in vacuum, and the resulting residue was purified by prep-HPLC (column: Unisil 3-100 C18 Ultra 150*50mm*3μm; mobile phase: [1-18% CH_3CN in water (formic acid)]) to afford the title compound (200 mg, 0.38 mmol, 58% yield) as a yellow solid. LC/MS (ESI) *m/z*: 522.4 $[M+H]^+$.

Step 24: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl] ethoxy]-8-fluoro-7-[7-fluoro-3-hydroxy-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido [4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 3-[1-oxo-4-[4-[[4-(4-piperidylmethyl)-1-piperidyl] methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione (90 mg, 0.17 mmol, 1 eq) in 1,2-dichloroethane (5 mL) and dimethyl sulfoxide (5 mL) was added 4-methylmorpholine (26 mg, 0.26 mmol, 28 µL, 1.5 eq), and the resulting mixture was stirred at 25 °C for 15 minutes. *tert*-Butyl 3-[8-fluoro-7-[7-fluoro-3-hydroxy-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (144 mg, 0.19 mmol, 1.1 eq) was then added, and the mixture was stirred for 0.5 h at 25 °C. Sodium triacetoxyborohydride (110 mg, 0.52 mmol, 3 eq) was added, and the reaction mixture was stirred at 25 °C for 2 hours. The reaction was quenched with water (20 mL), and the resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by preparative TLC (dichloromethane/methanol = 10/1) to afford the title compound (110 mg, 0.09 mmol, 50% yield) as a yellow solid. LC/MS (ESI) *m/z*: 1263.7 $[M+H]^+$.

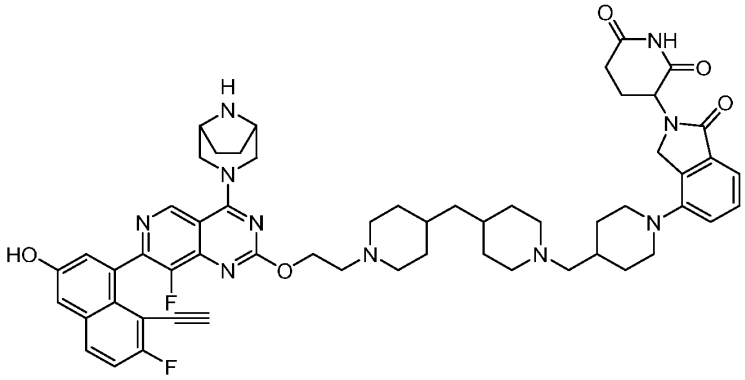
Step 25: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl] ethoxy]-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl] ethoxy]-8-fluoro-7-[7-fluoro-3-hydroxy-8-

(2-triisopropylsilylethynyl)-1-naphthyl]pyrido [4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.08 mmol, 1 eq) in DMF (3 mL) at 20 °C was added cesium fluoride (240 mg, 1.58 mmol, 20 eq), and the reaction mixture was stirred at 20 °C for 2 hours. The reaction was quenched with water (20 mL), and the resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the title compound (80 mg, 0.07 mmol, 91% yield) as a yellow oil. LC/MS (ESI) *m/z*: 1107.7 $[M+H]^+$.

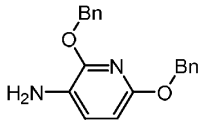
Step 26: Preparation of 3-[4-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl] oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl] piperidine-2,6-dione (**Compound 43**)



A solution of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl] ethoxy]-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.07 mmol, 1 eq) in formic acid (4 mL) was stirred at 25 °C for 2 hours. The reaction mixture was concentrated, and the resulting residue was purified by prep-HPLC {column: Phenomenex luna C18 150*40mm* 15μm;mobile phase: [2-32% CH_3CN in water (formic acid)]} to the title compound (62.7 mg, 0.05 mmol, 78% yield, formic acid salt) as a yellow solid.

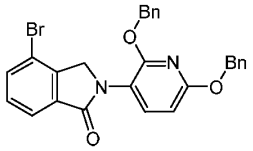
Example 2: Synthesis of 3-[4-[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 35**)

Step 1: Preparation of 2,6-dibenzyloxy pyridin-3-amine



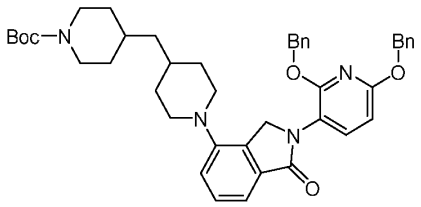
To a solution of phenylmethanol (16.59 g, 153.37 mmol, 16.0 mL, 2.5 *eq*) in tetrahydrofuran (200 mL) was added potassium *tert*-butoxide (17.21 g, 153.37 mmol, 2.5 *eq*) portion-wise, and the resulting mixture was stirred at 25 °C for 2 hours. 2,6-Dichloropyridin-3-amine (10 g, 61.35 mmol, 1 *eq*) was then added, and the reaction mixture was stirred at 75 °C for 24 hours. The mixture was cooled to 25 °C, then diluted with ethyl acetate (600 mL). The organic layer was washed with water (100 mL × 3), and the water layer wash extracted with ethyl acetate (100 mL × 2). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 50/1 to 10:1) followed by prep-HPLC (column: Welch Ultimate XB-Diol 250*50*10μm; mobile phase: [Heptane-EtOH(0.1% NH_4OH)]; B%: 1%-10%,15min) to get the title compound (3.1 g, 10.12 mmol, 16% yield) as a black orange oil. LC/MS (ESI) *m/z*: 307.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 - 7.30 (m, 10H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.28 (d, *J* = 8.0 Hz, 1H), 5.39 (s, 2H), 5.28 (s, 2H), 3.27 - 2.56 (m, 2H).

Step 2: Preparation of 4-bromo-2-(2,6-dibenzyloxy-3-pyridyl)isoindolin-1-one



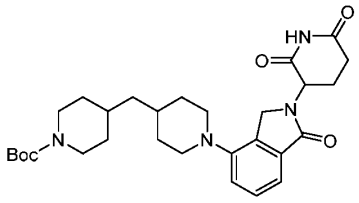
To a solution of 2,6-dibenzyloxypyridin-3-amine (1.2 g, 3.92 mmol, 1 *eq*) and methyl 3-bromo-2-(bromomethyl)benzoate (1.21 g, 3.92 mmol, 1 *eq*) in *N,N*-dimethylacetamide (12 mL) was added *N,N*-diisopropylethylamine (1.52 g, 11.75 mmol, 2.1 mL, 3 *eq*), and the reaction mixture was stirred at 120 °C for 12 hours. The mixture was cooled to 25 °C, diluted with water (50 mL),and extracted with ethyl acetate (30 mL × 3). The combined organic extract was washed with brine (30 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1/0 to 4:1) to afford the title compound (1.45 g, 2.89 mmol, 74% yield) as a yellow solid. LC/MS (ESI) *m/z*: 501.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.70 (dd, *J* = 2.0, 7.6 Hz, 2H), 7.49 - 7.28 (m, 11H), 6.50 (d, *J* = 8.4 Hz, 1H), 5.43 (s, 2H), 5.35 (s, 2H), 4.70 (s, 2H).

Step 3: Preparation of *tert*-butyl 4-[[1-[2-(2,6-dibenzyloxy-3-pyridyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]piperidine-1-carboxylate



To a mixture of 4-bromo-2-(2,6-dibenzyloxy-3-pyridyl)isoindolin-1-one (260 mg, 0.52 mmol, 1 *eq*), *tert*-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate (195 mg, 0.57 mmol, 1.1 *eq*, acetate), and cesium carbonate (507 mg, 1.56 mmol, 3 *eq*) in dioxane (5 mL) was added [2-(2-aminophenyl)phenyl]-chloro-palladium;dicyclohexyl-[3-(2,4,6-triisopropylphenyl)phenyl]phosphane (41 mg, 0.05 mmol, 0.1 *eq*), and the reaction mixture was degassed and purged with nitrogen (3X), then stirred at 100 °C for 12 hours. The reaction was cooled to 25 °C, diluted with water (30 mL), and extracted with ethyl acetate (20 mL × 2). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by prep-TLC (petroleum ether/ethyl acetate=3/1) to get the title compound (320 mg, 0.46 mmol, 87% yield) as a light yellow gum. LC/MS (ESI) *m/z*: 703.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, J = 8.4 Hz, 1H), 7.52 - 7.25 (m, 13H), 7.14 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 5.38 (d, J = 9.6 Hz, 4H), 4.73 (s, 2H), 3.92 (br d, J = 11.2 Hz, 2H), 3.36 (br s, 2H), 2.69 (br t, J = 10.8 Hz, 4H), 1.71 (br d, J = 11.2 Hz, 2H), 1.62 (br d, J = 12.8 Hz, 2H), 1.56 - 1.44 (m, 2H), 1.38 (s, 9H), 1.26 - 1.18 (m, 3H), 1.06 - 0.86 (m, 2H).

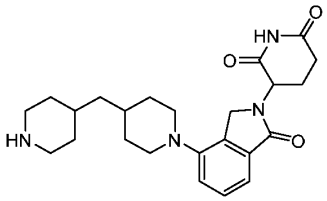
Step 4: Preparation of *tert*-butyl 4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]piperidine-1-carboxylate



To a solution of *tert*-butyl 4-[[1-[2-(2,6-dibenzyloxy-3-pyridyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]piperidine-1-carboxylate (320 mg, 0.46 mmol, 1 *eq*) in ethyl acetate (10 mL) was added palladium on activated carbon catalyst (0.1 g, 10% purity) under nitrogen, and the resulting suspension was degassed and purged with hydrogen (3X), then stirred at 25 °C under hydrogen (15 Psi) for 16 h. The mixture was filtered through a pad of Celite®, and the filtrate was concentrated under vacuum. The resulting residue was purified by prep-TLC (dichloromethane/methanol=10/1) to afford the title compound (110 mg, 0.21 mmol, 46% yield) as a white solid. LC/MS (ESI) *m/z*: 547.3 $[M+Na]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.49 - 7.39 (m, 1H), 7.29 (d, J = 7.2 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 5.11 (dd, J = 5.2,

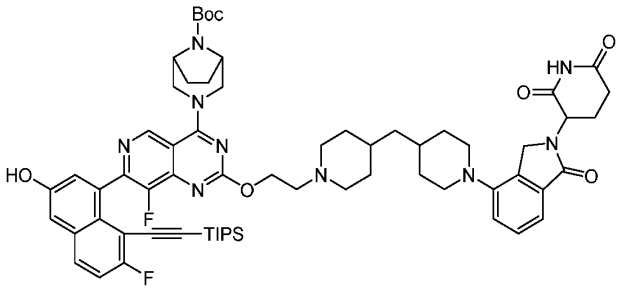
13.2 Hz, 1H), 4.49 - 4.36 (m, 1H), 4.34 - 4.22 (m, 1H), 3.92 (br d, *J* = 12.0 Hz, 2H), 3.42 - 3.34 (m, 2H), 3.31 (s, 1H), 2.99 - 2.83 (m, 1H), 2.80 - 2.55 (m, 5H), 2.05 - 1.90 (m, 1H), 1.75 (br d, *J* = 11.6 Hz, 2H), 1.63 (br d, *J* = 12.4 Hz, 2H), 1.58 - 1.47 (m, 2H), 1.39 (s, 9H), 1.25 (br d, *J* = 12.0 Hz, 2H), 1.17 (br t, *J* = 6.8 Hz, 2H), 1.04 - 0.87 (m, 2H).

Step 5: Preparation of 3-[1-oxo-4-[4-(4-piperidylmethyl)-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione



To a solution of *tert*-butyl 4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]piperidine-1-carboxylate (220 mg, 0.42 mmol, 1 *eq*) in dichloromethane (5 mL) was added trifluoroacetic acid (1.54 g, 13.51 mmol, 1 mL, 32.21 *eq*), and the reaction mixture was stirred at 25 °C for 0.5 hour. The solution was concentrated under vacuum to get the title compound (220 mg, crude, trifluoroacetic acid salt) as a white solid. LC/MS (ESI) *m/z*: 425.1 $[M+H]^+$.

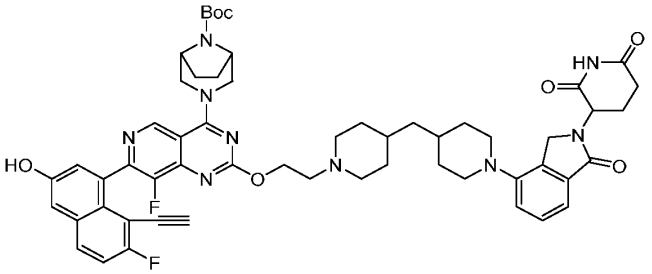
Step 6: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-hydroxy-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 3-[1-oxo-4-[4-(4-piperidylmethyl)-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione (220 mg, 0.41 mmol, 1 *eq*, trifluoroacetic acid salt) in DMSO (3 mL) and 1,2-dichloroethane (3 mL) was added 4-methylmorpholine (124 mg, 1.23 mmol, 0.1 mL, 3 *eq*) followed by tert-butyl 3-[8-fluoro-7-[7-fluoro-3-hydroxy-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (248 mg, 0.32 mmol, 0.8 *eq*) and acetic acid (25 mg, 0.41 mmol, 1 *eq*), and the resulting mixture was stirred at 25 °C for 0.5 hour. Sodium triacetoxyborohydride (260 mg, 1.23 mmol, 3 *eq*) was then added, and the reaction mixture was stirred at 25 °C for 12 hours. Water (20 mL) was

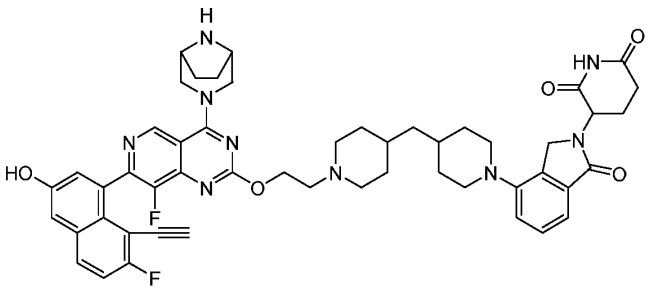
added, and the mixture was extracted with ethyl acetate (20 mL × 3). The combined organic extract was washed with brine (20 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by prep-TLC (dichloromethane/methanol=10/1) to afford the title compound (230 mg, 0.20 mmol, 48% yield) as a white solid. LC/MS (ESI) *m/z*: 1166.6 $[M+H]^+$.

Step 7: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-hydroxy-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (230 mg, 0.20 mmol, 1 *eq*) in DMF (6 mL) was added cesium fluoride (449 mg, 2.96 mmol, 15 *eq*), and the reaction mixture was stirred at 25 °C for 1.5 hours. The mixture was diluted with ethyl acetate (200 mL), and the organic layer was washed with brine (20 mL × 3), was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by prep-TLC (dichloromethane/methanol=10/1) to the title compound (110 mg, 0.11 mmol, 55% yield) as a light yellow solid. LC/MS (ESI) *m/z*: 1010.1 $[M+H]^+$.

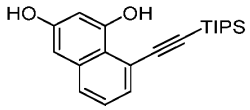
Step 8: Preparation of 3-[4-[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 35**)



To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (110 mg, 0.11 mmol, 1 *eq*) in dichloromethane (5 mL) was added trifluoroacetic acid (1.54 g, 13.51 mmol, 1 mL, 124.03 *eq*), and the reaction mixture was stirred at 25 °C for 0.5 hour. The solution was concentrated, and the resulting residue was purified by prep-HPLC (column: Unisil 3-100 C18 Ultra 150*50mm*3 μm; mobile phase: [9-39% CH_3CN in water (formic acid)]) followed by prep-HPLC (column: Unisil 3-100 C18 Ultra 150*50mm*3μm;mobile phase: [8-38% CH3CN in water (formic acid)]) to afford the title compound (14.8 mg, 0.01 mmol, 13% yield, formic acid salt) as a yellow solid.

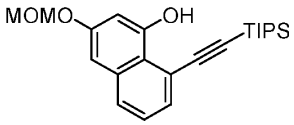
Example 3: Synthesis of 3-[4-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 55**)

Step 1: Preparation of 8-(2-triisopropylsilylethynyl)naphthalene-1,3-diol



A solution of naphthalene-1,3-diol (50 g, 312.17 mmol, 1 eq), 2-bromoethynyl(triisopropyl) silane (97.87 g, 374.60 mmol, 1.2 eq), dichlororuthenium;1-isopropyl-4-methyl-benzene (19.12 g, 31.22 mmol, 0.1 eq) and potassium acetate (61.27 g, 624.34 mmol, 2 eq) in dioxane (600 mL) was stirred for 12 hours at 110 °C under nitrogen. The reaction mixture was concentrated, and the resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate =1/0 to 20/1) to afford the title compound (70 g, 205.56 mmol, 65% yield) as a yellow solid. LC/MS (ESI) *m/z*: 341.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 6.4, 1H), 7.33 – 7.28 (m, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.64 (d, *J* = 2.8 Hz, 1H), 4.15 (s, 1H), 1.23 – 1.20 (m, 3H), 1.19 – 1.17 (m, 18H).

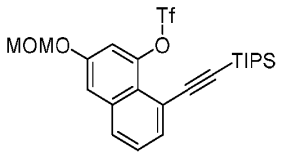
Step 2: Preparation of 3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl) naphthalen-1-ol



To a solution of 8-(2-triisopropylsilylethynyl)naphthalene-1,3-diol (270 g, 792.88 mmol, 1 *eq*) and *N,N*-diisopropylethylamine (307.42 g, 2.38 mol, 414 mL, 3 *eq*) in dichloromethane (2.5 L) at 0 °C was added chloro(methoxy)methane (96.44 g, 1.20 mol, 91 mL, 1.51 *eq*), and the

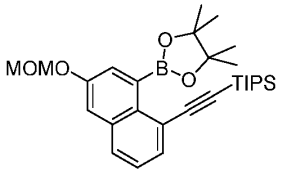
reaction mixture was stirred for 25 °C for 3 hours. The reaction mixture was diluted with water (1000 mL) and extracted with dichloromethane (1000 mL × 2). The combined organic extract was washed with brine (1000 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate= 1/0 to 10/1) to afford the title compound (185 g, 481.04 mmol, 61% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 6.4, 1H), 7.34 – 7.29 (m, 1H), 7.00 – 6.96 (m, 1H), 6.77 (d, J = 2.4 Hz, 1H), 5.27 (s, 2H), 3.51 (s, 3H), 1.27 – 1.22 (m, 3H), 1.20 – 1.17 (m, 18H).

Step 3: Preparation of [3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl] trifluoromethanesulfonate



To a solution of 3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)naphthalen-1-ol (175 g, 455.04 mmol, 1 eq) and *N,N*-Diisopropylethylamine (176.43 g, 1.37 mol, 238 mL, 3 eq) in dichloromethane (2 L) at -40 °C was added trifluoromethylsulfonyl trifluoromethanesulfonate (192.58 g, 682.56 mmol, 113 mL, 1.5 eq) dropwise, and the reaction mixture was stirred for 1 hour at - 40 °C under nitrogen. The reaction mixture was quenched with water (500 mL) and extracted with dichloromethane (300 mL × 2). The combined organic extract was washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1/0 to 20/1) to afford the title compound (91 g, 144.69 mmol, 92% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.71 (m, 2H), 7.47 – 7.41 (m, 2H), 7.31 (d, J = 2.4, 1H), 5.29 (s, 2H), 3.53 (s, 3H), 1.28 – 1.22 (m, 3H), 1.19 – 1.14 (m, 18H).

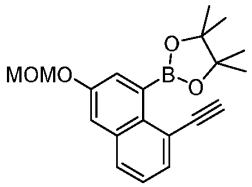
Step 4: Preparation of triisopropyl-[2-[6-(methoxymethoxy)-8-(4,4,5,5- tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl]silane



A mixture of [3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl] trifluoromethanesulfonate (192 g, 371.63 mmol, 1 *eq*), 4,4,5,5-tetramethyl-1,3,2- dioxaborolane (61.83 g, 483.12 mmol, 70 mL, 1.3 *eq*), triethylamine (112.82 g, 1.11 mol, 155 mL, 3 *eq*), and cyclopentyl(diphenyl)phosphane;dichloromethane;dichloropalladium;iron (30.35 g, 37.16 mmol,

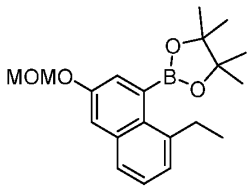
0.1 *eq*) in acetonitrile (2 L) was stirred for 12 hours at 80 °C under nitrogen. The reaction mixture was concentrated, and the resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1/0 to 20/1) to afford the title compound (165 g, 333.64 mmol, 89% yield) as a yellow solid. LC/MS (ESI) *m/z*: 495.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.65 (m, 2H), 7.47 (d, J = 2.4 Hz, 1H), 7.40 – 7.33 (m, 2H), 5.29 (s, 2H), 3.51 (s, 3H), 1.44 (s, 12H), 1.20 – 1.18 (m, 3H), 1.17 – 1.15 (m, 18H).

Step 5: Preparation of 2-[8-ethynyl-3-(methoxymethoxy)-1-naphthyl]- 4,4,5,5-tetramethyl-1,3,2-dioxaborolane



A solution of triisopropyl-[2-[6-(methoxymethoxy)-8-(4,4,5,5- tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl]silane (81 g, 163.79 mmol, 1 eq) and cesium fluoride (497.59 g, 3.28 mol, 20 eq) in DMF (1.6 L) was stirred for 5 hours at 20 °C. The reaction mixture was diluted with water (2000 mL) and extracted with ethyl acetate (2000 mL × 2). The combined organic extract was washed with brine (2000 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=10/0 to 1/1) to afford the title compound (17 g, 57.79 mmol, 94% yield) as a yellow oil. LC/MS (ESI) *m/z*: 339.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 10.0 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.39 – 7.34 (m, 1H), 5.29 (s, 2H), 3.52 (s, 3H), 3.36 (s, 1H), 1.45 (s, 12H).

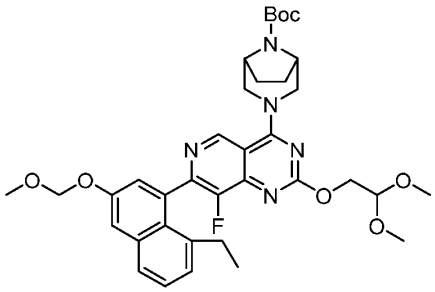
Step 6: Preparation of 2-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-4,4, 5,5-tetramethyl-1,3,2-dioxaborolane



To 2-[8-ethynyl-3-(methoxymethoxy)-1-naphthyl]- 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (25 g, 73.92 mmol, 1 eq) in methanol (300 mL) and tetrahydrofuran (300 mL) was added palladium on activated carbon (5 g, 10% purity), and the reaction mixture was stirred for 5 hours at 20 °C under hydrogen atmosphere (15 psi). The reaction mixture was filtered through Celite® and the filtrate was concentrated to afford the title compound (14 g, 46.95 mmol, 81% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.6 Hz, 1H),

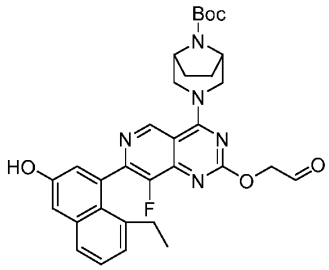
7.42 (d, *J* = 2.8, 1H), 7.40 – 7.37 (m, 1H), 7.35 (t, *J* = 4.0, 2.4 Hz, 3H), 7.27 – 7.24 (m, 1H), 5.29 (s, 2H), 3.52 (m, 3H), 1.45 (s, 12H), 1.36 (t, *J* = 7.6, 7.2 Hz, 3H).

Step 7: Preparation of *tert*-butyl 3-[2-(2,2-dimethoxyethoxy)-7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[7-chloro-2-(2,2-dimethoxyethoxy)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.6 g, 3.21 mmol, 1 eq) and 2-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.28 g, 3.73 mmol, 1.16 eq) in dioxane (15 mL) and H_2O (3 mL) were added Cs_2CO_3 (2.62 g, 8.03 mmol, 2.5 eq) and [1,1′-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (418.8 mg, 0.643 mmol, 0.2 eq), and the reaction mixture was stirred at 110 °C for 16 hours under N_2. The mixture was diluted with EtOAc (150 mL), and the combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting the residue was purified by flash chromatography on silica gel (gradient: 10~30% EtOAc in petroleum ether) to afford the title compound (0.922 g, 1.28 mmol, 40% yield) as a brown solid. LC/MS (ESI) *m/z*: 678.4 $[M+H]^+$.

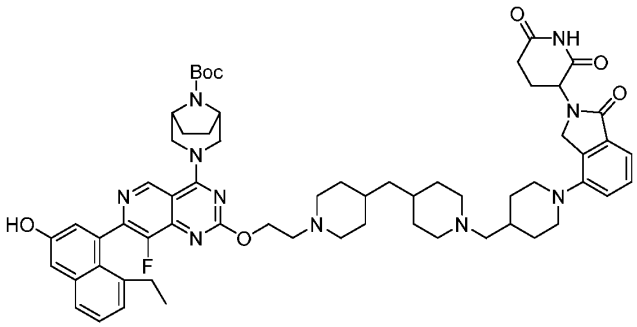
Step 8: Preparation of *tert*-butyl 3-[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-(2,2-dimethoxyethoxy)-7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.148 mmol, 1 eq) in acetone (0.37 mL) was added concentrated HCl (12 M, 0.37 mL, 30 eq) dropwise, and the reaction mixture was stirred at 20 °C for 5 minutes (9 batches were

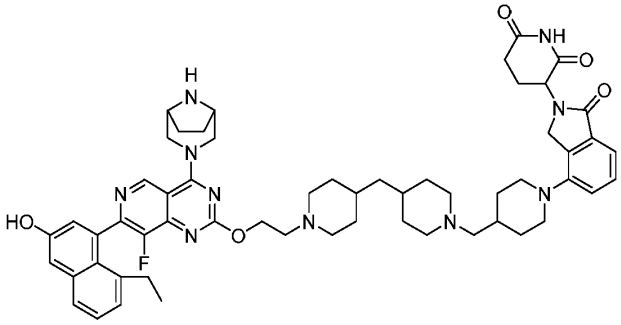
conducted in total). Saturated aqueous $NaHCO_3$ was then added until pH = 8, and the resulting mixture was filtered, washing with water (10 mL) and petroleum ether (10 mL) to give 2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyacetaldehyde (640 mg crude) as a yellow solid. Boc_2O (343.8 mg, 1.58 mmol, 1.2 eq) and a solution of $NaHCO_3$ (330.8 mg, 3.94 mmol, 3 eq) in H_2O (2.5 mL) were then added, and the reaction mixture was stirred at 20 °C for 2 hours. The mixture was diluted with EtOAc (120 mL), and the organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by flash chromatography on silica gel (gradient: 10~50% EtOAc in petroleum ether) to afford the title compound (430 mg, 46% yield) as a yellow solid. LC/MS (ESI) *m/z*: 588.4 $[M+H]^+$.

Step 9: Preparation of tert-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



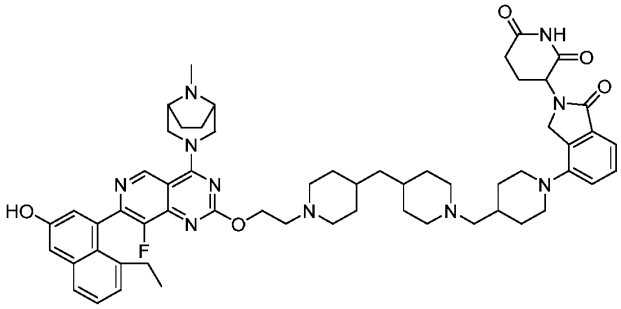
To a solution of tert-butyl 3-[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150 mg, 0.255 mmol, 1 *eq*) and 3-[1-oxo-4-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione (222 mg, 0.262 mmol, 75% purity, 1.03 *eq*, TFA) in isopropanol (3.5 mL) and dichloromethane (5 mL) were added NaOAc (42 mg, 0.51 mmol, 2 *eq*), AcOH (107 mg, 1.79 mmol, 102 µL, 7 *eq*), and 2-picoline borane complex (82 mg, 0.77 mmol, 3 *eq*), and the reaction mixture was stirred at 20 °C for 3 hours. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by flash chromatography on SiO_2 (gradient: 0~20% methanol/dichloromethane) to give the title compound (255 mg, 0.233 mmol, 91% yield) as a white solid. LC/MS (ESI) *m/z*: 1093.4 $[M+H]^+$.

Step 10: Preparation of 3-[4-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 55**)



A solution of tert-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (155 mg, 0.142 mmol, 1 *eq*) in HCOOH (5 mL) was stirred at 20 °C for 4 hours. The mixture was concentrated under reduced pressure, and the resulting crude product was purified by prep-HPLC (column: YMC Triart 30*150 mm*7 μm; mobile phase: [13-43% CH_3CN in water (formic acid)]). Pure fractions were combined and dried by lyophilization to give the title compound (51.4 mg, 0.048 mmol, 34% yield, formic acid salt) as a white solid.

Example 4: Synthesis of 3-[4-[4-[[4-[[1-[2-[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-4-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrido[4,3-d]pyrimidin-2-yl] oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl] piperidine-2,6-dione (**Compound 42**)

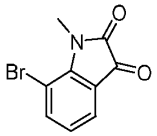


To a solution of 3-[4-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (110 mg, 0.10 mmol, 1 eq, trifluoroacetate) in dichloromethane (2 mL) and methanol (2 mL) was added 4-methylmorpholine (15 mg, 0.15 mmol, 1.5 eq), and the mixture was stirred at 25 °C for 15 minutes. Formaldehyde (40 mg, 0.50 mmol, 37% purity, 5 eq) was then added, and the resulting mixture was stirred for 0.5 h at 25 °C. Sodium triacetoxyborohydride (63 mg, 0.30 mmol, 3 eq) was then added, and the reaction mixture was stirred at 25 °C for 2 hours. The reaction mixture was concentrated, and the resulting residue was purified by prep-HPLC

{column: Unisil 3-100 C18 Ultra 150*50 mm*3μm; mobile phase: [1-31% CH_3CN in water (formic acid)]} to afford the title compound (61.0 mg, 0.06 mmol, 56% yield) as a white solid.

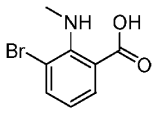
Example 5: Synthesis of 3-[4-[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 28**)

Step 1: Preparation of 7-bromo-1-methylindoline-2,3-dione



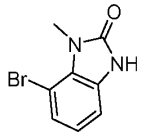
To a mixture of 7-bromoindoline-2,3-dione (12 g, 53.09 mmol, 1 eq), and potassium carbonate (11.01 g, 79.64 mmol, 1.5 eq), and water (1.2 mL) in DMF (60 mL) was added a solution of methyl iodide (8.44 g, 59.43 mmol, 3.7 mL, 1.12 eq) in DMF (24 mL) dropwise. And the reaction mixture was stirred at 25 °C for 2 hours. Water (120 mL) was then added, and the mixture was stirred at 0 °C for 1 hour. The resulting precipitate was collected by filtration, washed with water (50 mL × 2), and dried in vacuo to afford the title compound (8 g, 33.33 mmol, 62% yield) as a red solid. LC/MS (ESI) *m/z*: 242.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.81 (br d, J = 7.6 Hz, 1H) 7.55 (br d, J = 7.2 Hz, 1H) 7.05 (t, J = 8.0 Hz, 1H) 3.47 (s, 3H).

Step 2: Preparation of 3-bromo-2-(methylamino)benzoic acid



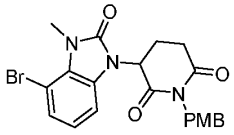
Aqueous hydrogen peroxide (38 g, 335.15 mmol, 32.20 mL, 30% purity, 10.06 eq) was added dropwise to a mixture of 7-bromo-1-methylindoline-2,3-dione (8 g, 33.33 mmol, 1 eq) and sodium hydroxide (2 M, 199.96 mL, 12 eq) below 15 °C, and the reaction mixture was stirred at 25 °C for 5 hours. After the pH was adjusted to 4.0 with hydrochloric acid (1 M), the mixture was stirred at 10 °C for 1 hour, then extracted with ethyl acetate (80 mL x 3). The combined organic extract was washed with water (60 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford the title compound (6.0 g, crude) as a brown oil. LC/MS (ESI) *m/z*: 252.2 $[M+Na]^+$.

Step 3: Preparation of 7-bromo-1-methyl-1H-benzo[*d*]imidazol-2(3H)-one



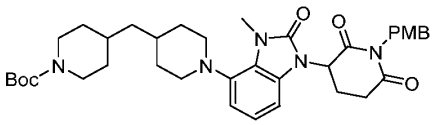
To a solution of 3-bromo-2-(methylamino)benzoic acid (6 g, 26.08 mmol, 1 eq, crude) and *N,N*-diisopropylethylamine (5.04 g, 39.01 mmol, 6.80 mL, 1.50 eq) in DMF (40 mL) was added diphenylphosphoryl azide (10.76 g, 39.10 mmol, 8.47 mL, 1.50 eq) dropwise at 75 °C, and the reaction mixture was stirred at 75 °C for 3 hours. Water (30 mL) was added at 25 °C, and the mixture was stirred at 0 °C for 0.5 hours. The resulting precipitate was collected by filtration, washed with water (30 mL) and diisopropylether (15 mL), then dried in vacuo at 50 °C to give the title compound (4 g, 17.62 mmol, 67% yield) as an off-white solid. LC/MS (ESI) *m/z*: 226.9 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (br s, 1 H) 7.14 (dd, *J*=8.0, 1.2 Hz, 1 H) 6.96 - 6.99 (m, 1 H) 6.88 - 6.93 (m, 1 H) 3.55 (s, 3 H).

Step 4: Preparation of 3-(4-bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-1-(4-methoxybenzyl)piperidine-2,6-dione



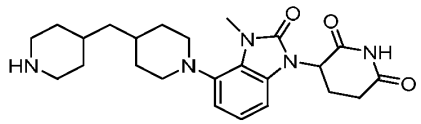
To a solution of 7-bromo-1-methyl-1H-benzo[d]imidazol-2(3H)-one (2.00 g, 8.81 mmol, 1 *eq*) in tetrahydrofuran (40 mL) was added potassium 2-methylpropan-2-olate (1 M, 10.67 mL, 1.21 *eq*), and the resulting mixture was stirred at 0 °C for 0.5 hours. 1-(4-Methoxybenzyl)-2,6-dioxopiperidin-3-yl trifluoromethanesulfonate (4.2 g, 11.01 mmol, 1.25 *eq*) in tetrahydrofuran (20 mL) was then added dropwise, and the reaction mixture was stirred at 0-25 °C for 0.5 hours. The reaction mixture was quenched by addition of 10 % ammonium chloride solution (10 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 hour, then extracted with ethyl acetate (50 mL × 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=6/1 to 1/1) to afford the title compound (3.5 g, 7.64 mmol, 87% yield) as a white solid. LC/MS (ESI) *m/z*: 460.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 (dd, J = 0.8, 8.0 Hz, 1H), 7.22 - 7.18 (m, 2H), 7.11 - 7.04 (br m, 1H), 6.97 - 6.92 (m, 1H), 6.88 - 6.82 (m, 2H), 5.57 (dd, J = 5.6, 12.8 Hz, 1H), 4.79 (q, J = 14.4 Hz, 2H), 3.72 (s, 3H), 3.64 (s, 3H), 3.12 - 2.97 (m, 1H), 2.89 - 2.64 (m, 2H), 2.13 - 2.01 (m, 1H).

Step 5: Preparation of *tert*-butyl 4-[[1-[1-[1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-4-yl]-4-piperidyl]methyl]piperidine-1-carboxylate



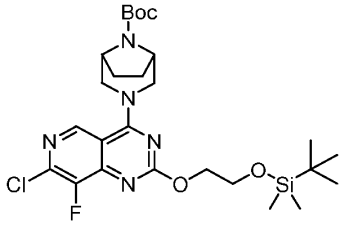
To a solution of 3-(4-bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-1-(4-methoxybenzyl)piperidine-2,6-dione (1 g, 2.18 mmol, 1 *eq*) and *tert*-butyl 4-(4-piperidylmethyl) piperidine-1-carboxylate (1.12 g, 3.27 mmol, 1.5 *eq*, acetic acid) in *N,N*-dimethylacetamide (20 mL) were added cesium carbonate (2.13 g, 6.54 mmol, 3 *eq*) and 1,3-bis[2,6-bis(1-propylbutyl)phenyl]-4,5-dichloro-2H-imidazol-1-ium-2-ide;3-chloropyridine; dichloropalladium (212 mg, 0.22 mmol, 9.99e-2 *eq*), and the reaction mixture was stirred at 90 °C for 2 hours. The mixture was cooled to 25 °C, and the residue was poured into water (50 mL) and stirred for 2 minutes. The aqueous phase was extracted with ethyl acetate (10 mL × 3), and the combined organic extract was washed with brine (10 mL × 2) and dried over anhydrous sodium sulfate. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*40mm* 15μm;mobile phase: [68-98% CH_3CN in water (formic acid)]) to afford the title compound (150 mg, 0.23 mmol, 10% yield) as a yellow solid. LC/MS (ESI) m/z: 660.4 $[M+H]^+$.

Step 6: Preparation of 3-[3-methyl-2-oxo-4-[4-(4-piperidylmethyl)-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione



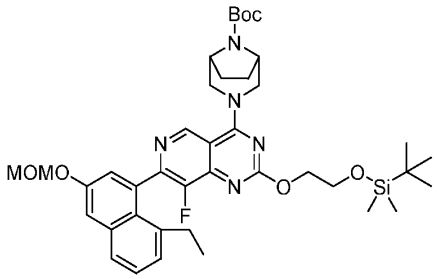
To a solution of *tert*-butyl 4-[[1-[1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-4-yl]-4-piperidyl]methyl]piperidine-1-carboxylate (160 mg, 0.24 mmol, 1 *eq*) in toluene (1 mL) was added methanesulfonic acid (405 mg, 4.21 mmol, 0.3 mL, 17.38 *eq*), and the reaction mixture was stirred at 120 °C for 2 hours. The mixture was concentrated under reduced pressure at 45 °C to afford the title compound (110 mg, crude) as a white solid.

Step 7: Preparation of *tert*-butyl 3-[2-[2-[*tert*-butyl(dimethyl)silyl]oxyethoxy]-7-chloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



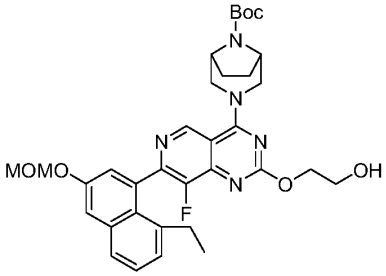
To a solution of *tert*-butyl 3-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (5 g, 11.67 mmol, 1 *eq*) and 1,4-diazabicyclo [2.2.2]octane (261.90 mg, 2.33 mmol, 256.77 µL, 0.2 *eq*) in acetonitrile (50 mL) at 25 °C were added 2-[tertbutyl(dimethyl)silyl]oxyethanol (2.47 g, 14.01 mmol, 1.2 *eq*) and cesium carbonate (11.41 g, 35.02 mmol, 3 *eq*), and the reaction mixture was stirred at 50 °C for 5 hours. The mixture was filtered, and the filtrate was concentrated. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate =10/1 to 3/1) to afford the title compound (4 g, 7.04 mmol, 60% yield) as a yellow solid. LC/MS (ESI) *m/z*: 568.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 4.56 (t, *J* = 5.6 Hz, 2H), 4.48 (br d, *J* = 12.8 Hz, 2H), 4.42 – 4.28 (m, 2H), 4.07 – 3.98 (m, 2H), 3.74 – 3.60 (m, 2H), 2.00 – 1.90 (m, 2H), 1.72 (br d, *J* = 7.6 Hz, 2H), 1.52 (s, 9H), 0.92 – 0.86 (m, 9H), 0.09 (s, 6H).

Step 8: Preparation of *tert*-butyl 3-[2-[2-[*tert*-butyl(dimethyl)silyl]oxyethoxy]-7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



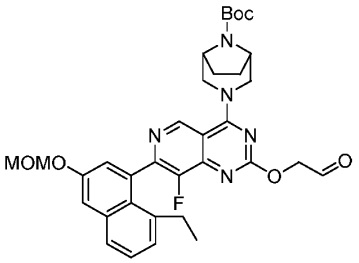
A mixture of *tert*-butyl *tert*-butyl 3-[2-[2-[*tert*-butyl(dimethyl)silyl]oxyethoxy]-7-chloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (4 g, 7.04 mmol, 1 *eq*), 2-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.13 g, 9.15 mmol, 1.3 *eq*), potassium phosphate (4.48 g, 21.12 mmol, 3 *eq*), and [2-(2-aminophenyl)phenyl]palladium(1+);bis(1-adamantyl)-butyl-phosphane;methanesulfonate (513 mg, 704.03 µmol, 0.1 *eq*) in dioxane (50 mL) and water (6 mL) was stirred for 12 hours at 90 °C under nitrogen. The reaction mixture was concentrated, and the resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1 to 1/1) to afford the title compound (4.4 g, 5.88 mmol, 83% yield) as a yellow solid.

Step 9: Preparation of *tert*-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-(2-hydroxyethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[2-[*tert*-butyl(dimethyl)silyl]oxyethoxy]-7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (4.4 g, 5.88 mmol, 1 *eq*) in DMF (40 mL) at 25 °C was added cesium fluoride (26.81 g, 176.48 mmol, 30 *eq*), and the reaction mixture was stirred for 12 hours at 25 °C. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic extract was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1 to 1/1) to afford the title compound (3.7 g, 5.84 mmol, 99% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 2.8 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 2.8 Hz, 1H), 5.31 (d, *J* = 1.7 Hz, 2H), 4.70 – 4.59 (m, 3H), 4.53 (br d, *J* = 12.4 Hz, 1H), 4.48 – 4.32 (m, 2H), 4.06 – 3.98 (m, 2H), 3.83 – 3.61 (m, 2H), 3.52 (s, 3H), 2.35 (br dd, *J* = 7.6, 10.8 Hz, 2H), 2.04 – 1.97 (m, 2H), 1.86 – 1.64 (m, 2H), 1.53 (s, 9H), 0.95 (t, *J* = 7.6 Hz, 3H).

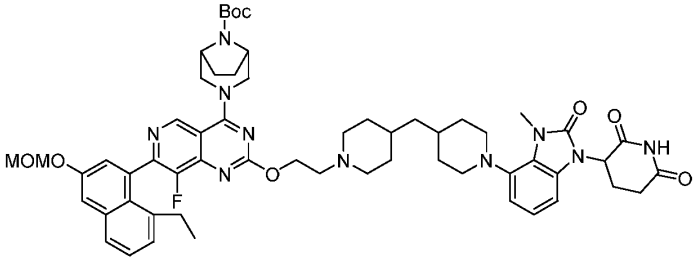
Step 10: Preparation of *tert*-butyl (1R,5S)-3-(7-(8-ethyl-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



A solution of dimethyl sulfoxide (771 mg, 9.86 mmol, 0.8 mL, 2.5 *eq*) in dichloromethane (10 mL) was added dropwise to a solution of oxalyl chloride (751 mg, 5.92 mmol, 0.5 mL, 1.5 *eq*) in dichloromethane (10 mL) at -78 °C. After 15 minutes, a solution of *tert*-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-(2-hydroxyethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.5 g, 3.95 mmol, 1 *eq*) in dichloromethane (10 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 30 minutes. Triethylamine (2.00 g, 19.73 mmol, 2.8 mL, 5 *eq*) was then added, and the reaction mixture was stirred at -78

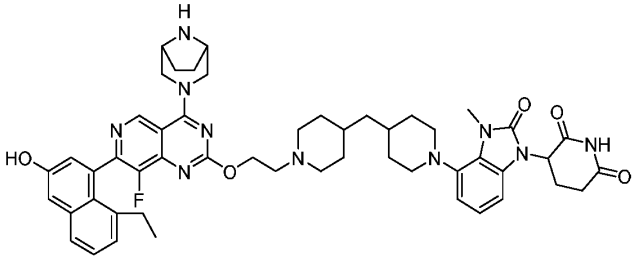
°C the same temperature for 30 minutes, then allowed to warm to 25 °C over 1 hour. The reaction was quenched with saturated sodium sulfite solution (20 mL), and the resulting mixture was extracted with dichloromethane (20 mL × 3). The combined organic phase was washed with saturated sodium bicarbonate solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1 to 1/1) to afford the title compound (1.8 g, 2.85 mmol, 72% yield) as a yellow solid. LC/MS (ESI) *m/z*: 632.3 $[M+H]^+$.

Step 11: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-4-yl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



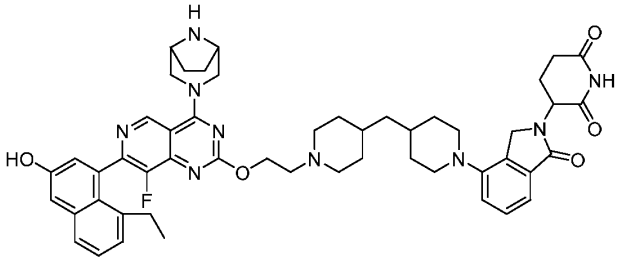
To a solution of 3-[3-methyl-2-oxo-4-[4-(4-piperidylmethyl)-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione (102 mg, 0.18 mmol, 1 *eq*, trifluoroacetic acid) in dichloromethane (1 mL) and isopropyl alcohol (1 mL) were added diisopropylethylamine (119 mg, 0.92 mmol, 0.2 mL, 5 *eq*) and *tert*-butyl (1R,5S)-3-(7-(8-ethyl-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (128 mg, 0.20 mmol, 1.1 *eq*), and the resulting mixture was stirred at 25 °C for 1 hour. Sodium triacetoxyborohydride (117 mg, 0.55 mmol, 3 *eq*) was then added, and the reaction mixture was stirred at 25 °C for 1 hour. The reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (15 mL × 3). The combined organic extract was washed with brine (50 mL), dried obver anhydrous sodium sulfate, filtered, and concentrated in vacuum. The resulting residue was purified by prep-TLC (dichloromethane/methanol= 10/1) to afford the title compound (86 mg, 0.08 mmol, 44% yield) as a white solid. LC/MS (ESI) *m/z*: 1055.7 $[M+H]^+$.

Step 12: Preparation of 3-[4-[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 28**)



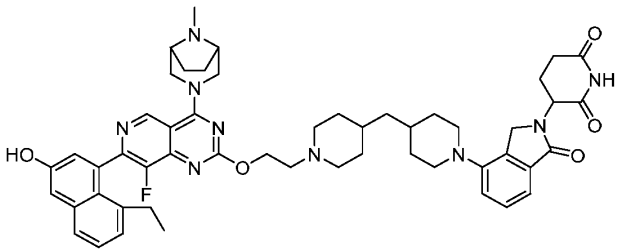
To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-4-yl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (82 mg, 0.08 mmol, 1 *eq*) in dichloromethane (1 mL) was added trifluoroacetic acid (1.54 g, 13.51 mmol, 1 mL, 173.81 *eq*), and the reaction mixture was stirred at 25 °C for 0.5 hours. The solvent was concentrated under nitrogen flow, and the crude product was purified by reverse-phase HPLC (column: Phenomenex luna C18 150*25mm* 10μm;mobile phase: [9-39% CH_3CN in water (formic acid)]) to afford the title compound (26.2 mg, 0.03 mmol, 32% yield, bis-formic acid salt) as a white solid.

Example 6: Synthesis of 3-[4-[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 56**)



The title compound was prepared in an analogous manner to 3-[4-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione(bis-formic acid salt; as a white solid).

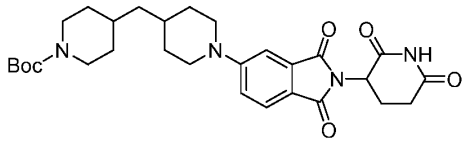
Example 7: Synthesis of 3-[4-[4-[[1-[2-[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-4-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrido[4,3-d]pyrimidin-2-yl] oxyethyl]-4-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 41**)



To a solution of formaldehyde (28 mg, 0.35 mmol, 37% purity, 5 eq) in dichloromethane (2 mL) and methanol (2 mL) was added 4-methylmorpholine (10 mg, 0.10 mmol, 1.5 eq), and the resulting mixture was stirred at 25 °C for 15 minutes. 3-[4-[4-[[1-[2-[4-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (70 mg, 0.07 mmol, 1 eq, trifluoroacetate) was then added, and the mixture was stirred for 0.5 hours at 25 °C. Sodium triacetoxyborohydride (44 mg, 0.21 mmol, 3 eq) was then added, and the reaction mixture was stirred at 25 °C for 2 hours. The reaction mixture was concentrated, and the resulting residue was purified by prep-HPLC {column: Unisil 3-100 C18 Ultra 150*50mm*3μm; mobile phase: 9-39% CH_3CN in [water (formic acid)]} to afford the title compound (65.1 mg, 0.06 mmol, 94% yield, formic acid salt) as a white solid.

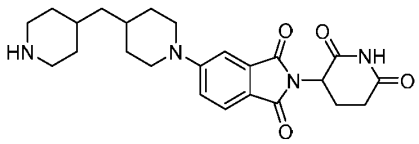
Example 8: Synthesis of 5-[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (**Compound 67**)

Step 1: Preparation of tert-butyl 4-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl]piperidine-1-carboxylate



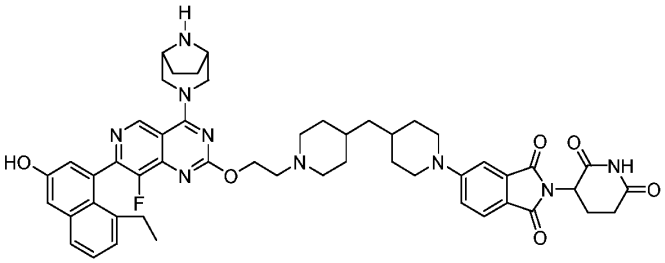
To a mixture of 2-(2,6-dioxo-3-piperidyl)-5-fluoro-isoindoline-1,3-dione (500 mg, 1.81 mmol, 1.0 eq) and tert-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate (613 mg, 2.17 mmol, 1.2 eq) in DMSO (10 mL) was added diisopropylethylamine (5.43 mmol, 946 μL, 3.0 eq) in one portion at 25°C, and the reaction mixture was stirred at 100 °C for 2 hours. The mixture was diluted with water (20 mL), and the aqueous phase was extracted with ethyl acetate (30 mL x 4). The combined organic extract was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuum. The crude product was purified flash chromatography on SiO_2 (gradient: 0~41% ethyl acetate in petroleum ether) to afford the title compound (310 mg, 0.541 mmol, 30% yield) as a yellow solid. LC/MS (ESI) *m/z*: 539.3 $[M+H]^+$.

Step 2: Preparation of 2-(2,6-dioxo-3-piperidyl)-5-[4-(4-piperidylmethyl)-1-piperidyl]isoindoline-1,3-dione



To a solution of tert-butyl 4-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl]piperidine-1-carboxylate (93 mg, 0.173 mmol, 1.0 eq) in dichloromethane (2 mL) was added HCl/dioxane (4 M, 432 µL, 10.0 eq), and the reaction mixture was stirred at 25 °C for 2 hours. The reaction mixture was concentrated in vacuum to afford the title compound (75 mg, 0.147 mmol, 85% yield) as a white solid. LC/MS (ESI) *m/z*: 439.0 $[M+H]^+$.

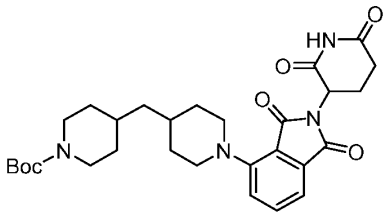
Step 3: Preparation of 5-[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (**Compound 67**)



The title compound was prepared in an analogous manner to 3-[4-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione starting from tert-butyl 3-[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and 2-(2,6-dioxo-3-piperidyl)-5-[4-(4-piperidylmethyl)-1-piperidyl]isoindoline-1,3-dione, and purified by prep-HPLC (column: Xtimate C18 100*30 mm*10µm; mobile phase: [5-50% CH_3CN in water (formic acid)]). Pure fractions were combined, then lyophilized to afford the title compound (32.1 mg, 0.035 mmol, 79% yield, formic acid salt) as a yellow solid.

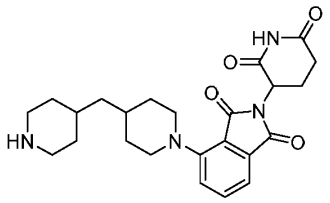
Example 9: Synthesis of 4-[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (**Compound 66**)

Step 1: Preparation of tert-butyl 4-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]-4-piperidyl]methyl]piperidine-1-carboxylate



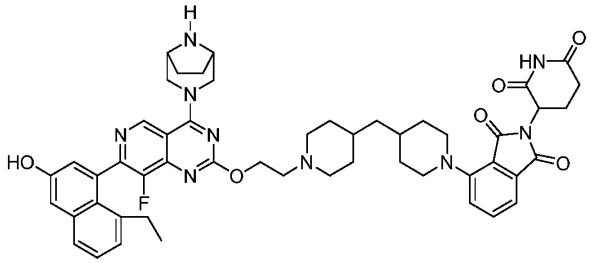
To a solution of 2-(2, 6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1, 3-dione (400 mg, 1.45 mmol, 1.0 eq) and tert-butyl 4-(4-piperidylmethyl) piperidine-1-carboxylate (450 mg, 1.59 mmol, 1.1 eq) in DMSO (10 mL) was added diisopropylethylamine (4.34 mmol, 757 µL, 3.0 eq), and the reaction mixture was stirred at 100 °C for 2 hours. The mixture was diluted with ethyl acetate (60 mL), then washed with water (20 mL x 9), brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by flash chromatography on SiO_2 (gradient: 0~29% ethyl acetate in petroleum ether) to afford the title compound (610 mg,0.789 mmol, 55% yield) as a yellow solid. LC/MS (ESI) *m/z*: 483.3 [M-C_4H_8+H]$^+$.

Step 2: Preparation of 2-(2,6-dioxo-3-piperidyl)-4-[4-(4-piperidylmethyl)-1-piperidyl]isoindoline-1,3-dione



To a solution of tert-butyl 4-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]-4-piperidyl]methyl]piperidine-1-carboxylate (200 mg, 0.371 mmol, 1.0 eq) in dichloromethane (2 mL) was added HCl/dioxane (4 M, 928 µL, 10.0 eq), and the reaction mixture was stirred at 25°C for 2 hours. The reaction mixture was concentrated in vacuum to afford the title compound (139 mg, 285 mmol, 77% yield) as a yellow solid. LC/MS (ESI) *m/z*: 439.3 [M+H]$^+$.

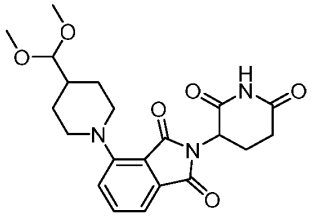
Step 3: Preparation of 4-[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (**Compound 66**)



The title compound was prepared in an analogous manner to 3-[4-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione starting from tert-butyl 3-[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and 2-(2,6-dioxo-3-piperidyl)-4-[4-(4-piperidylmethyl)-1-piperidyl]isoindoline-1,3-dione, and purified by prep-HPLC (column: Xtimate C18 100*30mm*10μm; mobile phase: [10-50% CH_3CN in water (formic acid)]). Pure fractions were combined, then lyophilized to afford the title compound (21.2 mg, 0.022 mmol, 57% yield, formic acid salt) as a yellow solid.

Example 10: Synthesis of 4-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (**Compound 57**)

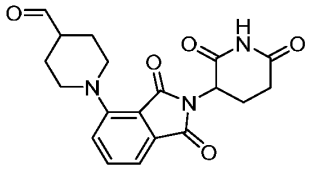
Step 1: Preparation of 4-[4-(dimethoxymethyl)-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione



To a solution of 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (800 mg, 2.90 mmol, 1.0 *eq*) in dimethyl sulfoxide (8 mL) was added 4-(dimethoxymethyl)piperidine (553 mg, 3.48 mmol, 1.2 eq), and the reaction mixture was stirred at 100 °C for 3 hours. The reaction mixture was diluted with water (10 mL), then extracted with ethyl acetate (20 mL × 3). The combined organic extracts were washed with water (20 mL × 3) and concentrated under reduced pressure. The crude product was purified by flash chromatography on SiO_2 (gradient: 0~4% methanol in dichloromethane) to afford the title compound (929 mg, 2.10 mmol, 72% yield) as a yellow solid. LC/MS (ESI) *m/z*: 416.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (s,

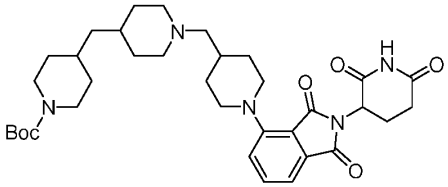
1H), 7.64-7.60 (m, 1H), 7.46-7.43 (m, 1H), 5.00-4.95 (m, 1H), 3.79-3.75 (m, 2H), 3.40 (s, 6H). 2.93-2.72 (m, 4H), 2.16-2.11 (m, 1H), 1.94-1.91 (m, 2H), 1.87-1.82 (m, 1H), 1.70-1.57 (m, 4H).

Step 2: Preparation of 1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]piperidine-4-carbaldehyde



To a solution of 4-[4-(dimethoxymethyl)-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (460 mg, 1.11 mmol, 1.0 *eq*) in tetrahydrofuran (9 mL) was added hydrochloric acid (1 M, 8.30 mL, 7.5 *eq*), and the reaction mixture was stirred at 20 °C for 1 hour. The reaction mixture was adjusted to pH = 7 by addition of saturated sodium bicarbonate solution, then extracted with ethyl acetate (20 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the title compound (398 mg, 0.98 mmol, 88% yield) as a yellow solid. LC/MS (ESI) *m/z*: 370.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.96 (s, 1H), 7.68-7.64 (m, 1H), 7.53-7.51 (m, 1H), 5.00-4.96 (m, 1H), 3.72-3.70 (m, 2H), 3.21 (s, 2H). 2.94-2.73 (m, 4H), 2.55-2.52 (m, 1H), 2.18-2.14 (m, 2H), 1.58 (s, 2H).

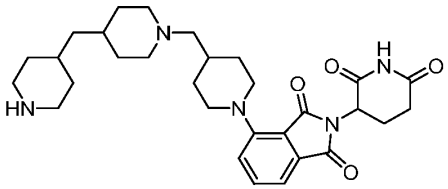
Step 3: Preparation of tert-butyl 4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate



To a solution of 1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]piperidine-4-carbaldehyde (398 mg, 1.08 mmol, 1 eq) and tert-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate (304 mg, 1.08 mmol, 1 eq) in isopropanol (3 mL) and dichloromethane (3 mL) were added acetic acid (259 mg, 4.31 mmol, 0.25 mL, 4 eq) and 2-methylpyridine borane (461 mg, 4.31 mmol, 4 eq) in one portion at 20 °C, and the reaction mixture was stirred at 20 °C for 1 hour. The reaction mixture was adjusted to pH = 6 by addition of triethylamine, then concentrated. The crude product was purified by flash chromatography (gradient: 0~100% ethyl acetate in petroleum ether) to afford the title compound (541 mg, 0.77 mmol, 71% yield) as a yellow solid. LC/MS (ESI) *m/z*: 636.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.59-7.55 (m, 1H), 7.37 (d, *J* = 3.2 Hz, 1H), 7.17 (d, *J* = 4.4 Hz, 1H), 4.98-4.94 (m, 1H), 4.10-4.08 (m, 2H), 3.76-

3.71 (m, 2H), 3.15-3.09 (m, 2H), 2.95-2.65 (m, 7H), 2.47 (s, 2H), 2.23-2.16 (m, 1H), 2.14-2.09 (m, 1H), 2.05 (s, 2H), 1.98-1.88 (m, 3H), 1.72-1.49 (m, 8H), 1.46 (s, 9H), 1.43 (s, 1H), 1.20 (s, 2H), 1.11-1.01 (m, 2H).

Step 4: Preparation of 2-(2,6-dioxo-3-piperidyl)-4-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]isoindoline-1,3-dione



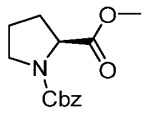
To a solution of tert-butyl 4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate (130 mg, 0.20 mmol, 1 eq) in dichloromethane (2 mL) was added trifluoroacetic acid (466 mg, 4.09 mmol, 0.3 mL, 20 eq), and the reaction mixture was stirred at 20 °C for 1 hour. The mixture was concentrated to afford the title compound (328 mg, crude, TFA) as a yellow oil. LC/MS (ESI) *m/z*: 536.3 $[M+H]^+$.

Step 5: Preparation of 4-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (**Compound 57**)

The title compound was prepared in an analogous manner to 3-[4-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione starting from tert-butyl 3-[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and 2-(2,6-dioxo-3-piperidyl)-4-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]isoindoline-1,3-dione, and purified by prep-HPLC (column: Phenomenex C18 75*30mm*3μm; mobile phase: [3-43% CH_3CN in water (formic acid)]) followed by prep-HPLC (column: Phenomenex C18 75*30mm*3μm; mobile phase: [3-33% CH_3CN in water (formic acid)]). Pure fractions were combined and dried by lyophilization to afford the title compound (49.1 mg, 0.05 mmol, 48% yield, 27% yield, formic acid salt) as a yellow solid.

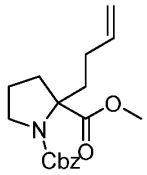
Example 11: Synthesis of [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 63**)

Step 1: Preparation of 1-benzyl 2-methyl (2S)-pyrrolidine-1,2-dicarboxylate



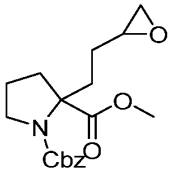
To a solution of methyl (2S)-pyrrolidine-2-carboxylate hydrochloride (40.0 g, 242 mmol, 1 *eq*) in CH_2Cl_2 (500 mL) were added TEA (56.2 g, 556 mmol, 2.3 *eq*) and CbzCl (53.6 g, 314 mmol, 1.3 *eq*), and the reaction mixture was stirred at 25 °C under N_2 for 16 hours. The reaction mixture was washed with water (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica gel chromatography (gradient: 0~10% THF in petroleum ether) to give the title compound (60.6 g, 230 mmol, 95% yield) as a colorless oil. LC/MS (ESI) *m/z*: 264.0 $[M+H]^+$.

Step 2: Preparation of 1-benzyl 2-methyl 2-but-3-enylpyrrolidine-1,2-dicarboxylate



To a stirred solution of 1-benzyl 2-methyl (2S)-pyrrolidine-1,2-dicarboxylate (27.5 g, 104 mmol, 1 *eq*) in THF (300 mL) at -78 °C was added LiHMDS (1 M, 125 mL, 1.2 *eq*), and the reaction mixture was stirred at -78 °C under N_2 for 0.5 hour. 4-Bromobut-1-ene (28.2 g, 209 mmol, 2 *eq*) was then added at -78 °C, and the reaction mixture was stirred at 20 °C under N_2 for 16 hours. Two batches were conducted. The reaction mixture was quenched by addition of saturated NH_4Cl solution (300 mL) and extracted with EtOAc (2 x 300 mL). The combined organic extract was washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica gel chromatography (gradient: 0~8% THF in petroleum ether) to give the title compound (44.9 g, 141 mmol, 68% yield) as a yellow oil. LC/MS (ESI) *m/z*: 318.0 $[M+H]^+$.

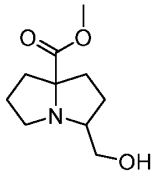
Step 3: Preparation of 1-benzyl 2-methyl 2-[2-(oxiran-2-yl)ethyl]pyrrolidine-1,2-dicarboxylate



To a solution of 1-benzyl 2-methyl 2-but-3-enylpyrrolidine-1,2-dicarboxylate (44.9 g, 141 mmol, 1 *eq*) in CH_2Cl_2 (600 mL) was added m-CPBA (33.6 g, 156 mmol, 80% purity, 1.1 *eq*), and the reaction mixture was stirred at 20 °C for 16 hours. The reaction mixture was filtered, and the filtrate was washed with saturated aqueous $NaHSO_3$ (300 mL), $NaHCO_3$ (2 x 200 mL),

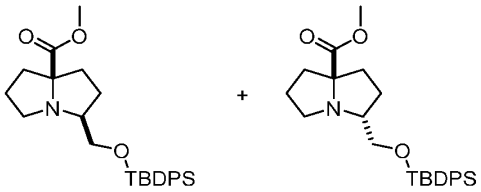
and brine (200 mL), then dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica gel chromatography (gradient: 0~15% THF in petroleum ether) to give the title compound (37.5 g, 112 mmol, 80% yield) as a colorless oil. LC/MS (ESI) *m/z*: 334.2 $[M+H]^+$.

Step 4: Preparation of methyl 3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizine-8-carboxylate



To a solution of 1-benzyl 2-methyl 2-[2-(oxiran-2-yl)ethyl]pyrrolidine-1,2-dicarboxylate (37.5 g, 112 mmol, 1 *eq*) in CH_3OH (400 mL) was added Pd/C (3.0 g, 10% purity), and the reaction mixture was stirred at 25 °C under H_2 (15 psi) (degassed under vacuum and purged with H_2 several times) for 16 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give the title compound (22.4 g, 112 mmol, 100% yield) as a yellow oil.

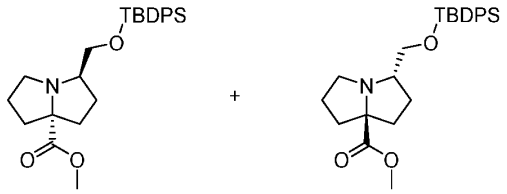
Step 5: Preparation of methyl (3S,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydro-1H-pyrrolizine-7a(5H)-carboxylate and methyl (3R,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydro-1H-pyrrolizine-7a(5H)-carboxylate



To a solution of methyl 3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizine-8-carboxylate (22.4 g, 112 mmol, 1 *eq*) and imidazole (9.95 g, 146 mmol, 1.3 *eq*) in CH_2Cl_2 (300 mL) was added TBDPSCl (37.1 g, 135 mmol, 1.2 *eq*), and the reaction mixture was stirred at 25 °C under N_2 for 16 hours. The reaction mixture was quenched by addition of water (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extract was washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica gel chromatography (gradient: 0~10% THF in petroleum ether). Methyl (3S,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (24.3 g, 39.7 mmol, 35% yield) was eluted first and isolated as a colorless oil (LC/MS (ESI) *m/z*: 438.2 $[M+H]^+$), then methyl (3R,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydro-1H-

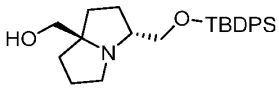
pyrrolizine-7a(5H)-carboxylate (20.8 g, 43.0 mmol, 38% yield) was eluted and isolated as a colorless oil (LC/MS (ESI) *m/z*: 438.3 $[M+H]^+$).

Step 6: Preparation of methyl (3R,8R)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizine-8-carboxylate and methyl (3S,8S)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizine-8-carboxylate



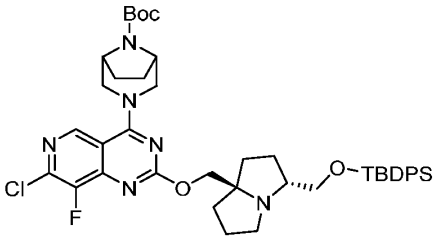
Methyl (3R,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (20.8 g, 47.5 mmol, 1 *eq*) was separated by SFC (column: REGIS (s,s) WHELK-O1 (250 mm*50 mm, 10 μm); mobile phase: [0.1%NH_4OH EtOH]; B%: 25%, Flow Rate: 140 mL/min) to afford first eluted enantiomer methyl (3R,8R)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizine-8-carboxylate (9.78 g, 22.35 mmol, 47% yield) as a colorless oil (LC/MS (ESI) *m/z*: 438.2 $[M+H]^+$), and the later eluted enantiomer methyl (3S,8S)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizine-8-carboxylate (8.81 g, 20.1 mmol, 42.36% yield) as a colorless oil (LC/MS (ESI) *m/z*: 438.3 $[M+H]^+$).

Step 7: Preparation of [(3R,8R)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol



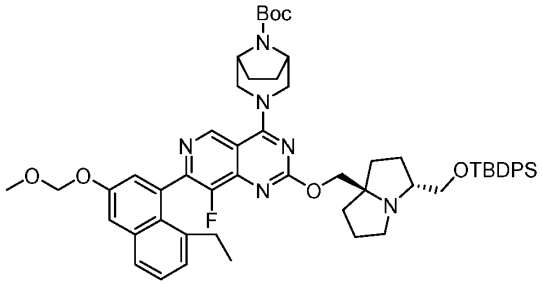
To a solution of methyl (3R,8R)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizine-8-carboxylate (2.69 g, 6.15 mmol, 1 *eq*) in THF (30 mL) at 0 °C was added $LiAlH_4$ (280 mg, 7.38 mmol, 1.2 *eq*), and the reaction mixture was stirred at 0 °C under N_2 for 1 hour. The reaction mixture was quenched by sequential addition of water (300 μL), 15% aq. NaOH (300 μL), and water (900 μL), then diluted with EtOAc (30 mL). The resulting suspension was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica gel chromatography (gradient: 0~10% CH_3OH in CH_2Cl_2) to give the title compound (2.07 g, 5.05 mmol, 82% yield) as a yellow oil. LC/MS (ESI) *m/z*: 410.1 $[M+H]^+$.

Step 8: Preparation of *tert*-butyl 3-[2-[[(3R,8R)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-chloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



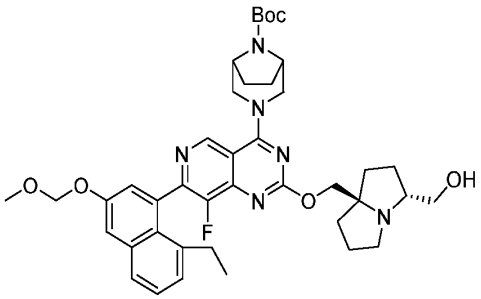
To a solution of [(3R,8R)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (1.00 g, 2.44 mmol, 1 *eq*) and *tert*-butyl 3-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.05 g, 2.44 mmol, 1 *eq*) in dioxane (30 mL) were added Cs_2CO_3 (954 mg, 2.93 mmol, 1.2 *eq*) and DABCO (109 mg, 0.976 mmol, 0.4 *eq*), and the reaction mixture was stirred at 25 °C under N_2 for 40 hours. The reaction mixture was filtered, and the filtrate was concentrated. The crude product was purified by flash silica gel chromatography (gradient: 0~20% THF in petroleum ether) to give the title compound (1.16 g, 1.13 mmol, 46% yield) as a yellow solid. LC/MS (ESI) *m/z*: 801.2 $[M+H]^+$.

Step 9: Preparation of *tert*-butyl 3-[2-[[(3R,8R)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



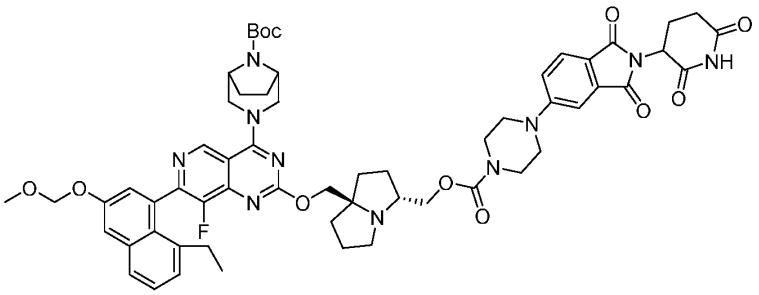
To a solution of *tert*-butyl 3-[2-[[(3R,8R)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-chloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (800 mg, 0.998 mmol, 1 *eq*) and 2-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (376 mg, 1.10 mmol, 1.1 *eq*) in dioxane (20 mL) were added CataCXium® A Pd G3 (145 mg, 0.199 mmol, 0.2 *eq*) and K_2CO_3 (2.2 M, 2.04 mL, 4.5 *eq*), and the reaction mixture was stirred at 100 °C under N_2 (degassed under vacuum and purged with N_2 several times) for 12 hours. The reaction mixture was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica gel chromatography (gradient: 0~30% THF in petroleum ether) to give the title compound (695 mg, 0.446 mmol, 63% purity) as a yellow solid. LC/MS (ESI) *m/z*: 981.3 $[M+H]^+$.

Step 10: Preparation of *tert*-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3R,8R)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[[(3R,8R)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 0.192 mmol, 63% purity, 1 *eq*) in THF (3 mL) was added TBAF (1 M, 458.59 µL, 1.5 *eq*), and the reaction mixture was stirred at 25 °C for 3 hours. The reaction mixture was quenched by addition of water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extract was washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by prep-TLC (acidic silica gel, EtOAc) to give the title compound (201 mg, 0.271 mmol, 44% yield) as a yellow solid. LC/MS (ESI) *m/z*: 743.1 $[M+H]^+$.

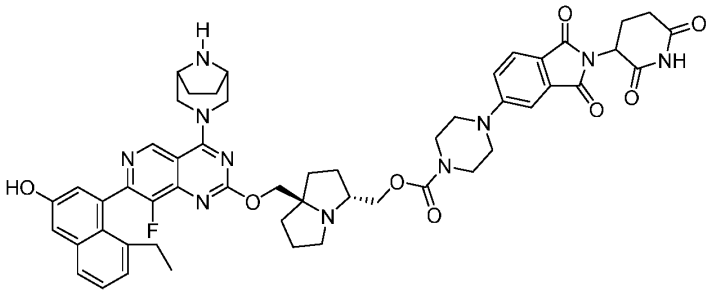
Step 11: Preparation of tert-butyl 3-[2-[[(3R,8R)-3-[[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazine-1-carbonyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of tert-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3R,8R)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.081 mmol, 1 *eq*) in THF (3 mL) were added triethylamine (65 mg, 0.65 mmol, 8 *eq*), DMAP (1 mg, 0.008 mmol, 0.1 *eq*), and (4-nitrophenyl) carbonochloridate (33 mg, 0.16 mmol, 2 *eq*), and the reaction mixture was stirred at 25 °C under N_2 for 16 hours. 2-(2,6-Dioxo-3-piperidyl)-5-piperazin-1-yl-isoindoline-1,3-

dione (40.55 mg, 88.84 μmol, 1.1 *eq*, TFA) was then added, and the reaction mixture was stirred at 25 °C under N_2 for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The resulting crude product was purified by flash chromatography on SiO_2 (gradient: 0~5% methanol in dichloromethane) to give the title compound (77 mg, 0.069 mmol, 86% yield) as a yellow solid. LC/MS (ESI) *m/z*: 1111.3 $[M+H]^+$.

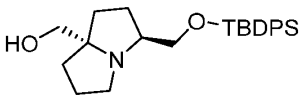
Step 12: Preparation of [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 63**)



A solution of tert-butyl 3-[2-[[(3R,8R)-3-[[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazine-1-carbonyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (77 mg, 0.069 mmol, 1 *eq*) in HCOOH (5 mL) was stirred at 25 °C for 3 hours. The reaction mixture was concentrated under reduced pressure, and the resulting crude product was purified by prep-HPLC (column: Phenomenex C18 75*30 mm*3μm; mobile phase: [0–40% CH_3CN in water (formic acid)]). Pure fractions were combined and dried by lyophilization to give the title compound (25.0 mg, 0.025 mmol, 36% yield, formic acid salt) as a yellow solid.

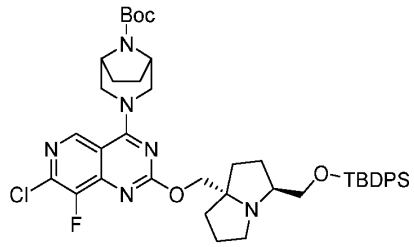
Example 12: Synthesis of [(3S,8S)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 62**)

Step 1: Preparation of [(3S,8S)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol



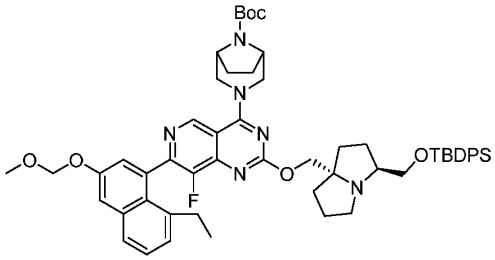
To a solution of methyl (3S,8S)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizine-8-carboxylate (1.57 g, 3.59 mmol, 1 *eq*) in THF (20 mL) at 0 °C was added $LiAlH_4$ (163 mg, 4.30 mmol, 1.2 *eq*), and the reaction mixture was stirred at 0 °C under N_2 for 1 hour. The reaction mixture was quenched by sequential addition of water (200 µL), 15% aq. NaOH (200 µL), and water (600 µL), then diluted with EtOAc (30 mL). The resulting suspension was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash silica gel chromatography (gradient: 0~10% CH_3OH in CH_2Cl_2) to give the title compound (911 mg, 2.22 mmol, 62% yield) as a yellow oil. LC/MS (ESI) *m/z*: 410.3 $[M+H]^+$.

Step 2: Preparation of *tert*-butyl 3-[2-[[(3S,8S)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-chloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



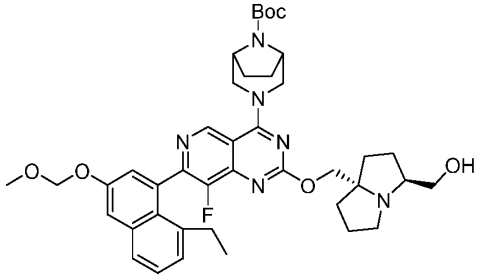
To a solution of [(3S,8S)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (911 mg, 2.22 mmol, 1 *eq*) and *tert*-butyl 3-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (951 mg, 2.22 mmol, 1 *eq*) in dioxane (30 mL) were added Cs_2CO_3 (868 mg, 2.66 mmol, 1.2 *eq*) and DABCO (75 mg, 0.67 mmol, 0.3 *eq*), and the reaction mixture was stirred at 25 °C under N_2 for 16 hours. Additional DABCO (25 mg, 0.22 mmol, 0.1 *eq*) was added, and the reaction mixture was stirred at 25 °C under N_2 for 16 hours. The reaction mixture was filtered, and the filtrate was concentrated. The crude product was purified by prep-HPLC (35-65% CH_3CN in water (0.225% formic acid)). Pure fractions were combined and dried by lyophilization to give the title compound (794 mg, 0.991 mmol, 45% yield) as a yellow solid. LC/MS (ESI) *m/z*: 801.2 $[M+H]^+$.

Step 3: Preparation of *tert*-butyl 3-[2-[[(3S,8S)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[[(3S,8S)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-chloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.125 mmol, 1 *eq*) and 2-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (51 mg, 0.15 mmol, 1.2 *eq*) in dioxane (2.5 mL) were added K_3PO_4 (1.5 M, 125 µL, 1.5 *eq*) and CataCXium® A Pd G3 (18 mg, 0.025 mmol, 0.2 *eq*), and the reaction mixture was stirred at 100 °C under N_2 (degassed under vacuum and purged with N_2 several times) for 12 hours. The reaction mixture was quenched by addition of water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extract was washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica gel chromatography (gradient: 0~20% THF in petroleum ether) to give the title compound (162 mg, 0.165 mmol, 66% yield) as a yellow solid. LC/MS (ESI) *m/z*: 981.3 $[M+H]^+$.

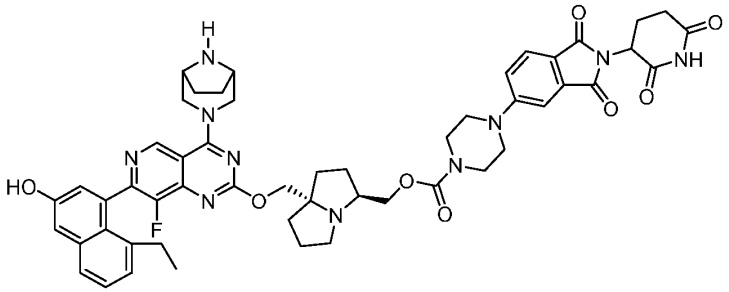
Step 4: Preparation of *tert*-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3S,8S)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[[(3S,8S)-3-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (162 mg, 0.165 mmol, 1 *eq*) in THF (2 mL) was added TBAF (1 M, 0.248 mL, 1.5 *eq*), and the reaction mixture was stirred at 25 °C for 3 hours. The reaction mixture was quenched by addition of water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extract was washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product

was purified by prep-TLC (acidic silica gel, EtOAc) to give the title compound (59 mg, 0.079 mmol, 48% yield) as a yellow solid. LC/MS (ESI) *m/z*: 743.1 $[M+H]^+$.

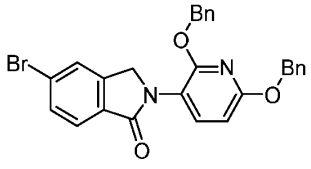
Step 5: Preparation of [(3S,8S)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 62**)



The title compound was prepared in an analogous manner to [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazine-1-carboxylate starting from *tert*-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3S,8S)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate, and purified by prep-HPLC (column: Phenomenex C18 75*30 mm*3μm; mobile phase: [0-40% CH_3CN in water (formic acid)]). Pure fractions were combined and dried by lyophilization to give the title compound (36.5 mg, 0.036 mmol, 56% yield, formic acid salt) as a yellow solid.

Example 13: Synthesis of [(3*R*,8*R*)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 59**)

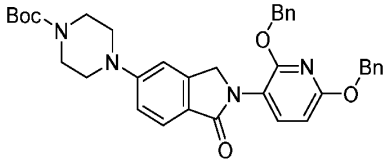
Step 1: Preparation of 5-bromo-2-(2,6-dibenzyloxy-3-pyridyl)isoindolin-1-one



To a mixture of 2,6-dibenzyloxypyridin-3-amine (2 g, 6.53 mmol, 1.0 *eq*) and methyl 4-bromo-2-(bromomethyl)benzoate (2.01 g, 6.53 mmol, 1.0 *eq*) in DMA (20 mL) was added

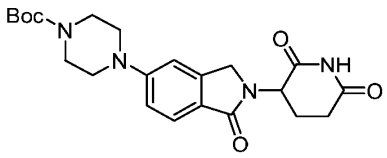
diisopropylethylamine (3.41 mL, 19.58 mmol, 3.0 *eq*), and the reaction mixture was stirred at 125 °C for 15 hours. The mixture was cooled, then diluted with EtOAc (40 mL) and water (30 mL). The organic layer was separated, and the aqueous was extracted with EtOAc (30 mL x 3). The combined organic extracts were washed with water (30 mL x 3), brine (30 mL x 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on SiO_2 (gradient: 0–15% ethyl acetate in petroleum ether) to afford the title compound (1.3 g, 2.44 mmol, 37% yield) as a yellow solid. LC/MS (ESI) *m/z*: 502.9 $[M+H]^+$.

Step 2: Preparation of tert-butyl 4-[2-(2,6-dibenzyloxy-3-pyridyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate



To 5-bromo-2-(2,6-dibenzyloxy-3-pyridyl)isoindolin-1-one (1.3 g, 2.44 mmol, 94% purity, 1.0 *eq*) in dioxane (20 mL) were added tert-butyl piperazine-1-carboxylate (680.93 mg, 3.66 mmol, 1.5 *eq*), Cs_2CO_3 (2.38 g, 7.31 mmol, 3.0 *eq*), and [2-(2-aminophenyl)phenyl]-chloro-palladium;dicyclohexyl-[3-(2,4,6-triisopropylphenyl)phenyl]phosphane (191.77 mg, 243.73 µmol, 0.1 *eq*), and the reaction mixture was stirred at 110 °C for 15 hours under N_2 atmosphere. The reaction was cooled, diluted with water (20 mL), and extracted with EtOAc (20 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on SiO_2 (gradient: 0-50% ethyl acetate in petroleum ether) to afford the title compound (0.8 g, 1.13 mmol, 47% yield) as a yellow solid. LC/MS (ESI) *m/z*: 607.2 $[M+H]^+$.

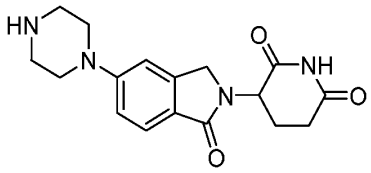
Step 3: Preparation of tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate



To a solution of tert-butyl 4-[2-(2,6-dibenzyloxy-3-pyridyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (800 mg, 1.13 mmol, 86% purity, 1.0 *eq*) in EtOAc (20 mL) was added Pd/C (0.1 g, 1.13 mmol, 10% purity, 1.0 *eq*) under Ar atmosphere, and the resulting suspension was degassed under vacuum and purged with H_2 several times. The reaction mixture was stirred under H_2 (15 psi) at 50 °C for 15 hours. The reaction mixture was filtered

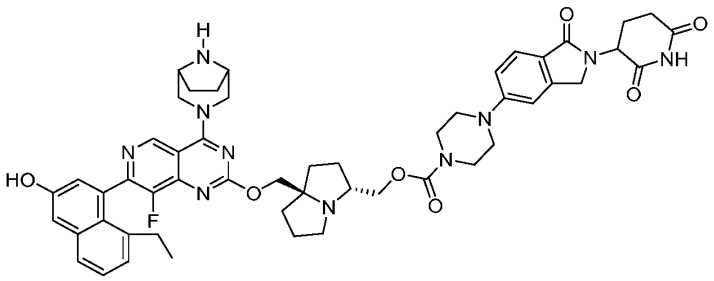
and concentrated under reduced pressure. The resulting residue was dissolved with EtOAc (20 mL). Pd/C (0.2 g, 1.13 mmol, 10% purity, 1.0 *eq*) was added under Ar, and the suspension was degassed under vacuum and purged with H_2 several times. The reaction mixture was stirred under H_2 (15 psi) at 50 °C for 15 hours. The mixture was filtered, and the cake was washed with 10:1 CH_2Cl_2/CH_3OH (50 mL). The solvent was concentrated under reduced pressure to afford the title compound (380 mg, crude) as a purple solid. LC/MS (ESI) *m/z*: 429.0 $[M+H]^+$.

Step 4: Preparation of 3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione



To tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (60 mg, 140.03 µmol, 1.0 *eq*) in CH_2Cl_2 (1 mL) was added TFA (1 mL, 13.51 mmol, 96.45 *eq*), and the reaction mixture was stirred at 25 °C for 1 hour. The mixture was concentrated under reduced pressure to afford the title compound (123.89 mg, crude, TFA salt) as a black brown oil. LC/MS (ESI) *m/z*: 329.1 $[M+H]^+$.

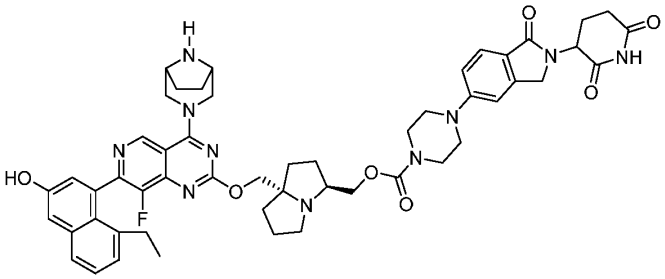
Step 5: Preparation of [(3*R*,8*R*)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 59**)



The title compound was prepared in an analogous manner to [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazine-1-carboxylate starting from tert-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3*R*,8*R*)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and 3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione, and purified by prep-HPLC (column: Phenomenex C18 75*30mm*3µm;mobile phase: [2-42% CH_3CN in water

(formic acid)]). Pure fractions were combined and concentrated under reduced pressure, then lyophilized to afford the title compound (32.0 mg, 31.65 µmol, 20% yield, formic acid salt) as an off-white solid.

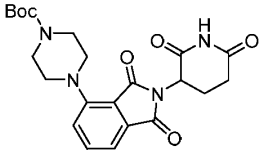
Example 14: Synthesis of [(3*S*,8*S*)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 58**)



The title compound was prepared in an analogous manner to [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazine-1-carboxylate starting from tert-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3*S*,8*S*)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and 3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione, and purified by pre-HPLC (column: Phenomenex C18 75*30mm*3µm;mobile phase: [2-42% CH_3CN in water (formic acid)]). Pure fractions were combined and concentrated under reduced pressure, then lyophilized to afford the title compound (31.6 mg, 32.43 µmol, 24% yield, formic acid salt) as an off-white solid.

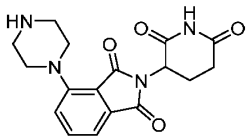
Example 15: Synthesis of [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl 4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]piperazine-1-carboxylate (**Compound 65**)

Step 1: Preparation of tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]piperazine-1-carboxylate



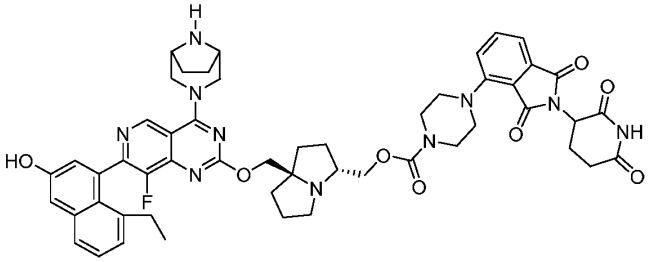
To a solution of 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (500 mg, 1.81 mmol, 1.0 *eq*) and tert-butyl piperazine-1-carboxylate (405 mg, 2.17 mmol, 1.2 *eq*) in DMSO (8 mL) was added diisopropylethylamine (0.946 mL, 5.43 mmol, *d* = 0.742 g/mL, 3.0 *eq*), and the reaction mixture was stirred at 100 °C for 3 hours. The mixture was diluted with H_2O (20 mL), and the aqueous phase was extracted with dichloromethane (30 mL x 3). The combined organic extract was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography on SiO_2 (gradient: 0~2% methanol in dichloromethane) to afford the title compound (600 mg, 1.10 mmol, 61% yield) as a yellow oil. LC/MS (ESI) *m/z*: 386.9 $[M-55]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.56 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.39 (d, *J* = 7.0 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 4.90 (dd, *J* = 5.2, 12.4 Hz, 1H), 3.60 (t, *J* = 4.8 Hz, 4H), 3.31 – 3.17 (m, 4H), 2.88 – 2.62 (m, 3H), 2.11 – 2.01 (m, 1H), 1.44 – 1.38 (m, 9H).

Step 2: Preparation of 2-(2,6-dioxo-3-piperidyl)-4-(piperazin-1-yl)isoindoline-1,3-dione



To a solution of tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]piperazine-1-carboxylate (600 mg, 1.10 mmol, 1.0 *eq*) in CH_2Cl_2 (8 mL) was added TFA (6.0 mL, 81.04 mmol, *d* = 1.54 g/mL, 59.8 *eq*), and the reaction mixture was stirred at 20 °C for 0.5 hours. The mixture was concentrated in vacuum to afford the title compound (620 mg, crude, TFA) as a yellow solid. LC/MS (ESI) *m/z*: 343.1 $[M+H]^+$.

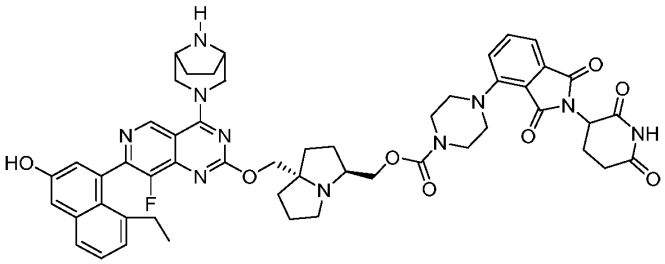
Step 3: Preparation of [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl 4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]piperazine-1-carboxylate (**Compound 65**)



The title compound was prepared in an analogous manner to [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1,3-

dioxo-isoindolin-5-yl]piperazine-1-carboxylate starting from tert-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3R,8R)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and 2-(2,6-dioxo-3-piperidyl)-4-(piperazin-1-yl)isoindoline-1,3-dione, and purified by prep-HPLC (Condition: [2-42% CH_3CN in water (formic acid)]; Column: Phenomenex C18 75 * 30 mm * 3 μm; Flow Rate: 25 mL/min). Pure fractions were combined and lyophilized to afford the title compound (36.3 mg, 0.037 mmol, 49% yield, formic acid salt) as a yellow solid.

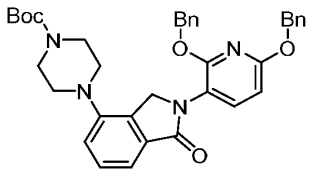
Example 16: Synthesis of [(3S,8S)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl 4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]piperazine-1-carboxylate (**Compound 64**)



The title compound was prepared in an analogous manner to [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazine-1-carboxylate starting from tert-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3S,8S)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and 2-(2,6-dioxopiperidin-3-yl)-4-(piperazin-1-yl)isoindoline-1,3-dione, and purified by prep-HPLC (Condition: [2-42% CH_3CN in water (formic acid)]; Column: Phenomenex C18 75 * 30 mm * 3 μm; Flow Rate: 25 mL/min). Pure fractions were combined and lyophilized to afford the title compound (31.0 mg, 0.031 mmol, 47% yield, formic acid salt) as a yellow solid.

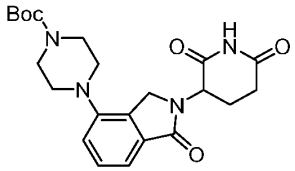
Example 17: Synthesis of [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate (**Compound 61**)

Step 1: Preparation of tert-butyl 4-[2-(2,6-dibenzyloxy-3-pyridyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate



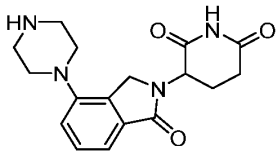
To a solution of 4-bromo-2-(2,6-dibenzyloxy-3-pyridyl)isoindolin-1-one (500 mg, 0.997 mmol, 1.0 *eq*) and tert-butyl piperazine-1-carboxylate (279 mg, 1.50 mmol, 1.5 *eq*) in dioxane (6 mL) were added Cs_2CO_3 (975 mg, 2.99 mmol, 3.0 *eq*) and [2-(2-aminophenyl)phenyl]-chloro-palladium;dicyclohexyl-[3-(2,4,6-triisopropylphenyl)phenyl]phosphane (78 mg, 0.100 mmol, 0.1 *eq*), and the reaction mixture was stirred at 110 °C for 12 hours. The mixture was filtered and concentrated, and the resulting residue was purified by flash chromatography on SiO_2 (gradient: 0~30% ethyl acetate in petroleum ether) to afford the title compound (410 mg, 0.642 mmol, 64% yield) as a yellow solid. LC/MS (ESI) m/z: 607.2 $[M+H]^+$.

Step 2: Preparation of tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate



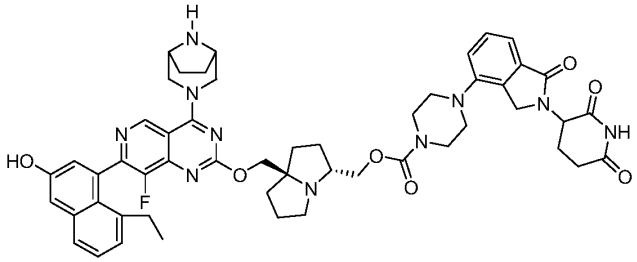
To a solution of tert-butyl 4-[2-(2,6-dibenzyloxy-3-pyridyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate (410 mg, 0.642 mmol, 1.0 *eq*) in EtOAc (10 mL) was added Pd/C (200 mg, 10% purity), and the reaction mixture was stirred at 50 °C for 12 hours under H_2(15 psi). The reaction was filtered and concentrated in vacuum to afford the title compound (300 mg, crude) as a light yellow oil. LC/MS (ESI) m/z: 429.1 $[M+H]^+$.

Step 3: Preparation of 3-(1-oxo-4-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione



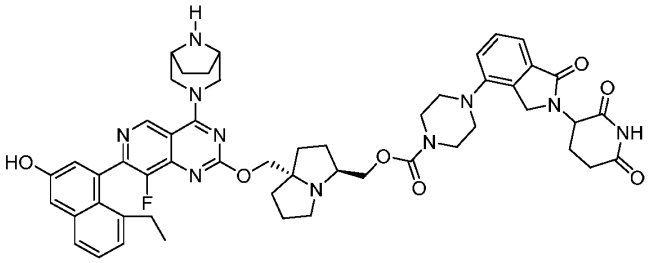
To a solution of tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate (300 mg, 0.700 mmol, 1.0 *eq*) in CH_2Cl_2 (4 mL) was added TFA (3.0 mL, 40.52 mmol, *d* = 1.54 g/mL, 57.9 *eq*), and the reaction mixture was stirred at 20 °C for 0.5 hours. The reaction was concentrated in vacuum to afford the title compound (310 mg, crude, TFA) as a yellow solid. LC/MS (ESI) m/z: 329.0 $[M+H]^+$.

Step 4: Preparation of [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate (**Compound 61**)



The title compound was prepared in an analogous manner to [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazine-1-carboxylate starting from tert-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3R,8R)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and 3-(1-oxo-4-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione, purified by prep-HPLC (5-40% CH_3CN in water (formic acid); Gradient time: 25 min; Column: Phenomenex C18 75 * 30 mm * 3 µm; Flow Rate: 25 mL/min). Pure fractions were combined and lyophilized to afford the title compound (28.3 mg, 29.14 µmol, 38% yield, formic acid salt) as a white solid.

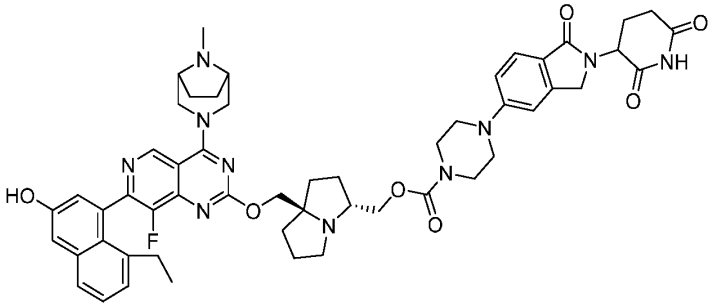
Example 18: Synthesis of [(3S,8S)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate (**Compound 60**)



The title compound was prepared in an analogous manner to [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazine-1-carboxylate starting from tert-butyl 3-[7-[8-ethyl-3-

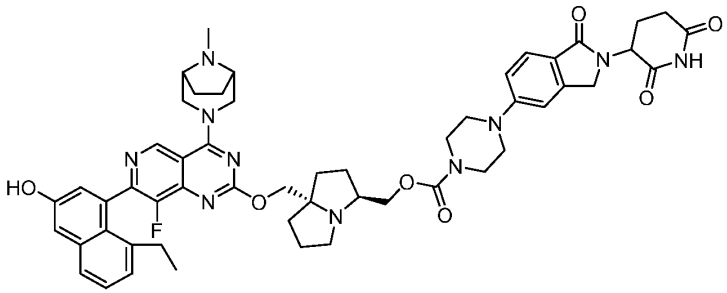
(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3S,8S)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and 3-(1-oxo-4-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione, and purified by prep-HPLC (5-40% CH_3CN in water (formic acid); Gradient time: 25 min; Column: Phenomenex C18 75 * 30 mm * 3 µm; Flow Rate: 25 mL/min). Pure fractions were combined and lyophilized to afford the title compound (22.9 mg, 0.024 mmol, 33% yield, formic acid salt) as a white solid.

Example 19: Synthesis of [(3R,8R)-8-[[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-4-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 48**)



To a solution of [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (85.0 mg, 0.086 mmol, 1.0 *eq*, HCl) in CH_2Cl_2 (2 mL) and CH_3OH (2 mL) were added formaldehyde (0.429 mmol, 32.0 µL, 37% purity, 5.0 *eq*) and 2-methylpyridine borane (14.0 mg, 0.129 mmol, 1.5 *eq*), and the reaction mixture was stirred at 25 °C for 1 hour. The mixture was concentrated, and the crude product was purified by prep-HPLC (column: Phenomenex C18 75 * 30 mm * 3 µm; mobile phase: [5-35% CH_3CN in water (formic acid)]). Pure fraction was lyophilized to afford the title compound (17.9 mg, 0.017 mmol, 20% yield, formic acid salt) as a yellow solid.

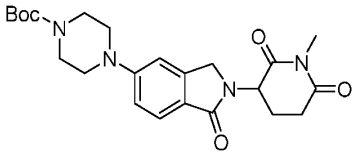
Example 20: Synthesis of [(3S,8S)-8-[[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-4-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 47**)



The title compounds was prepared in an analogous manner to [(3R,8R)-8-[[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-4-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate, and purified by prep-HPLC (column: Phenomenex C18 75 * 30 mm * 3 μm; mobile phase: [5-35% CH_3CN in water (formic acid)]). Pure fraction was lyophilized to afford the title compound (40.5 mg, 0.040 mmol, 29% yield, formic acid salt) as a yellow solid.

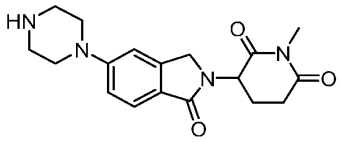
Example 21: Synthesis of [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 53**)

Step 1: Preparation of tert-butyl 4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate



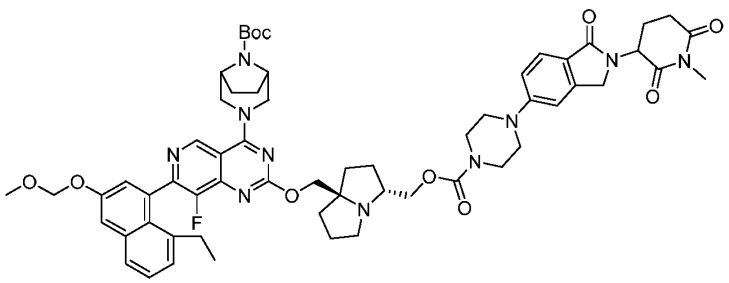
To a solution of tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (430 mg, 1.00 mmol, 1.0 *eq*) in DMA (5 mL) were added Cs_2CO_3 (654.0 mg, 2.01 mmol, 2.0 *eq*) and CH_3I (2.01 mmol, 125 μL, 2.0 *eq*), and the reaction mixture was stirred at 25 °C for 2 hours. The mixture was filtered, diluted with water (15 mL), and extracted with ethyl acetate (20 mL × 3). The combined organic extract was washed with brine (15 mL × 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound (420 mg, crude) as a yellow solid. LC/MS (ESI) *m/z*: 443.1 $[M+H]^+$.

Step 2: Preparation of 1-methyl-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione



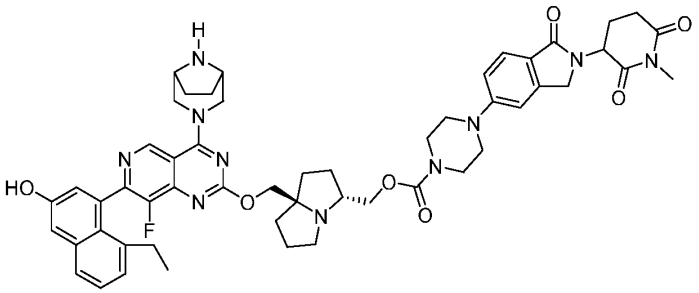
To a solution of tert-butyl 4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (420 mg, 949.14 μmol, 1 *eq*) in CH_2Cl_2 (5 mL) was added HCl/dioxane (5 mL, 4M), and the reaction mixture was stirred at 25 °C for 0.5 hour. Petroleum ether (30 mL) was then added, and the resulting mixture was stirred at 25 °C for 0.5 hour. The resulting precipitate was filtered to afford the title compound (350 mg, crude, HCl salt) as a yellow solid. LC/MS (ESI) *m/z*: 343.0 $[M+H]^+$.

Step 3: Preparation of tert-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3R,8R)-3-[[4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carbonyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



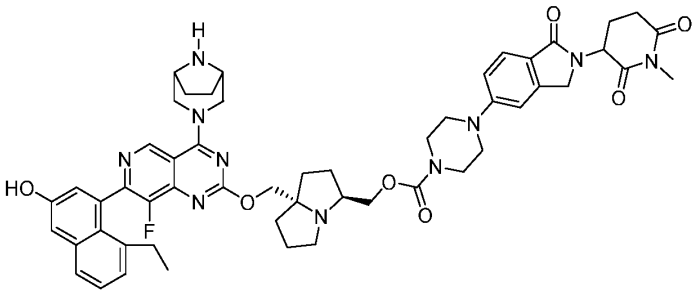
To a solution of tert-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3R,8R)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.1 mmol, 1.0 *eq*) in THF (3 mL) were added triethylamine (1.08 mmol, 150 μL, 10 *eq*), DMAP (1.0 mg, 0.001 mmol, 0.1 *eq*), and (4-nitrophenyl) carbonochloridate (37.0 mg, 0.183 mmol, 1.7 *eq*), and the reaction mixture was stirred at 40 °C for 15 hours. 1-Methyl-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (45.0 mg, 0.118 mmol, 1.1 *eq*, HCl) was then added, and the reaction mixture was stirred at 40 °C for 1 hour. The mixture was concentrated, and the resulting residue was purified by flash chromatography on SiO_2 (gradient: 0~5% methanol in dichloromethane) to afford the title compound (100 mg, 0.056 μmol, 53% yield) as a yellow solid. LC/MS (ESI) *m/z*: 1111.4 $[M+H]^+$.

Step 4: Preparation of [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 53**)



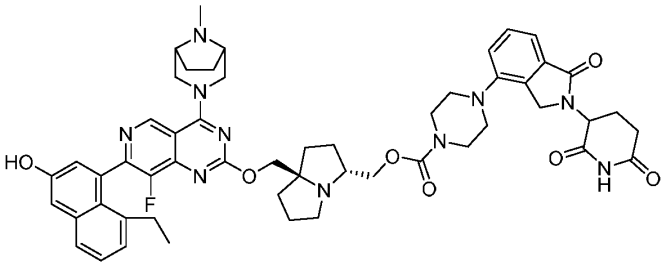
A mixture of tert-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3R,8R)-3-[[4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carbonyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.09 mmol, 1 *eq*) in CH_2Cl_2 (2 mL) and 4M HCl/dioxane (2mL) was stirred at 25 °C for 0.5 hour. Petroleum ether (30 mL) was then added, and the resulting mixture was stirred at 25 °C for 0.5 hour. The resulting precipitate was collected and purified by prep-HPLC (column: Phenomenex C18 75*30mm * 3μm; mobile phase: [5-40% CH_3CN in water (formic acid)]). Pure fractions were lyophilized to afford the title compound (29.7 mg, 28.79 μmol, 32% yield, formic acid salt) as a white solid.

Example 22: Synthesis of [(3S,8S)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 50**)



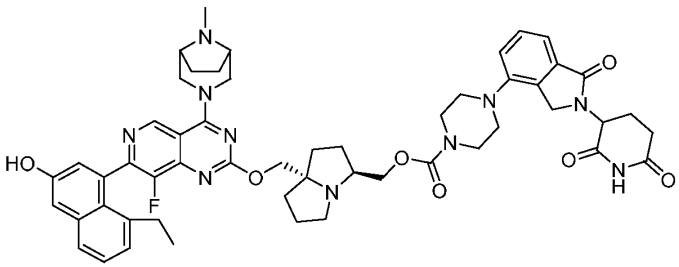
The title compound was prepared in an analogous manner to [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 53**) starting from tert-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3S,8S)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate, and purified by prep-HPLC (column: Phenomenex C18 75*30mm * 3μm; mobile phase: [5-40% CH_3CN in water (formic acid)]). Pure fractions were lyophilized to the title compound (30.2 mg, 0.029 mmol, 32% yield, formic acid salt) as a white solid.

Example 23: Synthesis of [(3R,8R)-8-[[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-4-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate (**Compound 51**)



The title compounds was prepared in an analogous manner to [(3R,8R)-8-[[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-4-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate starting from [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate, and purified by prep-HPLC (column: Phenomenex C18 75*30 mm*3 μm; mobile phase: [5-35% CH_3CN in water (formic acid)]) to give the title compound (22.2 mg, 0.021 mmol, 35% yield, formic acid salt) as a white solid.

Example 24: Synthesis of [(3S,8S)-8-[[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-4-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate (**Compound 49**)

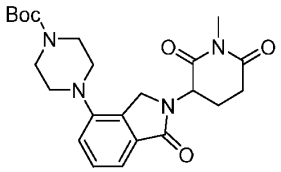


The title compounds was prepared in an analogous manner to [(3R,8R)-8-[[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-4-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate starting from [(3S,8S)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-

isoindolin-4-yl]piperazine-1-carboxylate, purified by prep-HPLC (Column: Phenomenex C18 75*30mm*3μm; gradient: 5%-35% CH_3CN in water (NH_4HCO_3); Gradient time: 25 min; Hold time: 4 min; Flow rate: 25 mL/min) to afford the title compound (58.3 mg, 0.059 mmol, 52% yield) as a yellow solid.

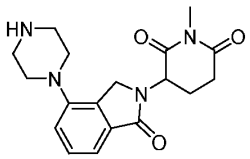
Example 25: Synthesis of [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate (**Compound 54**)

Step 1: Preparation of tert-butyl 4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate



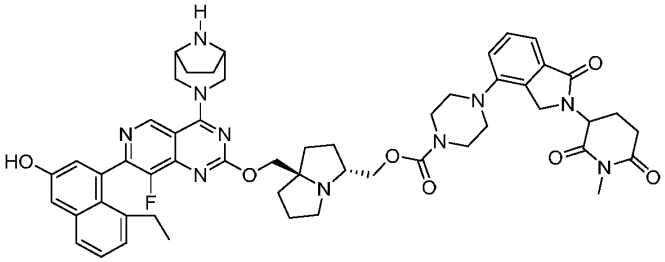
To a solution of tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate (400 mg, 0.934 mmol, 1.0 *eq*) in DMF (8 mL) at 0°C were added Cs_2CO_3 (608 mg, 1.87 mmol, 2.0 *eq*) and CH_3I (0.116 mL, 1.87 mmol, *d* = 2.28 g/mL, 2.0 *eq*), and the reaction mixture was stirred at 20 °C for 3 hours under N_2. The mixture was diluted with H_2O (30 mL), and the aqueous phase was extracted with ethyl acetate (40 mL x 3). The combined organic extract was washed with water (20 mL x 3) and brine (20 mL x 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to afford the title compound (490 mg, crude) as a yellow solid. LC/MS (ESI) *m/z*: 387.2 $[M-55]^+$.

Step 2: Preparation of 1-methyl-3-(1-oxo-4-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione



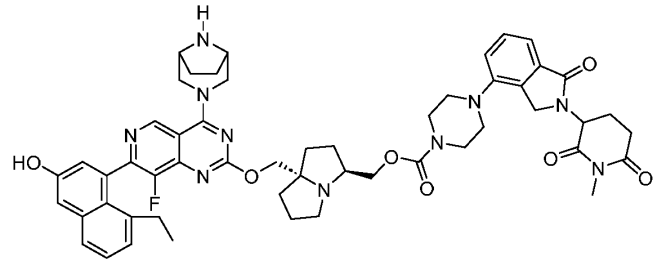
To a solution of tert-butyl 4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate (50 mg, 0.113 mmol, 1 *eq*) in CH_2Cl_2 (1 mL) was added 4M HCl/EtOAc (1 mL), and the reaction mixture was stirred at 20 °C for 20 min. The mixture was concentrated under reduced pressure to give the title compound (40 mg, 0.106 mmol, 93% yield, HCl salt) as a yellow solid. LC/MS (ESI) *m/z*: 343.0 $[M+H]^+$.

Step 3: Preparation of [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate (**Compound 54**)



The title compound was prepared in an analogous manner to [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 53**) starting from tert-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3R,8R)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and 1-methyl-3-(1-oxo-4-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione, and purified by prep-HPLC (column: Phenomenex C18 75*30 mm*3 μm; mobile phase: [5-40% CH_3CN in water (formic acid)]). Pure fractions were combined and dried by lyophilization to give the title compound (30.8 mg, 0.030 mmol, 46% yield, formic acid salt) as a white solid.

Example 26: Synthesis of [(3S,8S)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl 4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]piperazine-1-carboxylate (**Compound 52**)

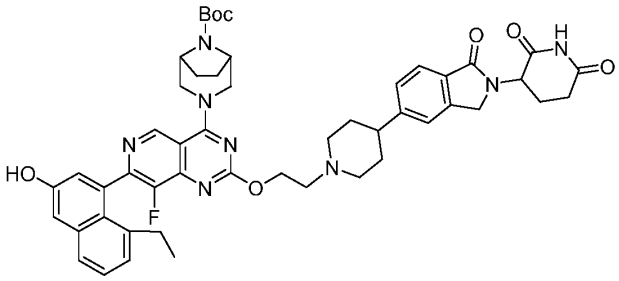


The title compound was prepared in an analogous manner to [(3R,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl4-[2-(1-methyl-2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (**Compound 53**) starting from tert-butyl 3-[7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3S,8S)-3-(hydroxymethyl)-1,2,3,5,6,7-

hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and 1-methyl-3-(1-oxo-4-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione, and purified by prep-HPLC (gradient: 5~45% CH_3CN in water (formic acid); Gradient time: 28 min; Hold time: 3 min; Flow rate: 25 mL/min). Pure fractions were combined and lyophilized under reduced pressure to afford the title compound (17.0 mg, 17.46 μmol, 28% yield, formic acid salt) as a white solid.

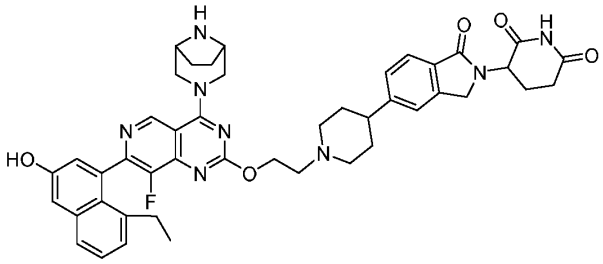
Example 27: Synthesis of 3-[6-(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)-1-oxo-2,3-dihydro-1H-isoindol-2-yl]piperidine-2,6-dione (**Compound 36**)

Step 1: Preparation of tert-butyl 3-(2-(2-(4-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisoindolin-5-yl)piperidin-1-yl)ethoxy)-7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of tert-butyl 3-[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (51 μmol) in dichloromethane (1 mL) and isopropyl alcohol (0.1 mL) was added 3-(1-oxo-5-(piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (54 μmol), 2-methylpyridine borane complex (255 μmol) and acetic acid (204 μmol), the mixture was stirred at 20 °C for 1 h. The reaction mixture was filtered and concentrated. The residue was purified by preparative thin layer chromatography (dichloromethane : methanol = 10:1) to afford product.

Step 2: Preparation of 3-[6-(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)-1-oxo-2,3-dihydro-1H-isoindol-2-yl]piperidine-2,6-dione (**Compound 36**)

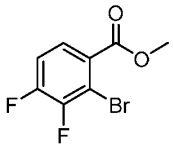


To a solution of tert-butyl 3-[2-[2-[4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-1-piperidyl]ethoxy]-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (44 μmol) in hexafluoroisopropanol (1 mL) was added trifluoroacetic acid (0.2 mL) and stirred at 25 °C for 0.5 h. The reaction mixture was purified by preparative HPLC (Welch Xtimate C18 150x25mmx5μm; A: water with 0.225% v/v FA, B: acetonitrile; B%: 20-60; 25 min) and was then lyophilized to afford the title compound.

Compounds 1-8, 10-22, 25-27, 31-34, and 37-40 were prepared using a procedure analogous to the procedure used to prepare Compound 36.

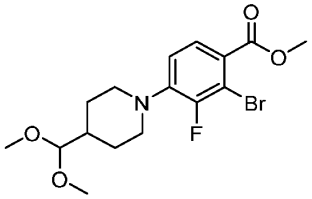
Example 28: Synthesis of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan- 3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 69**)

Step 1: Preparation of methyl 2-bromo-3,4-difluorobenzoate



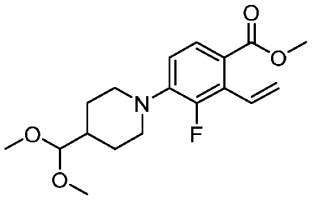
To a solution of 2-bromo-3,4-difluoro-benzoic acid (200 g, 843.8 mmol, 1 *eq*) in methanol (1.5L) at 0 °C was added thionyl dichloride (200.8 g, 1.69 mol, 122.4 mL, 2 *eq*) dropwise, and the reaction mixture was stirred at 70 °C for 12 hours. The mixture was concentrated under vacuum, and the residue was diluted with water (600 mL) and extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with brine (2 x 200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give the title compound (208 g, 98%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (ddd, J = 2.0, 5.4, 8.8 Hz, 1H), 7.25 – 7.14 (m, 1H), 3.94 (s, 3H).

Step 2: Preparation of methyl 2-bromo-4-(4-(dimethoxymethyl)piperidin-1-yl)-3-fluorobenzoate



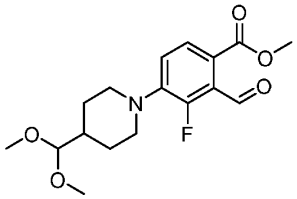
To a solution of methyl 2-bromo-3,4-difluoro-benzoate (208 g, 828.60 mmol, 1 *eq*) in dimethyl sulfoxide (1500 mL) were added diisopropylethylamine (321.3 g, 2.49 mol, 433.0 mL, 3 *eq*) and 4-(dimethoxymethyl)piperidine (138.5 g, 870.03 mmol, 1.05 *eq*), and the reaction mixture was stirred at 100 °C for 12 hours. The mixture was poured into water (1L), and the aqueous mixture was extracted with EtOAc (3 x 300 mL). The combined organic extracts were washed with brine (3 x 500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (gradient: 1–50% EtOAc in petroleum ether) to give the title compound (244 g, 75%) as a white solid. LC/MS (ESI) *m/z*: 390.0, 392.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 1.0, 8.6 Hz, 1H), 6.84 (t, J = 8.4 Hz, 1H), 4.09 (d, J = 7.0 Hz, 1H), 3.89 (s, 3H), 3.59 (br d, J = 12.2 Hz, 2H), 3.38 (s, 6H), 2.74 (br t, J = 11.6 Hz, 2H), 1.92 – 1.76 (m, 3H), 1.50 (br dd, J = 3.4, 11.8 Hz, 2H).

Step 3: Preparation of methyl 4-(4-(dimethoxymethyl)piperidin-1-yl)-3-fluoro-2-vinylbenzoate



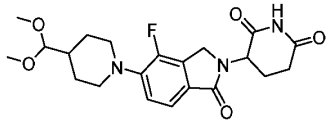
To a solution of methyl 2-bromo-4-(4-(dimethoxymethyl)piperidin-1-yl)-3-fluorobenzoate (170 g, 435.63 mmol, 1 *eq*) and potassium vinyltrifluoroborate (175.06 g, 1.31 mol, 3 *eq*) in dioxane (1.3 L) and water (250 mL) were added bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane (17.8 g, 21.78 mmol, 0.05 *eq*) and sodium carbonate (115.4 g, 1.09 mol, 2.5 *eq*), and the reaction mixture was stirred at 110 °C for 12 hours. Water (1L) was then added, and the aqueous mixture was extracted with EtOAc (3 x 600 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (1-25% EtOAc in petroleum ether) to afford the title compound (123 g, 83%) as a white solid. LC/MS (ESI) *m/z*: 338.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 1.2, 8.6 Hz, 1H), 7.04 (dd, J = 11.8, 17.8 Hz, 1H), 6.83 (t, J = 8.4 Hz, 1H), 5.74 - 5.46 (m, 2H), 4.11 (d, J = 7.2 Hz, 1H), 3.85 (s, 3H), 3.64 - 3.52 (m, 2H), 3.38 (s, 6H), 2.71 (dt, J = 1.8, 12.0 Hz, 2H), 1.86 (br dd, J = 1.6, 13.0 Hz, 3H), 1.53 (br dd, J = 3.6, 12.0 Hz, 2H).

Step 4: Preparation of methyl 4-(4-(dimethoxymethyl)piperidin-1-yl)-3-fluoro-2-formylbenzoate



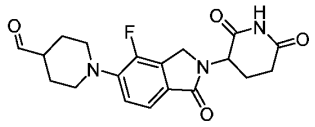
To a solution of methyl 4-(4-(dimethoxymethyl)piperidin-1-yl)-3-fluoro-2-vinylbenzoate (50 g, 148.20 mmol, 1 *eq*) in dioxane (450 mL) and water (150 mL) were added 2,6-lutidine (31.8 g, 296.40 mmol, 34.5 mL, 2 *eq*), potassium osmate(VI) dihydrate (1.1 g, 2.96 mmol, 0.02 *eq*), and sodium periodate (126.79 g, 592.79 mmol, 32.85 mL, 4 *eq*), and the reaction mixture was stirred at 20 °C for 1 hour. Water (300 mL) was then added, and the resulting mixture was filtered. The filtrate was extracted with EtOAc (2 x 200 mL), and the combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (1-50% EtOAc in petroleum ether) to afford the title compound (36 g, 72% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 7.65 (dd, J = 0.8, 8.4 Hz, 1H), 7.01 (t, J = 8.4 Hz, 1H), 4.09 (d, J = 7.0 Hz, 1H), 3.90 (s, 3H), 3.63 (br d, J = 12.2 Hz, 2H), 3.45 - 3.32 (m, 6H), 2.84 - 2.69 (m, 2H), 1.93 - 1.73 (m, 3H), 1.51 (br d, J = 3.6 Hz, 2H).

Step 5: Preparation of 3-(5-(4-(dimethoxymethyl)piperidin-1-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione



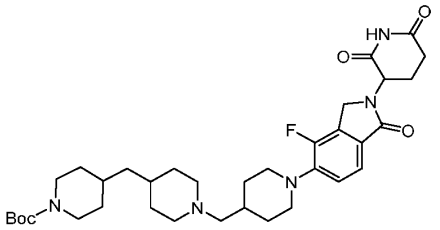
To a solution of 3-aminopiperidine-2,6-dione (20.4 g, 123.76 mmol, 1.2 *eq*, hydrochloride) in methanol (350 mL) was added sodium acetate (25.4 g, 309.41 mmol, 3 *eq*) followed by methyl 4-[4-(dimethoxymethyl)-1-piperidyl]-3-fluoro-2-formyl-benzoate (35 g, 103.14 mmol, 1 *eq*) and sodium cyanoborohydride (13.0 g, 206.27 mmol, 2 *eq*), and the reaction mixture was stirred at 40 °C for 12 hours. The mixture was filtered, and the cake was washed with methanol (2 x 20 mL). The cake was triturated twice with water (600 mL) at 20 °C for 30 minutes. The resulting material was collected and dried under vacuum to afford the title compound (37 g, 85%) as a purple solid. LC/MS (ESI) *m/z*: 420.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.23 - 7.05 (m, 1H), 5.15 - 4.99 (m, 1H), 4.52 - 4.42 (m, 1H), 4.36 - 4.26 (m, 1H), 4.12 (d, J = 6.4 Hz, 1H), 3.49 (br d, J = 4.8 Hz, 2H), 3.33 (s, 6H), 2.98 - 2.85 (m, 1H), 2.74 (br t, J = 12.0 Hz, 2H), 2.61 (br s, 1H), 2.46 - 2.34 (m, 1H), 2.03 - 1.93 (m, 1H), 1.74 (br d, J = 10.4 Hz, 3H), 1.40 (br d, J = 10.2 Hz, 2H).

Step 6: Preparation of 1-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)piperidine-4-carbaldehyde



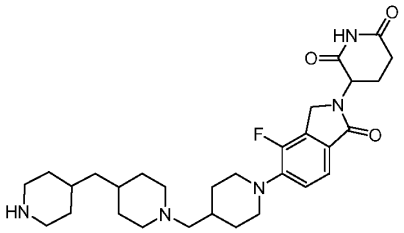
To a solution of 3-(5-(4-(dimethoxymethyl)piperidin-1-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (37 g, 88.21 mmol, 1 *eq*) in acetone (350 mL) and water (35 mL) was added *p*-toluenesulfonic acid (3.0 g, 17.64 mmol, 0.2 *eq*), and the reaction mixture was stirred at 70 °C for 12 hours. The mixture was filtered, and the cake was washed with acetone (3 x 30 mL). The resulting material was collected and dried under vacuum to afford the title compound (29 g, 88%) as a white. LC/MS (ESI) *m/z*: 374.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.65 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.17 (br t, *J* = 7.8 Hz, 1H), 5.07 (br dd, *J* = 5.0, 13.2 Hz, 1H), 4.56 - 4.43 (m, 1H), 4.38 - 4.22 (m, 1H), 3.50 - 3.37 (m, 2H), 3.00 - 2.82 (m, 3H), 2.64 - 2.52 (m, 2H), 2.43 (br d, *J* = 4.2 Hz, 1H), 2.03 - 1.93 (m, 3H), 1.66 (br d, *J* = 10.0 Hz, 2H).

Step 7: Preparation of *tert*-butyl 4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-4- fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate



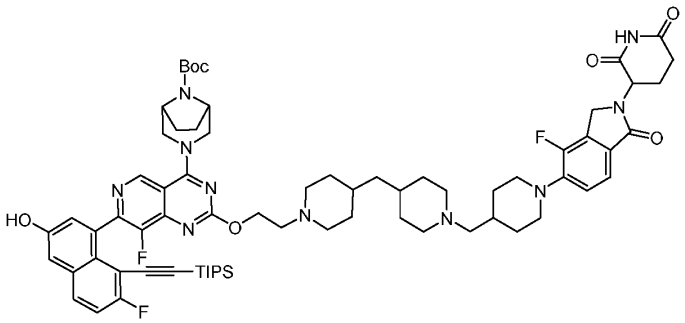
To a mixture of 1-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)piperidine-4-carbaldehyde (1.0 g, 2.68 mmol, 1 *eq*) and *tert*-butyl 4-(4-piperidylmethyl) piperidine-1-carboxylate (1.69 g, 3.21 mmol, 1.2 *eq*, acetate) in dichloromethane (10 mL) and dimethyl sulfoxide (10 mL) at 25 °C was added diisopropylethylamine (346 mg, 2.68 mmol, 0.4 mL, 1.0 *eq*), and the resulting mixture was stirred for 15 minutes under nitrogen. Sodium triacetoxyborohydride (1.70 g, 8.03 mmol, 3 *eq*) was then added, and the reaction mixture was stirred at 25 °C for 1 hour. The mixture was diluted with dichloromethane (50 mL), washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by prep-TLC (dichloromethane/methanol =5/1) to the title compound (1.3 g, 2.03 mmol, 75% yield) as a white solid. LC/MS (ESI) *m/z*: 640.3 $[M+H]^+$.

Step 8: Preparation of 3-[4-fluoro-1-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione



To a solution of *tert*-butyl 4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-4- fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate (570 mg, 0.89 mmol, 1 *eq*) in dichloromethane (6 mL) was added trifluoroacetic acid (3.08 g, 27.01 mmol, 2 mL, 30.32 *eq*), and the reaction mixture was stirred at 25 °C for 0.5 hours. The mixture was concentrated under vacuum to afford the title compound (580 mg, crude, trifluoroacetate) as a brown gum. LC/MS (ESI) *m/z*: 540.5 $[M+H]^+$.

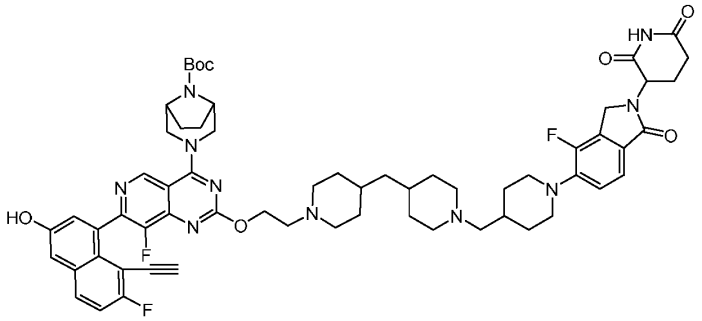
Step 9: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-hydroxy-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 3-[4-fluoro-1-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione (578 mg, 0.88 mmol, 1.49 *eq*, trifluoroacetate) in dichloromethane (5 mL) and isopropanol (5 mL) was added diisopropylethylamine (230 mg, 1.78 mmol, 0.3 mL, 3 *eq*) followed by tert-butyl 3-[8-fluoro-7-[7-fluoro-3-hydroxy-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (450 mg, 593.72 umol, 1 *eq*), and the resulting mixture was stirred at 25 °C for 10 minutes. Sodium triacetoxyborohydride (377 mg, 1.78 mmol, 3 *eq*) was then added, and the reaction mixture was stirred at 25 °C for 0.5 hours. The mixture was diluted with water (20 mL) and extracted with dichloromethane (2 x 30 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH = 20/1

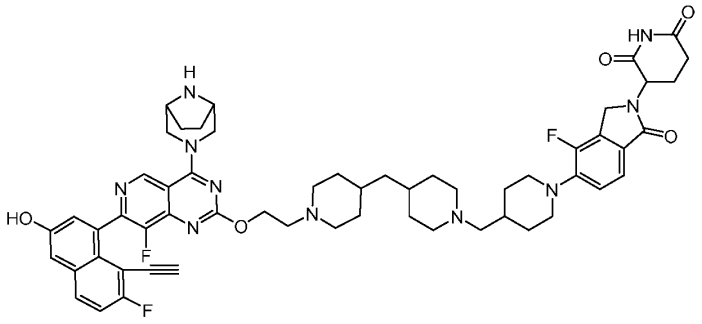
to 6/1) to afford the title compound (470 mg, 0.36 mmol, 61% yield) as a light yellow solid. LC/MS (ESI) *m/z*: 1281.9 $[M+H]^+$.

Step 10: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a mixture of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-hydroxy-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (460 mg, 0.35 mmol, 1 *eq*) in DMF (5 mL) at 25 °C was added cesium fluoride (1.09 g, 7.18 mmol, 0.2 mL, 20 *eq*), and the reaction mixture was stirred at 25 °C for 2 hours. The mixture was diluted with dichloromethane (50 mL), washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography (CH_2Cl_2/CH_3OH = 5/1) to afford the title compound (168 mg, 0.14 mmol, 41% yield) as a white solid. LC/MS (ESI) *m/z*: 563.6 $[M/2+H]^+$.

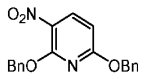
Step 11: Preparation of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan- 3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 69**)



To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (168 mg, 0.14 mmol, 1 *eq*) in dichloromethane (1.5 mL) was added hydrochloric acid/dioxane (4 M, 0.5 mL, 13.40 *eq*), and the reaction mixture was stirred at 25 °C for 15 minutes. The mixture was diluted with petroleum ether (6 mL) and the pH adjusted to 6. The mixture was concentrated in vacuum, and the residue was purified by prep-HPLC (column: Phenomenex Luna C18 150*25mm*10um; mobile phase: [6-36% CH_3CN in water (formic acid)]) to afford the title compound (91.0 mg, 0.08 mmol, 56% yield, formic acid salt) as a yellow solid.

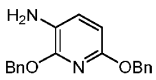
Example 29: Synthesis of 3-[5-[4-[[3-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl] piperidine-2,6-dione (**Compound 193**)

Step 1: Preparation of 2,6-bis(benzyloxy)-3-nitropyridine



To a mixture of 2,6-dichloro-3-nitropyridine (25.0 g, 156 mmol) and phenylmethanol (40.6 mL, 390 mmol) in acetonitrile (500 mL) was added cesium carbonate (127.21 g, 390 mmol) in one portion under nitrogen atmosphere, and the mixture was stirred at 60 °C for 6 h. The mixture was cooled to 20 °C and filtered, and the filtrate was concentrated under reduced pressure. The residue was triturated with petroleum ether/methyl tert-butyl ether (1:1, 500 mL) to afford the title compound (49 g, 93%) as a yellow solid.

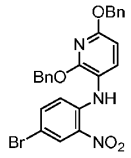
Step 2: Preparation of 2,6-bis(benzyloxy)pyridin-3-amine



To a mixture of 2,6-bis(benzyloxy)-3-nitropyridine (95.0 g, 282 mmol) and ammonium chloride (226.6 g, 4.2 mol) in isopropanol (950 mL) and water (475 mL) was added iron (126.19 g, 2.26 mol) under nitrogen atmosphere, and the mixture was stirred at 90 °C for 16 h. The mixture was cooled to 20 °C and filtered. The filtrate was poured into ice-water (w/w = 1/1, 1000 mL) and stirred for 5 minutes. The aqueous phase was extracted with ethyl acetate (2 x 1000 mL). The combined organic phase was washed with brine (3 x 1000 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by

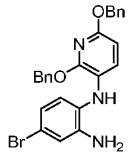
prep-HPLC (1% to 20% hexane/ethanol over 15 min) to afford the title compound (61 g, 70%) as a brown oil. LC/MS (ESI) *m/z*: 307.2 $[M+H]^+$.

Step 3: Preparation of 2,6-dibenzyloxy-N-(4-bromo-2-nitro-phenyl)pyridin-3-amine



To a solution of 2,6-bis(benzyloxy)pyridin-3-amine (5.0 g, 16 mmol) and 4-bromo-1-fluoro-2-nitro-benzene (2.4 mL, 20 mmol) in tetrahydrofuran (50 mL) was added lithium bis(trimethylsilyl)amide in tetrahydrofuran (1 M, 24.5 mL), and the mixture was stirred at -78 °C for 1 h, then stirred at 25 °C for 11 h under nitrogen atmosphere. The reaction was slowly quenched with saturated ammonium chloride solution to adjust the pH to 8-9, then extracted with ethyl acetate (300 mL). The organic layer was washed with brine (3 x 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/0 to 100/1) to afford the title compound (9 g, crude) as a brown oil. LC/MS (ESI) *m/z*: 508.1 $[M+H]^+$.

Step 4: Preparation of 4-bromo-N1-(2,6-dibenzyloxy-3-pyridyl)benzene-1,2-diamine



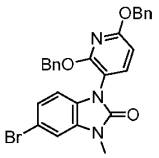
To a solution of 2,6-dibenzyloxy-N-(4-bromo-2-nitro-phenyl)pyridin-3-amine (8.0 g, 16 mmol) in ethanol (100 mL) and water (50 mL) were added iron (4.41 g, 79 mmol) and saturated aqueous ammonium chloride solution (8.45 g, 128 mmol), and the mixture was stirred at 80 °C for 4 h. The reaction mixture was filtered, and the filtrate was extracted with ethyl acetate (300 mL). The organic layer was washed with brine (3 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/0 then 10/1) to afford the title compound (2.8 g, 37%) as a brown solid.

Step 5: Preparation of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1H-benzimidazol-2-one



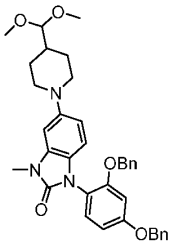
To a solution of 4-bromo-N1-(2,6-dibenzyloxy-3-pyridyl)benzene-1,2-diamine (2.8 g, 6 mmol) in *N,N*-dimethyl formamide (30 mL) was added 4-dimethylaminopyridine (4.77 g, 29 mmol), and the mixture was stirred at 120 °C for 2 h. The reaction was poured into water and the resulting precipitate was filtered and dried to afford the title compound (2.8 g, 94%) as a yellow solid. LC/MS (ESI) *m/z*: 504.1 $[M+H]^+$.

Step 6: Preparation of 5-bromo-1-(2,6-dibenzyloxy-3-pyridyl)-3-methyl-benzimidazol-2-one



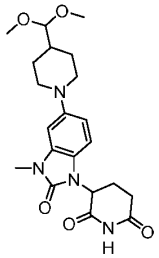
To a solution of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1H-benzimidazol-2-one (1.2 g, 2 mmol) in tetrahydrofuran (20 mL) was added sodium hydride (191 mg, 4.8 mmol, 60%) at 0 °C, and the reaction mixture was stirred for 0.5 h. Iodomethane (0.2 mL, 4 mmol) was then added at 0 °C, and the mixture was warmed to 25 °C and stirred for 15.5 h. The reaction mixture was diluted with saturated aqueous ammonium chloride solution (10 mL), and the resulting mixture was extracted with ethyl acetate (200 mL). The organic extract was washed with brine (3 x 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/0 to 5/1) to afford the title compound (1.1 g, crude) as a yellow oil. LC/MS (ESI) *m/z*: 516.4 $[M+H]^+$.

Step 7: Preparation of 1-(2,6-dibenzyloxy-3-pyridyl)-5-[4-(dimethoxymethyl)-1-piperidyl]-3-methyl-benzimidazol-2-one



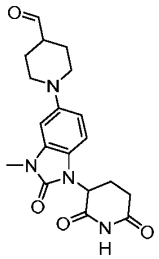
To a solution of 5-bromo-1-(2,6-dibenzyloxy-3-pyridyl)-3-methyl-benzimidazol-2-one (1 g, 2 mmol) and 4-(dimethoxymethyl) piperidine (308 mg, 1.9 mmol) in 1,4-dioxane (15 mL) were added XPhos Pd G2 (152 mg, 0.2 mmol) and cesium carbonate (1.89 g, 5.8 mmol), and the mixture was stirred at 100 °C for 16 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/1 then 1/2) to afford the title compound (760 mg, 66%) as a brown oil. LC/MS (ESI) *m/z*: 595.4 $[M+H]^+$.

Step 8: Preparation of 3-[5-[4-(dimethoxymethyl)-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



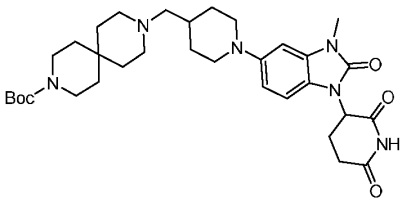
To a solution of 1-(2,6-dibenzyloxy-3-pyridyl)-5-[4-(dimethoxymethyl)-1-piperidyl]-3-methyl-benzimidazol-2-one (1.2 g, 2 mmol) in tetrahydrofuran (10 mL) was added 10% palladium on carbon (300 mg) under nitrogen atmosphere, and the suspension was degassed under vacuum and purged with hydrogen several times. The reaction mixture was stirred under hydrogen (50 psi) at 50 °C for 16 h. The mixture was filtered and concentrated under reduced pressure to afford the title compound (430 mg, 51%) as a brown oil. LC/MS (ESI) *m/z*: 417.3 $[M+H]^+$.

Step 9: Preparation of 1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde



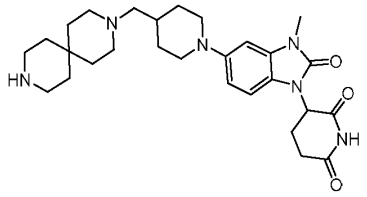
To a solution of 3-[5-[4-(dimethoxymethyl)-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (430 mg, 1 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (0.1 mL, 1 mmol), and the mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated under reduced pressure. The residue was triturated with ethyl acetate/methyl *tert*-butyl ether (1/10, 60 mL) to afford the title compound (380 mg, 99%) as a green oil. LC/MS (ESI) *m/z*: 389.3 $[M+H_3O]^+$.

Step 10: Preparation of *tert*-butyl 9-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate



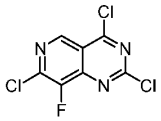
To a solution of 1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (250 mg, 0.7 mmol) and *tert*-butyl 3,9-diazaspiro[5.5]undecane- 3-carboxylate (189 mg, 0.7 mmol) in dichloromethane (5 mL) and dimethyl sulfoxide (2 mL) were added acetic acid (41 mg, 0.7 mmol) and sodium triacetoxyborohydride (286 mg, 1.4 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with water (15 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (280 mg, 68%) as a green oil. LC/MS (ESI) *m/z*: 609.4 $[M+H]^+$.

Step 11: Preparation of 3-[5-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



To a solution of *tert*-butyl 9-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate (410 mg, 0.7 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (3.0 mL, 40 mmol) at 25 °C, and the reaction mixture was stirred for 1 h. The mixture was concentrated under reduced pressure, and the residue was triturated with ethyl acetate/methyl tert-butyl ether (1/10, 50 mL) to afford the title compound (490 mg, crude, di-trifluoroacetate salt) as a light yellow solid. LC/MS (ESI) *m/z*: 509.3 $[M+H]^+$.

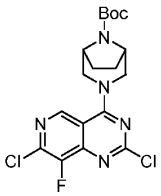
Step 12: Preparation of 2,4,7-trichloro-8-fluoro-pyrido[4,3-d]pyrimidine



To a mixture of phosphorus oxychloride (240 mL, 2.6 mol) in *N,N*-diisopropylethylamine (100 mL) was added 7-chloro-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol (24.0 g, 111 mmol) at 0 °C, and the mixture was stirred for 2 h at 90 °C. The reaction mixture was concentrated, and the residue was diluted with water (500 mL) and extracted with ethyl acetate (3 x 500 mL). The

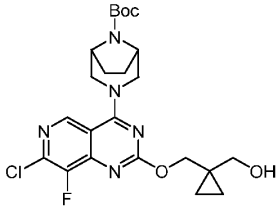
combined organic extract was washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1 then 3/1) to afford the title compound (14 g, 49%) as a yellow solid.

Step 13: Preparation of *tert*-butyl 3-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 2,4,7-trichloro-8-fluoro-pyrido[4,3-d]pyrimidine (11 g, 43 mmol) and *N,N*-diisopropylethylamine (22.8 mL, 131 mmol) in *N,N*-dimethylformamide (100 mL) at -60 °C was added *tert*-butyl (1S,5R)-3,8-diazabicyclo[3.2.1] octane-8-carboxylate (8.32 g, 39 mmol), and the reaction mixture was stirred for -60 °C for 1 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure to afford the title compound (14 g, 81%) as a yellow oil. LC/MS (ESI) *m/z*: 428.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 4.65 – 4.35 (m, 4H), 3.90 – 3.55 (m, 2H), 2.05 – 1.90 (m, 2H), 1.72 – 1.60 (m, 2H), 1.53 (s, 9H).

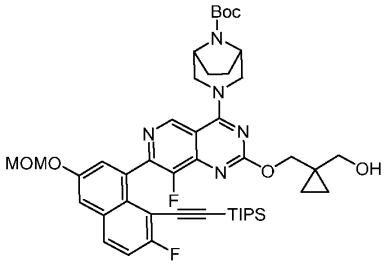
Step 14: Preparation of *tert*-butyl 3-[7-chloro-8-fluoro-2-[[1-(hydroxymethyl)cyclopropyl]methoxy] pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of [1-(hydroxymethyl)cyclopropyl]methanol (9.54 g, 93 mmol) in tetrahydrofuran (200 mL) was added lithium tert-butoxide (1 M, 70 mL), and the resulting mixture was stirred for 0.5 h. *tert*-Butyl 3-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (20 g, 47 mmol) in tetrahydrofuran (200 mL) was then added dropwise at 20 °C, and the reaction mixture was stirred at 50 °C for 1.5 h. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (petroleum ether/dichloromethane = 5/1 then petroleum ether/dichloromethane/ethyl acetate = 5/1/5) to afford the title compound (9.54 g, 41%) as a white solid. LC/MS (ESI) *m/z*: 494.3 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 4.63

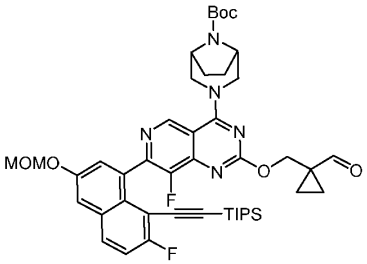
(s, 1H), 4.47 (d, *J* = 12.4 Hz, 2H), 4.32 - 4.20 (m, 4H), 3.61 (d, *J* = 12.4 Hz, 2H), 3.40 - 3.27 (m, 2H), 1.78 (d, *J* = 4.0 Hz, 2H), 1.62 (d, *J* = 7.6 Hz, 2H), 1.46 (s, 9H), 0.60 - 0.42 (m, 4H).

Step 15: Preparation of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropyl silylethynyl)-1-naphthyl]-2-[[1-(hydroxymethyl)cyclopropyl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



A mixture of *tert*-butyl 3-[7-chloro-8-fluoro-2-[[1-(hydroxymethyl)cyclopropyl]methoxy] pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (9.54 g, 19 mmol), 2-[2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl-triisopropyl-silane (10.9 g, 21 mmol), potassium phosphate (12.3 g, 58 mmol), and methanesulfonato(diadamantyl-n-butylphosphino)-2'-amino-1,1'-biphenyl-2-yl)palladium(II) (1.41 g, 2 mmol) in 1,4-dioxane (180 mL) and water (30 mL) was degassed and purged with nitrogen (3X), then stirred at 90 °C for 12 h under nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (0 to 50% ethyl acetate/petroleum ether) to afford the title compound (15.88 g, 97%) as a yellow solid. LC/MS (ESI) *m/z*: 844.7 $[M+H]^+$.

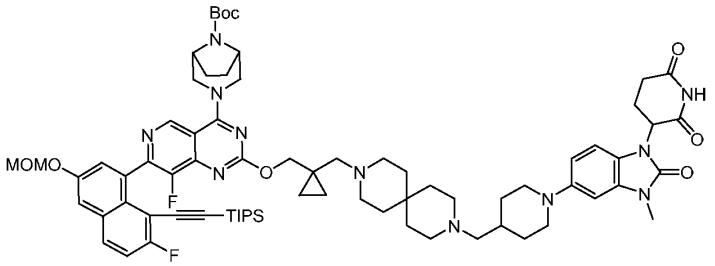
Step 16: Preparation of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-[(1-formylcyclopropyl)methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropyl silylethynyl)-1-naphthyl]-2-[[1-(hydroxymethyl)cyclopropyl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (5 g, 6 mmol) in dichloromethane (100 mL) was added Dess-Martin periodinane (7.0 mL, 12 mmol), and the mixture was stirred at 20 °C for 12

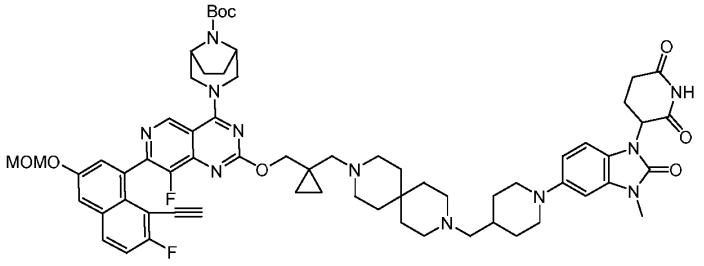
h. The mixture was poured into a mixture of saturated sodium thiosulfate solution (50 mL), sodium bicarbonate solution (50 mL), and water (50 mL). After stirring for 5 minutes, the aqueous phase was extracted with dichloromethane (2 x 50 mL). The combined organic extract was washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 10/1 then 2/1) to afford the title compound (3.51 g, 70%) as a yellow solid. LC/MS (ESI) *m/z*: 842.4 $[M+H]^+$.

Step 17: Preparation of *tert*-butyl 3-[2-[[1-[[9-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-3-yl]methyl]cyclopropyl]methoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



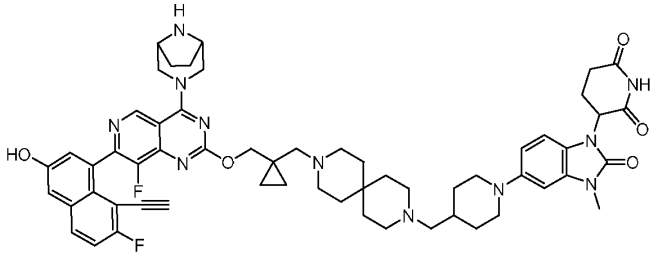
To a solution of 3-[5-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (648 mg, 0.9 mmol, 2 trifluoroacetate) in dichloromethane (7 mL) and dimethyl sulfoxide (7 mL) was added *N,N*-diisopropylethylamine (0.8 mL, 4 mmol), and the resulting mixture was stirred at 25 °C for 0.5 h. *tert*-Butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-[(1-formylcyclopropyl)methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (741 mg, 0.9 mmol), acetic acid (0.5 mL, 9 mmol), and 2-methylpyridine borane (470 mg, 4 mmol) were then added, and the reaction mixture was stirred at 40 °C for 12 h. The reaction was diluted with water (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extract was washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 1:0 then 10:1) to afford the title compound (334 mg, 28%) as a yellow oil. LC/MS (ESI) *m/z*: 1335.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.16 (s, 1H), 8.10 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.74 (d, *J* = 2.8 Hz, 1H), 7.56 (t, *J* = 8.8 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.82 (s, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 5.75 (s, 2H), 5.36 (s, 4H), 4.38 - 4.16 (m, 6H), 3.81 - 3.69 (m, 1H), 3.66 - 3.51 (m, 3H), 3.50 - 3.39 (m, 5H), 3.17 (d, *J* = 5.2 Hz, 5H), 3.01 - 2.87 (m, 3H), 2.74 - 2.56 (m, 6H), 2.44 - 2.32 (m, 5H), 1.93 - 1.85 (m, 5H), 1.70 - 1.60 (m, 4H), 1.46 (s, 9H), 1.40 - 1.28 (m, 4H), 0.81 (t, J = 7.6 Hz, 18H), 0.64 (s, 2H), 0.52 - 0.41 (m, 5H).

Step 18: Preparation of *tert*-butyl 3-[2-[[1-[[9-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-3-yl]methyl]cyclopropyl] methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d] pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[[1-[[9-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-3-yl]methyl]cyclopropyl] methoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl] pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (334 mg, 0.3 mmol) in *N,N*-dimethylformamide (5 mL) was added cesium fluoride (1.14 g, 7.5 mmol), and the reaction mixture was stirred at 25 °C for 1 h. The reaction was poured into ice-water (40 mL), and the aqueous phase was extracted with tetrahydrofuran/ethyl acetate (1/1, 2 x 20 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (2 x 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (256 mg, 86%) as a yellow solid. LC/MS (ESI) *m/z*: 1178.8 $[M+H]^+$.

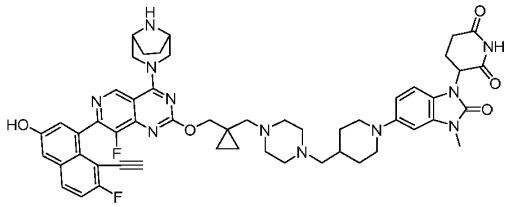
Step 19: Preparation of 3-[5-[4-[[3-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl] piperidine-2,6-dione



To a solution of *tert*-butyl 3-[2-[[1-[[9-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-3-yl]methyl]cyclopropyl] methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d] pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (256 mg, 0.2 mmol) in dichloromethane (3 mL) was added 4 M HCl in 1,4-dioxane (3 mL), and the reaction mixture was stirred at 25 °C for

15 min. The reaction mixture was suspended in petroleum ether (20 mL) and filtered, the filtered cake was dissolved with dimethyl sulfoxide (3 mL) and basified with *N,N*-diisopropylethylamine. The residue was purified by prep-HPLC (1% to 28% acetonitrile in water (formic acid) over 10 min) to afford the title compound (31.9 mg, 12%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1034.6 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.04 (s, 1H), 8.20 (s, 2H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.51 - 7.35 (m, 2H), 7.16 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.62 (dd, J = 2.0, 8.8 Hz, 1H), 5.28 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.36 - 4.22 (m, 4H), 3.95 - 3.90 (m, 2H), 3.56 (d, J = 12.4 Hz, 6H), 3.29 (s, 4H), 2.89 (s, 1H), 2.74 - 2.54 (m, 4H), 2.41 - 2.30 (m, 9H), 2.19 (d, J = 6.8 Hz, 2H), 2.02 - 1.94 (m, 1H), 1.82 - 1.67 (m, 6H), 1.62 (s, 1H), 1.38 (s, 7H), 1.28 - 1.16 (m, 3H), 0.64 (s, 2H), 0.42 (s, 2H).

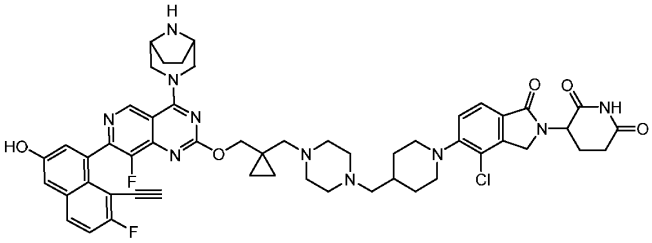
Example 30: Synthesis of 3-{5-[4-({4-[(1-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}cyclopropyl)methyl]piperazin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 188**)



The title compound was made in an analogous manner to 3-[5-[4-[[3-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl] piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 966.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.04 (s, 1H), 8.21 (s, 2H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.61 (dd, *J* = 2.0, 8.8 Hz, 1H), 5.27 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.53 (d, *J* = 12.4 Hz, 1H), 4.37 - 4.27 (m, 3H), 3.93 (s, 1H), 3.69 (s, 5H), 3.61 (d, *J* = 13.2 Hz, 4H), 3.55 (d, *J* = 11.6 Hz, 4H), 3.29 (s, 3H), 2.91 - 2.83 (m, 1H), 2.70 - 2.64 (m, 1H), 2.62 (d, *J* = 2.4 Hz, 1H), 2.61 - 2.55 (m, 2H), 2.36 - 2.26 (m, 5H), 2.12 (d, *J* = 7.2 Hz, 2H), 2.02 - 1.94 (m, 1H), 1.81 - 1.68 (m, 6H), 1.65 - 1.53 (m, 1H), 1.27 - 1.15 (m, 2H), 0.64 (s, 2H), 0.41 (s, 2H).

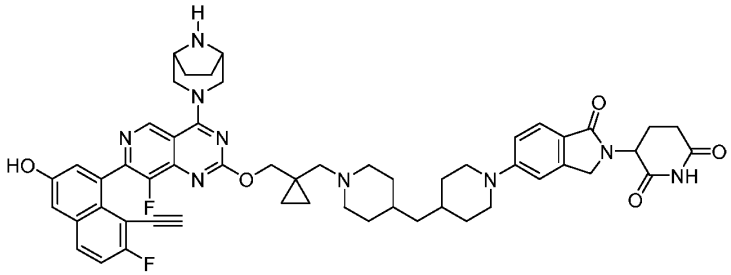
Example 31: Synthesis of 3-{4-chloro-5-[4-({4-[(1-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-

yl)oxy]methyl}cyclopropyl)methyl]piperazin-1-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 186**)



The title compound was made in an analogous manner to 3-[5-[4-[[3-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl] piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 985.6 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.03 (s, 1H), 8.21 (s, 1H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.8 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.29 - 7.21 (m, 1H), 7.17 (d, J = 2.4 Hz, 1H), 5.09 (dd, J = 5.2, 13.6 Hz, 1H), 4.56 - 4.47 (m, 1H), 4.45 - 4.36 (m, 1H), 4.34 - 4.20 (m, 4H), 3.94 (s, 1H), 3.71 - 3.54 (m, 6H), 3.39 - 3.34 (m, 2H), 2.94 - 2.85 (m, 1H), 2.75 2.65 (m, 2H), 2.62 - 2.56 (m, 1H), 2.47 - 2.22 (m, 10H), 2.18 - 2.11 (m, 2H), 2.04 - 1.93 (m, 1H), 1.84 - 1.75 (m, 2H), 1.74 - 1.56 (m, 5H), 1.36 - 1.18 (m, 2H), 0.69 - 0.58 (m, 2H), 0.47 - 0.35 (m, 2H).

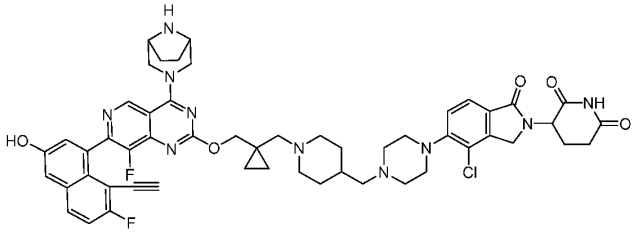
Example 32: Synthesis of 3-{5-[4-({1-[(1-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}cyclopropyl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 99**)



The title compound was made in an analogous manner to 3-[5-[4-[[3-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl] piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 950.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD-d_4) δ 9.01 (s, 1H), 7.89-7.83 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.36-7.29 (m, 2H), 7.21 (d, J = 2.4 Hz, 1H), 7.07-7.02 (m, 2H),

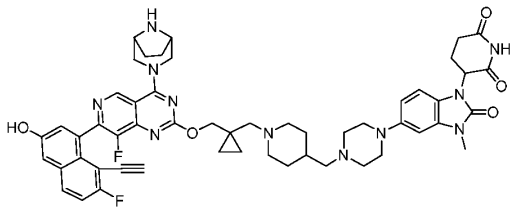
5.13-5.07 (m, 1H), 4.63 (br t, J = 13.6 Hz, 3H), 4.51-4.47 (m, 1H), 4.40-4.32 (m, 3H), 3.88 (br d, J = 11.6 Hz, 2H), 3.75-3.65 (m, 4H), 3.37 (s, 1H), 3.23-3.13 (m, 2H), 2.91-2.74 (m, 4H), 2.62-2.39 (m, 3H), 2.18-2.07 (m, 2H), 1.90-1.69 (m, 8H), 1.64-1.53 (m, 1H), 1.51-1.40 (m, 1H), 1.29-1.14 (m, 6H), 0.80-0.71 (m, 2H), 0.56 (br s, 2H).

Example 33: Synthesis of 3-{4-chloro-5-[4-({1-[(1-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}cyclopropyl)methyl]piperidin-4-yl}methyl)piperazin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 187**)



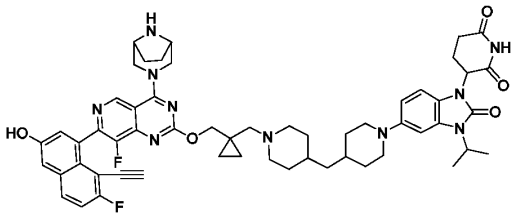
The title compound was made in an analogous manner to 3-[5-[4-[[3-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl] piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 985.6 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.04 (s, 1H), 8.19 (s, 2H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 5.09 (dd, *J* = 5.2, 13.2 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.41 (d, *J* = 17.6 Hz, 1H), 4.35 - 4.26 (m, 4H), 3.93 (s, 1H), 3.70 - 3.65 (m, 4H), 3.62 - 3.57 (m, 2H), 3.07 (s, 4H), 3.00 - 2.85 (m, 4H), 2.63 - 2.56 (m, 1H), 2.48 - 2.41 (m, 2H), 2.36 - 2.29 (m, 2H), 2.16 (d, *J* = 7.2 Hz, 2H), 2.03 - 1.95 (m, 1H), 1.89 (t, *J* = 10.0 Hz, 2H), 1.77 - 1.63 (m, 6H), 1.56 - 1.43 (m, 1H), 1.08 (d, *J* = 12.8 Hz, 2H), 0.65 (s, 2H), 0.42 (s, 2H).

Example 34: Synthesis of 3-{5-[4-({1-[(1-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}cyclopropyl)methyl]piperidin-4-yl}methyl)piperazin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 189**)



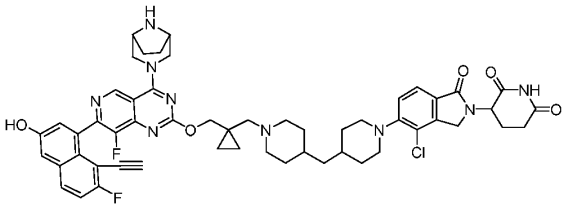
The title compound was made in an analogous manner to 3-[5-[4-[[3-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl] piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 966.6 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.03 (s, 1H), 8.20 (s, 1H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.46 (t, *J* = 9.6 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 6.96 - 6.90 (m, 1H), 6.83 - 6.79 (m, 1H), 6.60 (dd, *J* = 1.6, 8.4 Hz, 1H), 5.28 (dd, J = 5.2, 12.4 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.35 - 4.23 (m, 3H), 3.93 (s, 1H), 3.70 - 3.58 (m, 5H), 3.29 (s, 3H), 3.08 - 3.01 (m, 4H), 2.99 - 2.92 (m, 2H), 2.90 - 2.84 (m, 1H), 2.72 - 2.57 (m, 2H), 2.47 - 2.43 (m, 4H), 2.34 - 2.29 (m, 2H), 2.13 (d, J = 6.8 Hz, 2H), 2.01 - 1.94 (m, 1H), 1.92 - 1.84 (m, 2H), 1.74 - 1.62 (m, 6H), 1.52 - 1.44 (m, 1H), 1.12 - 1.00 (m, 2H), 0.64 (s, 2H), 0.41 (s, 2H).

Example 35: Synthesis of 3-{5-[4-({1-[(1-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}cyclopropyl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 191**)



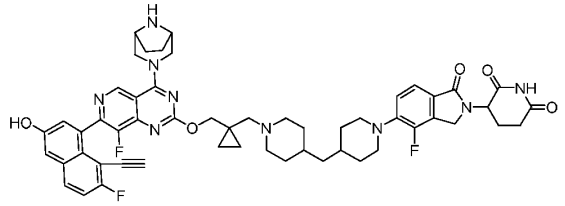
The title compound was made in an analogous manner to 3-[5-[4-[[3-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl] piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 993.7 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 10.24 (s, 1H), 9.13 (s, 1H), 8.14 (s, 1H), 8.03 – 7.95 (m, 1H), 7.47 (t, *J* = 8.8 Hz, 1H), 7.42 - 7.39 (m, 1H), 7.20 - 7.15 (m, 1H), 6.95 - 6.84 (m, 2H), 6.64 – 6.57 (m, 1H), 5.32- 5.21 (m, 1H), 4.71 - 4.50 (m, 3H), 4.42 - 4.30 (m, 2H), 4.23 – 4.15 (m, 2H), 3.90 (s, 1H), 3.89 – 3.82 (m, 2H), 3.61 – 3.45 (m, 4H), 2.94 – 2.83 (m, 2H), 2.70 – 2.55 (m, 5H), 2.04 – 1.90 (m, 6H), 1.88 – 1.79 (m, 2H), 1.73 – 1.53 (m, 4H), 1.44 (d, J = 6.8 Hz, 9H), 1.27 – 1.07 (m, 5H), 0.87 – 0.63 (m, 4H).

Example 36: Synthesis of 3-{4-chloro-5-[4-({1-[(1-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}cyclopropyl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 190**)



The title compound was made in an analogous manner to 3-[5-[4-[[3-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl] piperidine-2,6-dione. (yellow solid). LC/MS (ESI) *m/z*: 984.6 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 10.56 - 9.64 (m, 1H), 9.07 (s, 1H), 8.15 (s, 1H), 7.98 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 5.09 (dd, *J* = 5.2, 13.2 Hz, 1H), 4.59 (d, *J* = 12.4 Hz, 1H), 4.45 - 4.36 (m, 2H), 4.33 - 4.20 (m, 3H), 3.93 (s, 3H), 3.76 (dd, *J* = 13.2, 17.6 Hz, 2H), 3.13 - 3.02 (m, 3H), 2.97 - 2.83 (m, 2H), 2.74 - 2.66 (m, 2H), 2.63 - 2.56 (m, 1H), 2.49 - 2.42 (m, 3H), 2.13 - 1.94 (m, 3H), 1.85 (s, 4H), 1.76 - 1.62 (m, 4H), 1.55 - 1.37 (m, 2H), 1.37 - 1.21 (m, 3H), 1.20 - 1.06 (m, 4H), 0.69 (s, 2H), 0.49 (s, 2H).

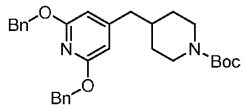
Example 37: Synthesis of 3-{5-[4-({1-[(1-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}cyclopropyl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 192**)



The title compound was made in an analogous manner to 3-[5-[4-[[3-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl] piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 968.7 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.04 (s, 1H), 8.19 (s, 2H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.49 - 7.42 (m, 2H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.19 - 7.10 (m, 2H), 5.07 (dd, *J* = 5.2, 13.2 Hz, 1H), 4.54 - 4.44 (m, 2H), 4.34 - 4.26 (m, 4H), 3.95 - 3.91 (m, 1H), 3.66 (s, 3H), 3.59 (d, *J* = 12.4 Hz, 2H), 3.45 (s, 3H), 3.00 - 2.88 (m, 4H), 2.77 - 2.70 (m, 2H), 2.32 (s, 2H), 2.00 - 1.93 (m, 1H), 1.91 - 1.83 (m, 2H), 1.76 - 1.67 (m, 6H), 1.60 (d, J = 10.8 Hz, 2H), 1.51 - 1.44 (m, 1H), 1.36 - 1.18 (m, 4H), 1.16 - 1.04 (m, 4H), 0.67 - 0.59 (m, 2H), 0.41 (s, 2H).

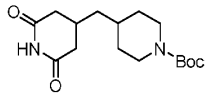
Example 38: Synthesis of 3-[5-[4-[[4-[[1-[(1S)-2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxy-1-methyl-ethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 194**)

Step 1: Preparation of *tert*-butyl 4-[(2,6-dibenzyloxy-4-pyridyl)methyl]piperidine-1-carboxylate



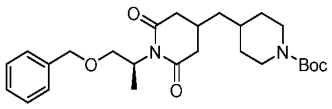
A mixture of *tert*-butyl 4-methylenepiperidine-1-carboxylate (12.5 g, 63 mmol) and 9-borabicyclo[3.3.1]nonane (0.5 M, 189 mL) was stirred at 85 °C for 2 h. The mixture was cooled to 25 °C, and 2,6-dibenzyloxy-4-iodo-pyridine (34.0 g, 81 mmol), potassium carbonate (26.2 g, 189 mmol), and $Pd(dppf)Cl_2$ (5.16 g, 6 mmol) in water (250 mL) and THF (500 mL) were then added. The resulting mixture was stirred at 75 °C for 15 h under nitrogen atmosphere. The reaction was cooled to room temperature and extracted with ethyl acetate (3 x 200 mL). The combined organic extract was washed with brine (3 x 500 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was suspended in ethyl acetate/petroleum ether (400 mL, V/V = 1/1), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0-8% of THF in petroleum ether) to afford the title compound (61.7 g, 100%) as a black brown oil. LC/MS (ESI) *m/z*: 489.4 $[M+H]^+$.

Step 2: Preparation of *tert*-butyl 4-[(2,6-dioxo-4-piperidyl)methyl]piperidine-1-carboxylate



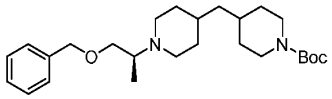
To tert-butyl 4-[(2,6-dibenzyloxy-4-pyridyl)methyl]piperidine-1-carboxylate (57.7 g, 118 mmol) in ethyl acetate (2000 mL) was added 10% palladium on carbon (12.0 g, 11 mmol) under argon atmosphere, and the suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (30 psi) at 50 °C for 16 h. The mixture was filtered, washed with ethyl acetate, and the filtrate was concentrated under reduced pressure to afford the title compound (36.6 g, crude) as a white solid. LC/MS (ESI) *m/z*: 333.1 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 4.10 (m, 2H), 2.75 - 2.62 (m, 4H), 2.30 - 2.24 (m, 2H), 1.92 - 1.81 (m, 1H), 1.62 (br d, *J* = 12.4 Hz, 3H), 1.45 (s, 9H), 1.33 (br t, *J* = 6.4 Hz, 2H), 1.09 (br dd, *J* = 4.0, 12.0 Hz, 2H).

Step 3: Preparation of *tert*-butyl 4-[[1-[(1S)-2-benzyloxy-1-methyl-ethyl]-2,6-dioxo-4-piperidyl]methyl]piperidine-1-carboxylate



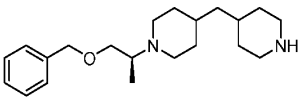
To a mixture of *tert*-butyl 4-[(2,6-dioxo-4-piperidyl)methyl]piperidine-1-carboxylate (13.6 g, 44 mmol), (2R)-1-benzyloxypropan-2-ol (9.47 g, 57 mmol), and PPh_3 (17.24 g, 66 mmol) in THF (200 mL) was added DIAD (12.74 mL, 66 mmol) at 0 °C under nitrogen atmosphere, and the mixture was stirred at 70 °C for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0-10% THF in petroleum ether over 40 min) to afford the title compound (18.5 g, 92%) as a colorless oil. LC/MS (ESI) *m/z*: 459.1 $[M+H]^+$.

Step 4: Preparation of *tert*-butyl 4-[[1-[(1S)-2-benzyloxy-1-methyl-ethyl]-4-piperidyl]methyl]piperidine-1-carboxylate



To *tert*-butyl 4-[[1-[(1S)-2-benzyloxy-1-methyl-ethyl]-2,6-dioxo-4-piperidyl]methyl]piperidine-1-carboxylate (8.0 g, 17 mmol) in THF (100 mL) at 0 °C was added BH_3-Me_2S (10 M, 17.4 mL) dropwise, and the resulting suspension was stirred at 70 °C for 1 h. The reaction mixture was cooled to room temperature and quenched with water (25 mL) at 0 °C. The resulting mixture was extracted with ethyl acetate (3 x 50 mL), and the combined organic extract was washed with brine (2 x 50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved DMF (60 mL), Oxone (21.4 g, 35 mmol) was added, and the resulting suspension was stirred at 25 °C for 3 h. The mixture was filtered and washed with ethyl acetate (100 mL). The filtrate was diluted with water (150 mL) and adjusted the pH to 8 by adding solid sodium bicarbonate. The mixture was extracted with ethyl acetate (3 x 100 mL), and the combined organic extract was washed with saturated sodium sulfite solution (2 x 50 mL), water (3 x 50 mL), and brine (100 mL), then dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 4% methanol in dichloromethane) to afford the title compound (2.8 g, 37%) as a colorless oil. LC/MS (ESI) *m/z*: 431.4 $[M+H]^+$.

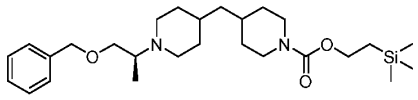
Step 5: Preparation of 1-[(1S)-2-benzyloxy-1-methyl-ethyl]-4-(4-piperidylmethyl)piperidine



To a mixture of *tert*-butyl 4-[[1-[(1S)-2-benzyloxy-1-methyl-ethyl]-4-piperidyl]methyl]piperidine-1-carboxylate (2.8 g, 6 mmol) in dichloromethane (20 mL) was added 4 M HCl in 1,4-dioxane (16 mL), and the reaction mixture was stirred at 20 °C for 0.5 h.

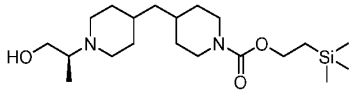
The mixture was concentrated under reduced pressure to afford the title compound (2.39 g, crude, HCl salt) as a colorless oil. LC/MS (ESI) *m/z*: 331.3 $[M+H]^+$.

Step 6: Preparation of 2-trimethylsilylethyl 4-[[1-[(1S)-2-benzyloxy-1-methyl-ethyl]-4-piperidyl]methyl]piperidine-1-carboxylate



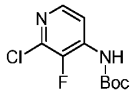
To a solution of 1-[(1S)-2-benzyloxy-1-methyl-ethyl]-4-(4-piperidylmethyl)piperidine (2.39 g, 6 mmol, HCl) in dichloromethane (30 mL) at 0 °C were added Et_3N (9 mL, 65 mmol) and Teoc-OSu (1.69 g, 6 mmol), and the reaction mixture was allowed to warmed to 20 °C and stirred for 16 h. The mixture was diluted with water (30 mL) and extracted with dichloromethane (2 x 30 mL). The combined organic extract was washed with saturated sodium bicarbonate solution (10 mL) followed by brine (10 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 3% methanol in dichloromethane) to afford the title compound (2.6 g, 84%) as a yellow oil. LC/MS (ESI) *m/z*: 475.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.28 (m, 5H), 4.53 (s, 2H), 4.21 - 4.06 (m, 4H), 3.58 (dd, *J* = 5.6, 9.6 Hz, 1H), 3.38 (br d, *J* = 2.4 Hz, 1H), 2.93 - 2.79 (m, 3H), 2.76 - 2.66 (m, 2H), 2.26 (br t, *J* = 10.8 Hz, 2H), 1.64 (br d, *J* = 12.4 Hz, 4H), 1.50 (br s, 1H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.17 - 1.12 (m, 2H), 1.10 - 0.98 (m, 7H), 0.07 - 0.02 (m, 9H).

Step 7: Preparation of 2-trimethylsilylethyl 4-[[1-[(1S)-2-hydroxy-1-methyl-ethyl]-4-piperidyl]methyl]piperidine-1-carboxylate



To a solution of 2-trimethylsilylethyl 4-[[1-[(1S)-2-benzyloxy-1-methyl-ethyl]-4-piperidyl]methyl]piperidine-1-carboxylate (2.6 g, 5.5 mmol) in isopropanol (500 mL) was added 10% $Pd(OH)_2$ on carbon (1 g). The mixture was degassed under vacuum and purged with hydrogen several times, then stirred at 60 °C under hydrogen (50 psi) for 16 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford the title compound (1.95 g, 93%) as a colorless oil. LC/MS (ESI) *m/z*: 385.2 $[M+H]^+$.

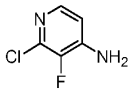
Step 8: Preparation of tert-butyl N-(2-chloro-3-fluoro-4-pyridyl)carbamate



To a solution of 2-chloro-3-fluoro-pyridine-4-carboxylic acid (40.0 g, 228 mmol) in toluene (200 mL) and tert-butyl alcohol (262 mL, 2.73 mol) were added 4A molecular sieves (68

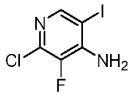
g) and triethylamine (95.0 mL, 684 mmol), and the reaction mixture was stirred at 110 °C under nitrogen for 30 min. The reaction mixture was cooled to 20 °C, diphenylphosporyl azide (DPPA) (74.0 mL, 342 mmol) was added, and the resulting mixture was stirred at 110 °C under nitrogen for 16 h. The reaction mixture was filtered, and the filtrate was poured into water (300 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extract was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 8% ethyl acetate in petroleum ether over 15 min) to afford the title compound (108.8 g, 93%) as a yellow oil. LC/MS (ESI) *m/z*: 247.0 $[M+H]^+$.

Step 9: Preparation of 2-chloro-3-fluoro-pyridin-4-amine



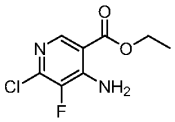
To a solution of tert-butyl N-(2-chloro-3-fluoro-4-pyridyl)carbamate (108.8 g, 422 mmol) in acetonitrile (120 mL) was added 4 M HCl in 1,4-dioxane (250 mL), and the mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with water (100 mL) and saturated sodium bicarbonate solution to adjust the pH to 8-9. The mixture was then extracted with ethyl acetate (2 x 200 mL), and the combined organic extract was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford the title compound (58.6 g, 85%) as a white solid. LC/MS (ESI) *m/z*: 147.2 $[M+H]^+$.

Step 10: Preparation of 2-chloro-3-fluoro-5-iodo-pyridin-4-amine



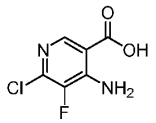
To a solution of 2-chloro-3-fluoro-pyridin-4-amine (58.6 g, 376 mmol) in acetonitrile (800 mL) was added NIS (108 g, 480 mmol) and TsOH (3.4 g, 20 mmol), and the mixture was stirred at 70 °C for 16 h under nitrogen atmosphere. The reaction mixture was diluted with saturated $Na_2S_2O_3$ solution (800 mL) and extracted with ethyl acetate (3 x 500 mL). The combined organic extract was washed with saturated sodium bicarbonate solution (3 x 500 mL) followed by brine (3 x 500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (110 g, 99%) as a yellow solid. LC/MS (ESI) *m/z*: 272.9 $[M+H]^+$.

Step 11: Preparation of ethyl 4-amino-6-chloro-5-fluoro-pyridine-3-carboxylate



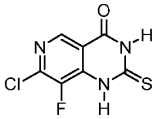
To a solution of 2-chloro-3-fluoro-5-iodo-pyridin-4-amine (108.8 g, 395 mmol) in ethanol (1000 mL) were added triethylamine (200 mL, 1.44 mol) and $Pd(PPh_3)_2Cl_2$ (14.0 g, 20 mmol). The resulting mixture was degassed under vacuum and purged with CO several times, then stirred at 80 °C under CO (15 psi) for 48 h. The reaction mixture was concentrated under reduced pressure and the suspension was filtered, washing with MTBE (2 x 300 mL). The filtrate was concentrated under reduced pressure to afford ethyl 4-amino-6-chloro-5-fluoro-pyridine-3-carboxylate (63.5 g, 60%) as a gray solid. LC/MS (ESI) *m/z*: 219.0 $[M+H]^+$.

Step 12: Preparation of 4-amino-6-chloro-5-fluoro-pyridine-3-carboxylic acid



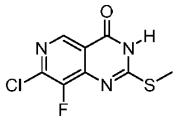
To a stirred solution of ethyl 4-amino-6-chloro-5-fluoro-pyridine-3-carboxylate (20.0 g, 91 mmol) in THF (180 mL) was added sodium hydroxide (14.6 g, 366 mmol) in water (90 mL), and the reaction mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with 2 N aqueous HCl solution to adjust the pH to 2. The resultant suspension was filtered, and the filter cake was dissolved in ethyl acetate/THF (300 mL, v/v= 2/1), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (17.1 g, crude) as a gray solid. LC/MS (ESI) *m/z*: 190.9 $[M+H]^+$.

Step 13: Preparation of 7-chloro-8-fluoro-2-thioxo-1H-pyrido[4,3-d]pyrimidin-4-one



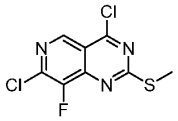
A mixture of 4-amino-6-chloro-5-fluoro-pyridine-3-carboxylic acid (17.1 g, 90 mmol) in $POCl_3$ (167 mL, 1.8 mol) was stirred at 90 °C for 2 h. The mixture was concentrated under reduced pressure, and the resulting residue was dissolved in THF (150 mL). NH_4SCN (13.7 mL, 179 mmol) in THF (150 mL) was then added, and the reaction mixture was stirred at 35 °C under nitrogen for 24 h. The reaction was diluted with water (400 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extract was washed with brine (3 x 300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with ethyl acetate/petroleum ether (50 mL, v/v = 1/1) to afford the title compound (12.14 g, 58%) as a yellow solid. LC/MS (ESI) *m/z*: 231.8 $[M+H]^+$.

Step 14: Preparation of 7-chloro-8-fluoro-2-methylsulfanyl-3H-pyrido[4,3-d]pyrimidin-4-one



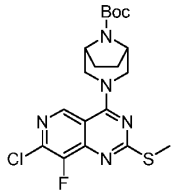
To a solution of 7-chloro-8-fluoro-2-thioxo-1H-pyrido[4,3-d]pyrimidin-4-one (12.14 g, 52 mmol) in DMF (120 mL) was added NaOMe (2.83 g, 52 mmol), and the reaction mixture was stirred at 20 °C under nitrogen for 10 min. CH_3I (3.3 mL, 52 mmol) was then added slowly, and the mixture was stirred at 20 °C under nitrogen for 2 h. The reaction mixture was poured into ice water (200 mL) and filtered, washed the filter cake with ice water (3 x 80 mL) and dried to afford the title compound (11.3 g, 88%) as a yellow solid. LC/MS (ESI) *m/z*: 245.8 $[M+H]^+$.

Step 15: Preparation of 4,7-dichloro-8-fluoro-2-methylsulfanyl-pyrido[4,3-d]pyrimidine



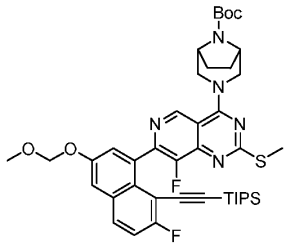
To 7-chloro-8-fluoro-2-methylsulfanyl-3H-pyrido[4,3-d]pyrimidin-4-one (5.0 g, 20 mmol) in toluene (50 mL) were added DIEA (7.1 mL, 41 mmol) and $POCl_3$ (7.6 mL, 81mmol), and the reaction mixture was stirred at 90 °C under nitrogen for 2 h. The reaction mixture was concentrated under reduced pressure to afford the title compound (5.35 g, crude) as a brown solid. LC/MS (ESI) *m/z*: 263.8 $[M+H]^+$.

Step 16: Preparation of tert-butyl 3-(7-chloro-8-fluoro-2-methylsulfanyl-pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



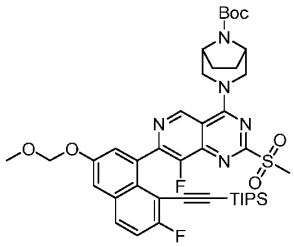
To 4,7-dichloro-8-fluoro-2-methylsulfanyl-pyrido[4,3-d]pyrimidine (5.35 g, 20 mmol) in DCM (50 mL) at -40 °C were added DIEA (17.6 mL, 101 mmol) and tert-butyl (1S,5R)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (4.30 g, 20 mmol) in DCM (50 mL), and the reaction mixture was stirred at -40 °C under nitrogen for 0.5 h. The reaction was poured into water (60 mL) and the mixture was extracted with DCM (2 x 60 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 25% ethyl acetate in petroleum ether) to afford the title compound (7.14 g, 80%) as a yellow solid. LC/MS (ESI) *m/z*: 440.0 $[M+H]^+$.

Step 17: Preparation of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-methylthio-pyrido[4,3-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a mixture of tert-butyl 3-(7-chloro-8-fluoro-2-methylsulfanyl-pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.6 g, 3.6 mmol) and 2-[2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl-triisopropyl-silane (2.2 g, 4.3 mmol) in 1,4-dioxane (60 mL) and water (12 mL) were added K_3PO_4 (2.3 g, 11 mmol) and (2'-amino-[1,1'-biphenyl]-2-yl)palladium(II) bis(1-adamantyl)-butyl-phosphaneylmethanesulfonate (521 mg, 0.7 mmol) under nitrogen atmosphere, and the reaction mixture was stirred at 90 °C for 15 h under nitrogen atmosphere. The reaction was cooled to room temperature and filtered, and the filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by flash column chromatography on silica gel (0 to 6% then up to 10% tetrahydrofuran in petroleum ether) to afford the title compound (2.80 g, 99%) as a yellow solid. LC/MS (ESI) m/z: 790.2 $[M+H]^+$.

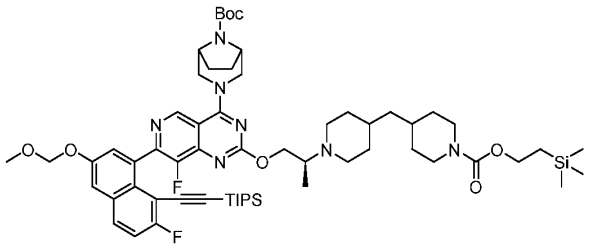
Step 18: Preparation of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-methylsulfonyl-pyrido[4,3-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a mixture of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-methylthio-pyrido[4,3-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.8 g, 3.5 mmol) and 4A molecular sieves (3.0 g) in DMF (30 mL) at 40 °C was added oxone (6.6 g, 11 mmol), and the reaction mixture was stirred at 40 °C for 16 h. The mixture was diluted with ethyl acetate (100 mL) and filtered, and the filtrate was washed with saturated sodium bicarbonate solution (20 mL), water (2 x 30 mL),

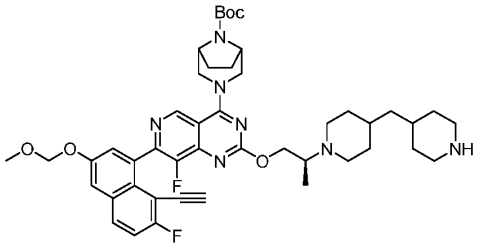
brine (30 mL), then dried over anhydrous sodium sulfate, filtered, and concentrated to afford the title compound (2.5 g, 70%) as a yellow solid. LC/MS (ESI) m/z: 822.1 $[M+H]^+$.

Step 19: Preparation of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-[(2S)-2-[4-[[1-(2-trimethylsilylethoxycarbonyl)-4-piperidyl]methyl]-1-piperidyl]propoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-methylsulfonyl-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2 g, 2 mmol) and 2-trimethylsilylethyl 4-[[1-[(1S)-2-hydroxy-1-methyl-ethyl]-4-piperidyl]methyl]piperidine-1-carboxylate (936 mg, 2.4 mmol) in 1,4-dioxane (30 mL) was added 4A molecular sieves (4 g), and the mixture was stirred at 40 °C for 20 min under nitrogen atmosphere. *t*-BuONa (2 M, 3.0 mL) was then added at 0 °C, and the mixture was stirred at 0 °C for 40 min. The reaction was quenched with saturated ammonium chloride solution (50 mL), filtered, and extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with brine (30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 3% methanol in dichloromethane) to afford the title compound (2.1 g, 77%) as a yellow solid. LC/MS (ESI) *m/z*: 1127.3 $[M+H]^+$.

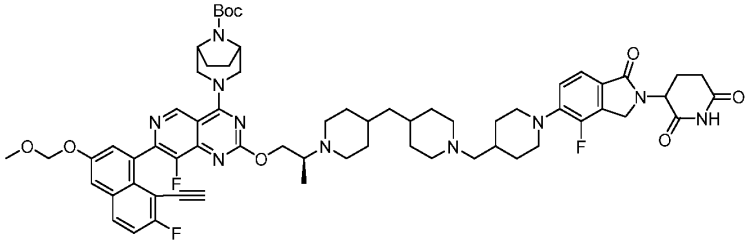
Step 20: Preparation of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[(2S)-2-[4-(4-piperidylmethyl)-1-piperidyl]propoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-[(2S)-2-[4-[[1-(2-trimethylsilylethoxycarbonyl)-4-

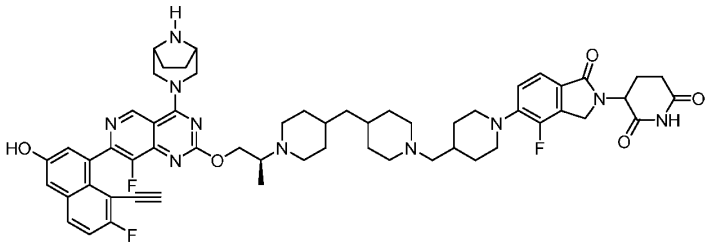
piperidyl]methyl]-1-piperidyl]propoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.1 g, 2 mmol) in DMF (20 mL) was added cesium fluoride (2.8 g, 19 mmol), and the reaction mixture was stirred at 60 °C for 6 h. The mixture was filtered and washed with ethyl acetate (50 mL). The filtrate was diluted with water (50 mL) and extracted with ethyl acetate (2 x 40 mL). The combined organic extract was washed with water (3 x 30 mL) followed by brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (1.5 g, 97%) as a yellow solid. LC/MS (ESI) *m/z*: 826.4 $[M+H]^+$.

Step 21: Preparation of *tert*-butyl 3-[2-[(2S)-2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]propoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



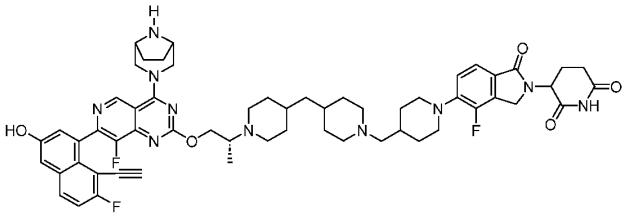
To a solution of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[(2S)-2-[4-(4-piperidylmethyl)-1-piperidyl]propoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 0.6 mmol) and 1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]piperidine-4-carbaldehyde (452 mg, 1.2 mmol) in dichloromethane (5 mL) and isopropanol (5 mL) were added acetic acid (0.14 mL, 2.4 mmol) and 2-methylpyridine borane (259 mg, 2.4 mmol), and the mixture was stirred at 20 °C for 16 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 10% methanol in dichloromethane) to afford the title compound (300 mg, 42%) as a yellow solid. LC/MS (ESI) *m/z*: 1183.8 $[M+H]^+$.

Step 22: Preparation of 3-[5-[4-[[4-[[1-[(1S)-2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxy-1-methyl-ethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione



To *tert*-butyl 3-[2-[(2S)-2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]propoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 0.25 mmol) in dichloromethane (2 mL) was added 4 M HCl in 1,4-dioxane (1.90 mL), and the reaction mixture was stirred at 25 °C for 0.5 h. The mixture was diluted with petroleum ether (40 mL) and filtered, and the filter cake was dissolved in tetrahydrofuran (30 mL). Triethylamine was added to adjust the pH to 9, and the resulting mixture was filtered. The filtrate was concentrated under reduced pressure, and the resulting crude product was purified by prep-HPLC (28% to 68% acetonitrile in water (ammonium bicarbonate) over 32 min) to afford the title compound (106.0 mg, 40%) as a yellow solid. LC/MS (ESI) *m/z*: 1039.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (br s, 1H), 10.15 (br dd, *J* = 2.8, 5.2 Hz, 1H), 9.03 (s, 1H), 7.97 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.52 - 7.35 (m, 3H), 7.20 - 7.09 (m, 2H), 5.06 (dd, *J* = 5.2, 1Step 2: Hz, 1H), 4.53 - 4.42 (m, 3H), 4.30 (br d, *J* = 16.8 Hz, 2H), 4.16 (br dd, *J* = 6.0, 10.8 Hz, 1H), 3.91 (d, *J* = 5.2 Hz, 1H), 3.62 (br d, *J* = 12.4 Hz, 1H), 3.59 - 3.51 (m, 3H), 3.50 - 3.43 (m, 2H), 3.02 - 2.88 (m, 2H), 2.87 - 2.74 (m, 6H), 2.72 (br s, 1H), 2.59 (br d, *J* = 16.8 Hz, 1H), 2.41 (br dd, *J* = 4.8, 1Step 2: Hz, 1H), 2.31 - 2.20 (m, 2H), 2.12 (br d, *J* = 6.8 Hz, 2H), 1.98 (br dd, *J* = 5.6, 11.2 Hz, 1H), 1.85 - 1.74 (m, 4H), 1.65 (br s, 5H), 1.56 (br d, *J* = 10.4 Hz, 4H), 1.31 - 1.20 (m, 4H), 1.11 - 0.95 (m, 9H).

Example 39: Synthesis of 3-[5-(4-{[4-({1-[(2R)-1-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]propan-2-yl]piperidin-4-yl}methyl)piperidin-1-yl]methyl}piperidin-1-yl)-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl]piperidine-2,6-dione (**Compound 185**)

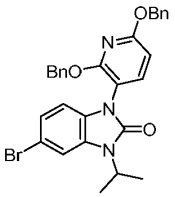


The title compound was made in an analogous manner to 3-[5-[4-[[4-[[1-[(1S)-2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxy-1-methyl-ethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-4-fluoro-

1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (off-white solid). LC/MS (ESI) *m/z*: 1039.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 10.49 - 9.89 (m, 1H), 9.03 (s, 1H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.50 - 7.43 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.21 - 7.09 (m, 2H), 5.06 (dd, J = 5.2, 13.2 Hz, 1H), 4.56 - 4.42 (m, 3H), 4.30 (d, J = 16.4 Hz, 2H), 4.16 (dd, J = 5.6, 10.4 Hz, 1H), 3.91 (d, J = 5.2 Hz, 1H), 3.62 (d, J = 12.0 Hz, 1H), 3.58 - 3.51 (m, 3H), 3.47 (s, 2H), 3.01 - 2.71 (m, 9H), 2.62 - 2.56 (m, 1H), 2.44 - 2.34 (m, 1H), 2.25 (q, J = 10.0 Hz, 2H), 2.12 (d, J = 6.8 Hz, 2H), 2.01 - 1.91 (m, 1H), 1.84 - 1.74 (m, 4H), 1.69 - 1.62 (5H), 1.56 (d, J = 9.2 Hz, 4H), 1.30 - 1.20 (m, 4H), 1.10 - 0.95 (m, 9H).

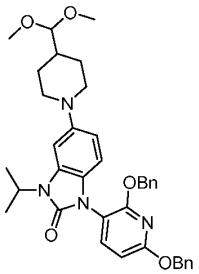
Example 40: Synthesis of 3-[5-[4-[[4-[[1-[(1S)-2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxy-1-methyl-ethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-isopropyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 195**)

Step 1: Preparation of 5-bromo-1-(2,6-dibenzyloxy-3-pyridyl)-3-isopropyl-benzimidazol-2-one



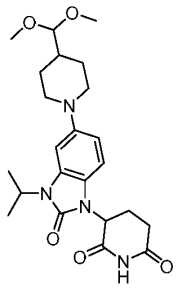
To a solution of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1H-benzimidazol-2-one (1.3 g, 2.6 mmol) and 2-iodopropane (2.6 mL, 26 mmol) in *N,N*-dimethylformamide (15 mL) was added cesium carbonate (2.53 g, 7.8 mmol), and the reaction mixture was stirred at 60 °C for 16 h. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/0 then 5/1) to afford the title compound (1 g, 71 %) as a brown oil. LC/MS (ESI) *m/z*: 544.2 $[M+H]^+$.

Step 2: Preparation of 1-(2,6-dibenzyloxy-3-pyridyl)-5-[4-(dimethoxymethyl)-1-piperidyl]-3-isopropyl-benzimidazol-2-one



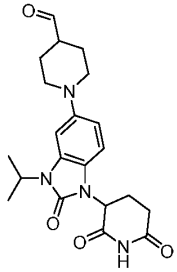
To a solution of 4-(dimethoxymethyl)piperidine (468 mg, 2.9 mmol) and 5-bromo-1-(2,6-dibenzyloxy-3-pyridyl)-3-isopropyl-benzimidazol-2-one (1.6 g, 2.9 mmol) in 1,4-dioxane (20 mL) were added XPhos Pd G2 (231 mg, 0.3 mmol) and cesium carbonate (1.92 g, 6 mmol), and the mixture was stirred at 100 °C for 16 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3/1 then 1/1) to afford the title compound (1.6 g, 87%) as an orange oil. LC/MS (ESI) *m/z*: 623.4 $[M+H]^+$.

Step 3: Preparation of 3-[5-[4-(dimethoxymethyl)-1-piperidyl]-3-isopropyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



To a solution of 1-(2,6-dibenzyloxy-3-pyridyl)-5-[4-(dimethoxymethyl)-1-piperidyl]-3-isopropyl-benzimidazol-2-one (1.35 g, 2 mmol) in tetrahydrofuran (10 mL) was added 10% palladium on carbon (300 mg) under nitrogen atmosphere. The suspension was degassed under vacuum and purged with hydrogen (3X), and the mixture was stirred under hydrogen at 50 °C for 16 h. The reaction mixture was filtered and concentrated under reduced pressure to afford the title compound (800 mg, 83%) as a green solid. LC/MS (ESI) *m/z*: 445.3 $[M+H]^+$.

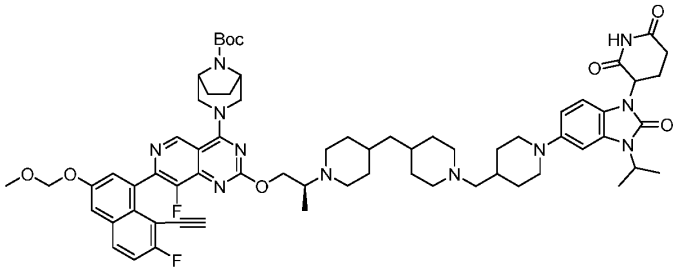
Step 4: Preparation of 1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde



To a solution of 3-[5-[4-(dimethoxymethyl)-1-piperidyl]-3-isopropyl-2-oxo-benzimidazol-1- yl]piperidine-2,6-dione (800 mg, 1.8 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (0.13 mL, 1.8 mmol), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was triturated with

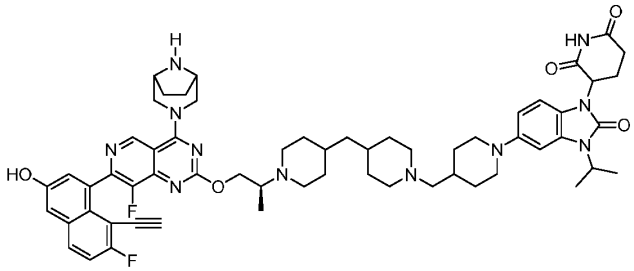
ethyl acetate/methyl tert-butyl ether (1/10, 100 mL) to afford the title compound (700 mg, 98%) as a green solid. LC/MS (ESI) *m/z*: 417.2 $[M+H_3O]^+$.

Step 5: Preparation of *tert*-butyl 3-[2-[(2S)-2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]propoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[(2S)-2-[4-(4-piperidylmethyl)-1-piperidyl]propoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (700 mg, 0.8 mmol) and 1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (506 mg, 1.3 mmol) in dichloromethane (3 mL) were added acetic acid (195 μL, 3 mmol) and 2-methylpyridine borane (453 mg, 4 mmol), and the reaction mixture was stirred at 20 °C for 12 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (0 to 8 % methanol in dichloromethane) to afford the title compound (0.4 g, 36%) as a yellow solid. LC/MS (ESI) *m/z*: 1208.6 $[M+H]^+$.

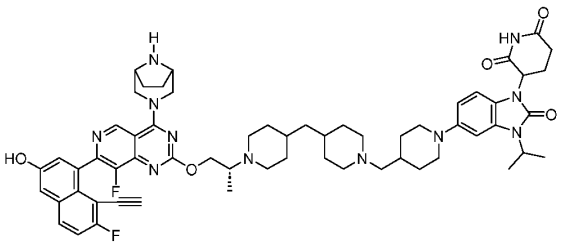
Step 6: Preparation of 3-[5-[4-[[4-[[1-[(1S)-2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxy-1-methyl-ethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-isopropyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



To a solution of *tert*-butyl 3-[2-[(2S)-2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]propoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-

diazabicyclo[3.2.1]octane-8-carboxylate (0.4 g, 0.3 mmol) in dichloromethane (3 mL) was added 4 M HCl in 1,4-dioxane (2.4 mL), and the reaction mixture was stirred at 20 °C for 0.25 h. The mixture was diluted with petroleum ether (40 mL) and filtered, and the filter cake was diluted with THF (30 mL). Triethylamine was added to adjust the pH to 9, and thee mixture was filtered, The filtrate was concentrated under reduced pressure, and the crude product was purified by prep-HPLC (58%-68% acetonitrile in water (ammonium bicarbonate) over 32 min) to afford the title compound (102.2 mg, 28%) as a yellow solid. LC/MS (ESI) *m/z*: 1064.5 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 9.00 (s, 1H), 7.86 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.37 - 7.27 (m, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.02 - 6.93 (m, 2H), 6.83 - 6.77 (m, 1H), 5.26 (dd, *J* = 5.2, 12.6 Hz, 1H), 4.69 - 4.55 (m, 4H), 4.43 - 4.34 (m, 1H), 3.75 - 3.63 (m, 4H), 3.54 (br d, *J* = 12.0 Hz, 2H), 3.36 (s, 1H), 3.13 - 3.06 (m, 1H), 3.02 - 2.87 (m, 5H), 2.80 - 2.65 (m, 4H), 2.49 - 2.38 (m, 2H), 2.27 (br d, *J* = 6.4 Hz, 2H), 2.18 - 2.11 (m, 1H), 2.00 - 1.78 (m, 8H), 1.69 (br t, J = 12.4 Hz, 5H), 1.58 - 1.51 (m, 6H), 1.44 - 1.34 (m, 4H), 1.28 - 1.15 (m, 9H).

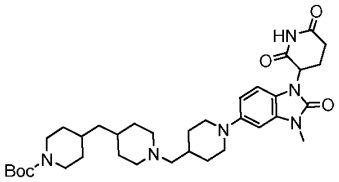
Example 41: Synthesis of 3-[5-(4-{[4-({1-[(2R)-1-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]propan-2-yl]piperidin-4-yl}methyl)piperidin-1-yl]methyl}piperidin-1-yl)-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl]piperidine-2,6-dione (**Compound 184**)



The title compound was made in an analogous manner to 3-[5-[4-[[4-[[1-[(1S)-2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxy-1-methyl-ethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-isopropyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione. (off-white solid). LC/MS (ESI) *m/z*: 1064.6 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 10.30 - 9.99 (m, 1H), 9.03 (s, 1H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.17 (s, 1H), 6.95 - 6.81 (m, 2H), 6.61 (dd, *J* = 1.6, 8.8 Hz, 1H), 5.25 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.63 - 4.53 (m, 1H), 4.52 - 4.42 (m, 2H), 4.30 (d, *J* = 12.4 Hz, 1H), 4.16 (dd, *J* = 6.0, 10.8 Hz, 1H), 3.91 (d, *J* = 5.2 Hz, 1H), 3.62 (d, *J* = 11.8 Hz, 1H), 3.58 - 3.46 (m, 5H), 3.03 - 2.94 (m, 1H), 2.89 - 2.74 (m, 5H), 2.65 - 2.55 (m, 4H), 2.31 - 2.19 (m, 2H), 2.11 (d, *J* = 6.8 Hz, 2H), 2.01 - 1.92 (m, 1H), 1.84 - 1.72 (m, 4H), 1.68 - 1.62 (m, 4H), 1.60 - 1.52 (m, 5H), 1.44 (d, *J* = 6.8 Hz, 6H), 1.34 - 1.13 (m, 5H), 1.12 - 0.96 (m, 9H).

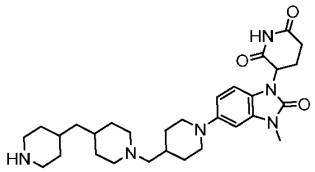
Example 42: Exemplary synthesis of 3-[5-[4-[[4-[[1-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido [4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-4-piperidyl]methyl]-1-piperidyl] methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 196**)

Step 1: Preparation of *tert*-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate



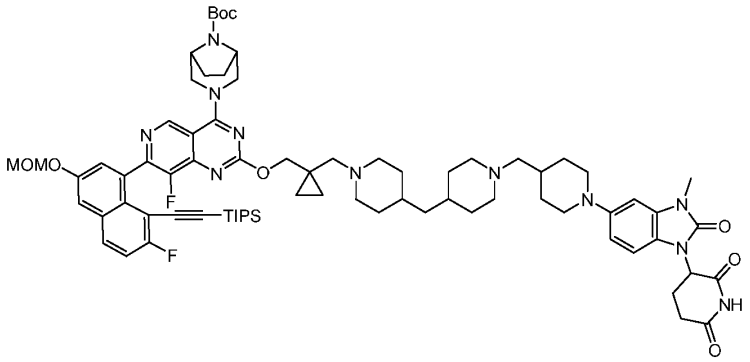
To a solution of tert-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate acetate (386 mg, 1 mmol) and 1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]piperidine -4-carbaldehyde (380 mg, 1 mmol) in dichloromethane (5 mL) and dimethyl sulfoxide (2 mL) were added sodium triacetoxyborohydride (435 mg, 2 mmol) and *N,N*-diisopropylethylamine (0.4 mL, 2 mmol), and the reaction mixture was stirred at 25 °C for 2 h. Th mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 40 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with ethyl acetate/methyl tert-butyl ether (1/10, 60 mL) to afford the title compound (550 mg, 84%) as an off-white solid. LC/MS (ESI) *m/z*: 637.5 $[M+H]^+$.

Step 2: Preparation of 3-[3-methyl-2-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione



To a solution of *tert*-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate (550 mg, 0.9 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (0.1 mL, 0.9 mmol), and the reaction mixture was stirred at 25 °C for 1 h. Th mixture was concentrated under reduced pressure, and the residue was triturated with ethyl acetate/methyl tert-butyl ether (1/10, 60 mL) to afford the title compound (530 mg, 80%, di-trifluoroacetate) as a gray solid. LC/MS (ESI) *m/z*: 537.5 $[M+H]^+$.

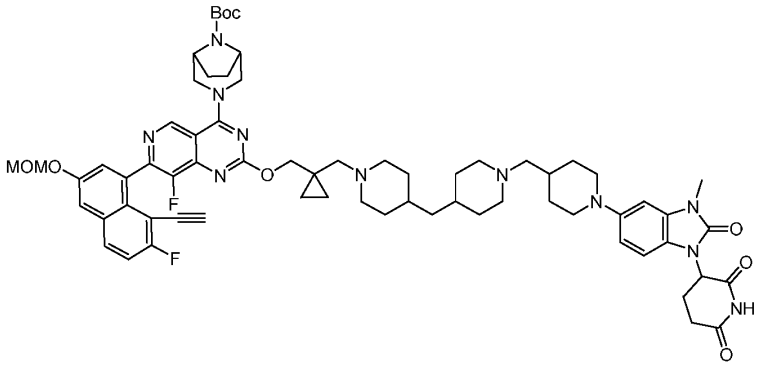
Step 3: Preparation of *tert*-butyl 3-[2-[[1-[[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]methyl]cyclopropyl]methoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 3-[3-methyl-2-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione (363 mg, 0.5 mmol, di-trifluoroacetate) in dichloromethane (4 mL) and dimethyl sulfoxide (4 mL) was added *N,N*-diisopropylethylamine (0.4 mL, 2 mmol), and the resulting mixture was stirred at 25 °C for 0.5 h. *tert*-Butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-[(1-formylcyclopropyl)methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo [3.2.1]octane-8-carboxylate (400 mg, 0.5 mmol), 2-methylpyridine borane (254 mg, 2.4 mmol) and acetic acid (0.3 mL, 5 mmol) were then added, and the reaction mixture was stirred at 35 °C for 12 h. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extract was washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (dichloromethane/methanol = 10/1) to afford the title compound (340 mg, 52%) as a yellow solid. LC/MS (ESI) *m/z*: 1363.9 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.17 (s, 1H), 8.11 (dd, J = 6.0, 9.2 Hz, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.57 (t, J = 8.8 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.82 (s, 1H), 6.62 (d, J = 8.4 Hz, 1H), 5.76 (s, 1H), 5.36 (s, 2H), 5.29 (dd, J = 5.6, 12.8 Hz, 1H), 4.75 (d, J = 12.4 Hz, 1H), 4.38 - 4.25 (m, 3H), 4.23 - 4.18 (m, 1H), 3.82 - 3.67 (m, 2H), 3.58 (d, J = 10.8 Hz, 3H), 3.47 - 3.40 (m, 4H), 3.32 - 3.24 (m, 6H), 3.16 (d, J = 5.2 Hz, 1H), 2.99 - 2.84 (m, 5H), 2.75 - 2.56 (m, 6H), 2.33 (d, J = 2.0 Hz, 3H), 1.93 - 1.83 (m, 6H), 1.67 - 1.56 (m, 5H), 1.46 (s, 9H), 1.35 - 1.17 (m, 5H), 1.16 - 1.01 (m, 4H), 0.81 (t, J = 8.0 Hz, 18H), 0.68 - 0.57 (m, 2H), 0.52 - 0.39 (m, 4H).

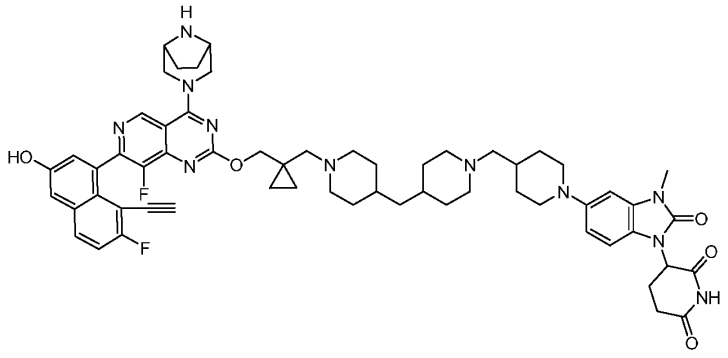
Step 4: Preparation of *tert*-butyl 3-[2-[[1-[[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-

piperidyl]methyl]cyclopropyl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[[1-[[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]methyl]cyclopropyl]methoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (340 mg, 0.25 mmol) in *N,N*-dimethylformamide (5 mL) was added cesium fluoride (0.3 mL, 7 mmol), and the reaction mixture was stirred at 25 °C for 1 h. The mixture was diluted with ice-water (40 mL) and extracted with tetrahydrofuran/ethyl acetate (1/1, 2 x 20 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (2 x 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (273 mg, 90%) as a yellow solid. LC/MS (ESI) *m/z*: 1207.9 $[M+H]^+$.

Step 5: Preparation of 3-[5-[4-[[4-[[1-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido [4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-4-piperidyl]methyl]-1-piperidyl] methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione

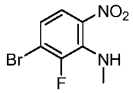


To a solution of *tert*-butyl 3-[2-[[1-[[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-

piperidyl]methyl]cyclopropyl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (273 mg, 0.2 mmol) in dichloromethane (3 mL) was added 4 M HCl in 1,4-dioxane (3 mL), and the reaction mixture was stirred at 25 °C for 15 min. The mixture was suspended in petroleum ether (20 mL) and filtered. The filtered cake was diluted with dimethyl sulfoxide (3 mL) and basified with *N,N*-diisopropylethylamine. The mixture was purified by prep-HPLC (1% to 25% acetonitrile in water(formic acid) over 10 min) to afford the title compound (157.7 mg, 57%, tri-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1062.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.05 (s, 1H), 8.21 (s, 3H), 7.98 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.62 (dd, *J* = 2.0, 8.8 Hz, 1H), 5.28 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.54 (d, *J* = 12.8 Hz, 2H), 4.43 - 4.15 (m, 4H), 3.93 (s, 1H), 3.76 - 3.50 (m, 6H), 3.30 (s, 3H), 3.01 - 2.79 (m, 5H), 2.73 - 2.56 (m, 4H), 2.41 - 2.27 (m, 2H), 2.20 (d, *J* = 6.8 Hz, 2H), 2.04 - 1.84 (m, 5H), 1.83 - 1.71 (m, 6H), 1.69 - 1.51 (m, 5H), 1.39 - 1.18 (m, 4H), 1.16 - 0.97 (m, 6H), 0.65 (s, 2H), 0.42 (s, 2H).

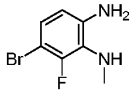
Example 43: Synthesis of 3-(5-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}-4-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 197**)

Step 1: Preparation of 3-bromo-2-fluoro-N-methyl-6-nitro-aniline



To a mixture of 1-bromo-2,3-difluoro-4-nitro-benzene (25 g, 0.1 mol) and methanamine hydrochloride (8.50 g, 126 mmol) in *N,N*-dimethylformamide (300 mL) was added potassium carbonate (43.5 g, 315 mmol), and the reaction mixture was stirred at 25 °C for 5 h. The mixture was diluted with water (400 mL) and extracted with ethyl acetate (1500 mL). The combined organic extracts were concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 30/1 then 15/1) to afford the title compound (26 g, 99%) as a yellow solid.

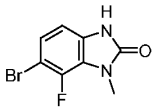
Step 2: Preparation of 4-bromo-3-fluoro-nitrogen-methyl-benzene-1,2-diamine



To a solution of 3-bromo-2-fluoro-N-methyl-6-nitro-aniline (26.0 g, 104 mmol) in ethanol (300 mL) and water (250 mL) was added iron powder (23.3 g, 418 mmol) and ammonium

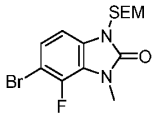
chloride (27.9 g, 522 mmol), and the reaction mixture was stirred at 80 °C for 3 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1 to 8/1) to afford the title compound (18 g, 78%) as a yellow solid.

Step 3: Preparation of 6-bromo-7-fluoro-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one



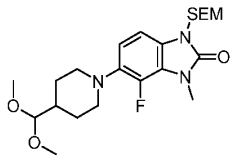
To a solution of 4-bromo-3-fluoro-nitrogen-methyl-benzene-1,2-diamine (18.0 g, 82.17 mmol) and triethylamine (10.8 g, 106.82 mmol, 14.9 mL) in tetrahydrofuran (200 mL) was added 1,1-carbonyldiimidazole (16.0 g, 98.61 mmol), and the reaction mixture was stirred at 70 °C for 10 h. The mixture was diluted with water (150 mL) and extracted with ethyl acetate (350 mL). The combined organic extracts were concentrated under reduced pressure, and the resulting residue was purified by column chromatography (petroleum ether/ethyl acetate = 5/1 then 1/2) to afford the title compound (14 g, 69%) as a yellow solid. LC/MS (ESI) *m/z*: 245.0 $[M+H]^+$.

Step 4: Preparation of 5-bromo-4-fluoro-3-methyl-1-(2-trimethylsilylethoxymethyl)benzimidazol-2-one



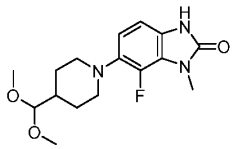
To a solution of 6-bromo-7-fluoro-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (13 g, 53 mmol) in tetrahydrofuran (300 mL) was added sodium hydride (2.7 g, 69 mmol, 60%), and the resulting mixture was stirred at 0 °C for 1 h. 2-(Trimethylsilyl)ethoxymethyl chloride (1 M, 63.7 mL) was then added, and the reaction mixture was stirred at 0 °C for 2 h. The mixture was diluted with saturated ammonium chloride solution (800 mL) at 0 °C, and then extracted with ethyl acetate (1500 mL). The organic extract was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1 then 10/1) to afford the title compound (15 g, 75%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 (dd, J = 8.4, 6.4 Hz, 1 H), 7.13 (d, J = 8.4 Hz, 1 H), 5.31 (s, 2 H), 3.61 (t, J = 8.0 Hz, 2 H), 3.54 (d, J = 1.6 Hz, 3 H), 0.88 - 0.93 (m, 2 H), 0.00 (s, 9 H).

Step 5: Preparation of 5-[4-(dimethoxymethyl)-1-piperidyl]-4-fluoro-3-methyl-1-(2-trimethylsilylethoxymethyl) benzimidazol-2-one



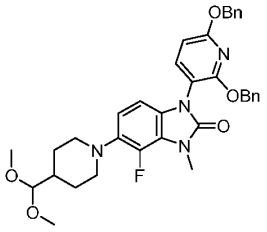
To a solution of 5-bromo-4-fluoro-3-methyl-1-(2-trimethylsilylethoxymethyl)benzimidazol-2-one (4.0 g, 11 mmol) and 4-(dimethoxymethyl)piperidine (2.0 g, 13 mmol) in 1,4-dioxane (50 mL) were added cesium carbonate (8.7 g, 27 mmol) and Pd-PEPPSI-IHeptCl (518 mg, 0.5 mmol), and the reaction mixture was stirred at 100 °C for 6 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 8/1 then 6/1) to afford the title compound (4.4 g, 91%) as a yellow oil. LC/MS (ESI) *m/z*: 454.4 $[M+H]^+$.

Step 6: Preparation of 5-[4-(dimethoxymethyl)-1-piperidyl]-4-fluoro-3-methyl-1H-benzimidazol-2-one



A solution of 5-[4-(dimethoxymethyl)-1-piperidyl]-4-fluoro-3-methyl-1-(2-trimethylsilylethoxymethyl) benzimidazol-2-one (4.4 g, 9.7 mmol) and tetrabutylammonium fluoride in THF (1 M, 48.5 mL) was stirred at 65 °C for 16 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (petroleum ether/ethyl acetate = 1/1) to afford the title compound (1.4 g, 44%) as a yellow solid.

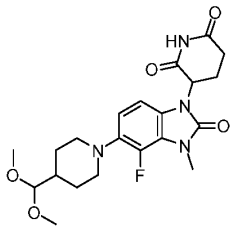
Step 7: Preparation of 1-(2,6-bis(benzyloxy)pyridin-3-yl)-5-(4-(dimethoxymethyl)piperidin-1-yl)-4-fluoro-3-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one



To a solution of 5-[4-(dimethoxymethyl)-1-piperidyl]-4-fluoro-3-methyl-1H-benzimidazol-2-one (2.6 g, 8 mmol) and 2,6-bis(benzyloxy)-3-iodopyridine (5.0 g, 12 mmol) in dimethyl sulfoxide (30 mL) were added cuprous oxide (230 mg, 1.6 mmol), N,N'-bis(2-furylmethyl)oxamide (798 mg, 3.2 mmol), and potassium phosphate (5.1 g, 24 mmol), and the reaction mixture was stirred at 120 °C for 10 h. The mixture was filtered and concentrated

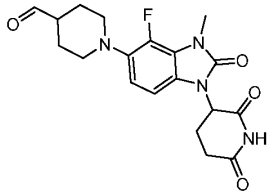
under reduced pressure. The residue was purified by prep-HPLC (65% to 95% acetonitrile in water (ammonium bicarbonate) over 20 min) to afford the title compound (1.8 g, 36%) as a yellow solid. LC/MS (ESI) *m/z*: 613.2 $[M+H]^+$.

Step 8: Preparation of 3-[5-[4-(dimethoxymethyl)-1-piperidyl]-4-fluoro-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



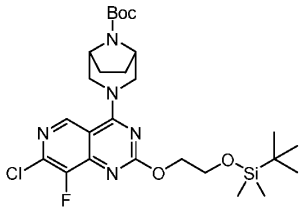
To a solution of 1-(2,6-bis(benzyloxy)pyridin-3-yl)-5-(4-(dimethoxymethyl)piperidin-1-yl)-4-fluoro-3-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (1.2 g, 2 mmol) in tetrahydrofuran (15 mL) was added 10% palladium on carbon (500 mg) under nitrogen atmosphere, and the mixture was degassed and purged with hydrogen (3X)., then stirred under hydrogen (50 psi) at 50 °C for 16 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (petroleum ether/ethyl acetate = 1/1) to afford the title compound (700 mg, 82%) as a yellow solid. LC/MS (ESI) *m/z*: 435.2 $[M+H]^+$.

Step 9: Preparation of 1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde



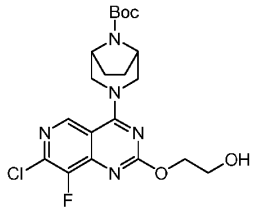
To a solution of 3-[5-[4-(dimethoxymethyl)-1-piperidyl]-4-fluoro-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (700 mg, 1.6 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (7.0 m, 94 mmol), and the reaction mixture was stirred at 25 °C for 1 h. The mixture was filtered and concentrated under reduced pressure. The crude product was triturated with methyl tert-butyl ether (80 mL) to afford the title compound (700 mg, crude) as a yellow solid. LC/MS (ESI) *m/z*: 407.1 $[M+H_3O]^+$.

Step 10: Preparation of *tert*-butyl 3-[2-[2-[*tert*-butyl(dimethyl)silyl]oxyethoxy]-7-chloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



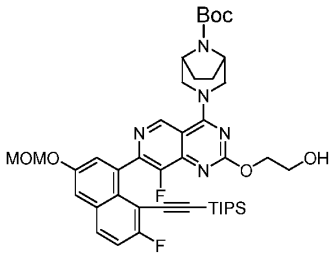
To a solution of tert-butyl 3-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (52.0 g, 121 mmol) and 1,4-diazabicyclo [2.2.2]octane (2.72 g, 25 mmol) in acetonitrile (1000 mL) were added 2-[tert-butyl(dimethyl)silyl]oxyethanol (25.69 g, 146 mmol) and cesium carbonate (118.68 g, 364 mmol) at 25 °C, and the reaction mixture was stirred for 50 °C for 5 h. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1 to 3/1) to afford the title compound (50 g, 72%) as a yellow solid. LC/MS (ESI) *m/z*: 568.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 4.56 (t, *J* = 5.6 Hz, 2H), 4.48 (br d, *J* = 12.8 Hz, 2H), 4.42 - 4.28 (m, 2H), 4.07 - 3.98 (m, 2H), 3.74 - 3.60 (m, 2H), 2.00 - 1.90 (m, 2H), 1.72 (br d, *J* = 7.6 Hz, 2H), 1.52 (s, 9H), 0.92 - 0.86 (m, 9H), 0.09 (s, 6H).

Step 11: Preparation of *tert*-butyl 3-[7-chloro-8-fluoro-2-(2-hydroxyethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



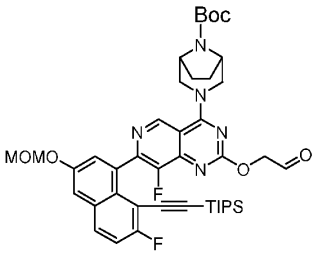
To a solution of *tert*-butyl 3-[2-[2-[tert-butyl(dimethyl)silyl]oxyethoxy]-7-chloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (6.0 g, 10 mmol) in *N, N*-dimethylformamide (50 mL) at 25 °C was added cesium fluoride (8 mL, 0.2 mol), and the reaction mixture was stirred for 12 h at 25 °C. The mixture was diluted with saturated ammonium chloride solution (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extract was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 then 1/1) to afford the title compound (3.5 g, 73%) as a yellow solid. LC/MS (ESI) *m/z*: 454.1 $[M+H]^+$.

Step 12: Preparation of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxy methoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-hydroxyethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



A mixture of *tert*-butyl 3-[7-chloro-8-fluoro-2-(2-hydroxyethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.7 g, 6 mmol), 2-[2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl-triisopropyl-silane (3.05 g, 6 mmol), potassium phosphate (3.79 g, 18 mmol), and cataCXium A Pd G3 (433 mg, 0.6 mmol) in 1,4-dioxane (60 mL) and water (7 mL) was degassed and purged with nitrogen (3X), then stirred at 90 °C for 12 h under nitrogen atmosphere. The reaction mixture was quenched with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extract was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 then 1/1) to afford the title compound (4.5 g, 94%) as a yellow solid. LC/MS (ESI) *m/z*: 804.5 $[M+H]^+$.

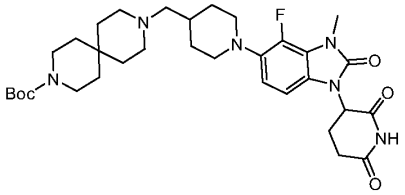
Step 13: Preparation of *tert*-butyl-3-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To dimethyl sulfoxide (1.0 mL) in dichloromethane (5 mL) at -78 °C was added oxalyl chloride (0.7 mL, 8 mmol) in dichloromethane (5 mL) dropwise, and the mixture was stirred at -78 °C for 30 min. A solution of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxy methoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-hydroxyethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (4.3 g, 5 mmol) in dichloromethane (5 mL) was then added dropwise, and the reaction mixture was stirred at -78 °C for 30 min. Triethylamine (0.3 mL, 2 mmol) was then added, And the resulting mixture was stirred at -78 °C for 30 minutes, then warmed to 25 °C and stirred for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic extract was washed

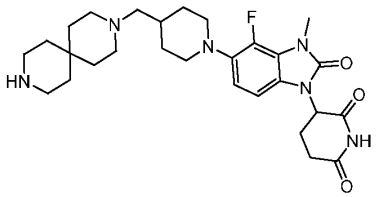
with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 then 1/1) to afford the title compound (4.0 g, 93%) as a yellow solid. LC/MS (ESI) *m/z*: 802.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 9.11 (s, 1H), 7.79 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.36 - 7.28 (m, 2H), 5.30 (d, *J* = Step 2: Hz, 2H), 5.07 - 4.96 (m, 1H), 4.92 - 4.84 (m, 1H), 4.84 - 4.66 (m, 1H), 4.54 - 4.31 (m, 3H), 4.24 (s, 1H), 3.94 - 3.72 (m, 1H), 3.51 (s, 3H), 2.03 - 1.92 (m, 2H), 1.78 - 1.65 (m, 2H), 1.54 - 1.51 (m, 9H), 0.87 (t, *J* = 7.6 Hz, 18H), 0.64 - 0.50 (m, 3H).

Step 14: Preparation of *tert*-butyl 9-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate



To a mixture of 1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl] piperidine-4-carbaldehyde (400 mg, 1 mmol) and *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (314 mg, 1 mmol) in dichloromethane (2 mL) and dimethyl sulfoxide (2 mL) were added sodium triacetoxyborohydride (546 mg, 3 mmol) and acetic acid (0.1 mL, 1 mmol), and the reaction mixture was stirred at 25 °C for 2 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (dichloromethane/methanol = 10/1) to afford the title compound (450 mg, 69%) as a yellow solid. LC/MS (ESI) *m/z*: 627.4 $[M+H]^+$.

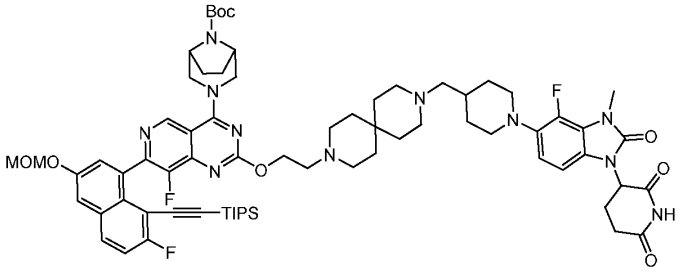
Step 15: Preparation of 3-[5-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-4-fluoro-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



To a solution of *tert*-butyl 9-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate (400 mg, 0.6 mmol) in dichloromethane (30 mL) was added trifluoroacetic acid (8 mL), and the reaction mixture was stirred at 25 °C for 2 h. The mixture was concentrated under reduced pressure,

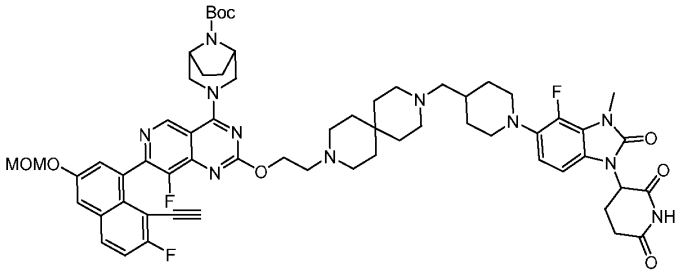
and the residue was triturated with *tert*-butyl methyl ether (40 mL) to afford the title compound (400 mg, 97%, TFA salt) as a yellow solid. LC/MS (ESI) *m/z*: 527.3 $[M+H]^+$.

Step 16: Preparation of *tert*-butyl 3-[2-[2-[3-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5] undecan-9-yl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilyl ethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



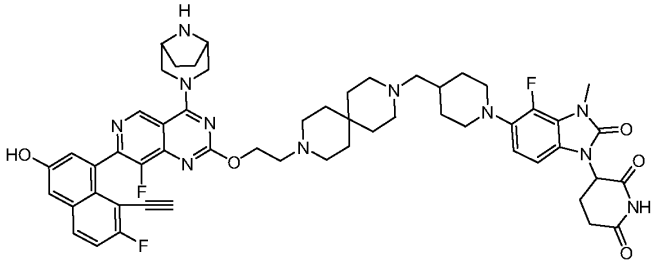
To a solution of 3-[5-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-4-fluoro-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione trifluoroacetate (400 mg, 0.6 mmol) in dichloromethane (6 mL) and isopropanol (6 mL) were added *N,N*-diisopropylethylamine (0.1 mL, 0.8 mmol), acetic acid (56 mg, 0.94 mmol), *tert*-butyl-3-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (551 mg, 0.7 mmol), and sodium triacetoxyborohydride (331 mg, 1.6 mmol), and the reaction mixture was stirred at 25 °C for 2 h. The mixture was diluted with water (20 mL) and extracted with dichloromethane (200 mL). The organic extract was concentrated under reduced pressure, and the residue was purified by prep-TLC (dichloromethane/methanol = 5/1) to afford the title compound (430 mg, 52%) as a yellow solid. LC/MS (ESI) *m/z*: 1312.9 $[M+H]^+$.

Step 17: Preparation of *tert*-butyl 3-[2-[2-[3-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5] undecan-9-yl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[2-[3-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5] undecan-9-yl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilyl ethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg, 0.3 mmol) in *N,N*-dimethylformamide (5 mL) was added cesium fluoride (1.4 g, 9 mmol), and the reaction mixture was stirred at 25 °C for 10 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (22% to 52% acetonitrile in water (trifluoroacetic acid) over 15 min) to afford the title compound (140 mg, 39%) as a yellow solid. LC/MS (ESI) *m/z*: 1156.6 $[M+H]^+$.

Step 18: Preparation of 3-(5-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}-4-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione

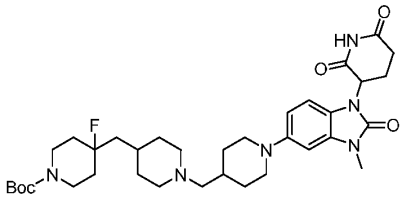


To a solution of *tert*-butyl 3-[2-[2-[3-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5] undecan-9-yl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (140 mg, 0.1 mmol) in dichloromethane (6 mL) was added 4 M HCl in 1,4-dioxane (1.7 mL), and the reaction mixture was stirred at 25 °C for 0.25 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (1% to 28% acetonitrile in water (formic acid) over 10 min) to afford the title compound (49.6 mg, 36%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1012.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H), 9.05 (s, 1H), 8.20 (s, 2H), 7.98 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.47 (t, *J* = 9.2 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 6.73 (t, *J* = 8.4 Hz, 1H), 5.33 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.54 - 4.43 (m, 3H), 4.35 (br d, *J* = 12.0 Hz, 1H), 3.93 (s, 1H), 3.69 - 3.60 (m, 6H), 3.47 (d, *J* = 1.6 Hz, 4H), 3.21 (br d, *J* = 11.6 Hz, 3H), 2.89 (br s, 1H), 2.75 - 2.69 (m, 2H), 2.66 - 2.59 (m, 3H), 2.46 (br s, 3H), 2.35 (br s, 4H), 2.22 (br d, *J* = 7.2 Hz, 2H), 2.05 - 1.95 (m, 1H), 1.81 - 1.69 (m, 6H), 1.63 (br dd, *J* = 5.2, 12.8 Hz, 1H), 1.42 (br s, 8H), 1.33 - 1.20 (m, 2H).

Example 44: Exemplary synthesis of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-fluoro-

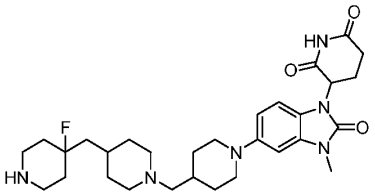
4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 198**)

Step 1: Preparation of tert-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-4-fluoro-piperidine-1-carboxylate



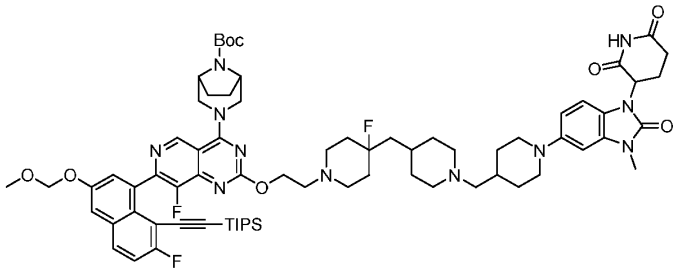
To a solution of 1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (600 mg, 1.6 mmol) and tert-butyl 4-fluoro-4-(4-piperidylmethyl)piperidine-1-carboxylate (535 mg, 1.8 mmol) in dichloromethane (6.0 mL) were added acetic acid (0.3 mL, 5 mmol) and $NaBH(OAc)_3$ (858 mg, 4 mmol), and the reaction mixture was stirred at 25 °C for 12 h. The mixture was diluted with sodium bicarbonate solution (15 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 9% methanol in dichloromethane) to afford the title compound (810 mg, 68%) as a white solid. LC/MS (ESI) *m/z*: 655.2 $[M/+H]^+$.

Step 2: Preparation of 3-[5-[4-[[4-[(4-fluoro-4-piperidyl)methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



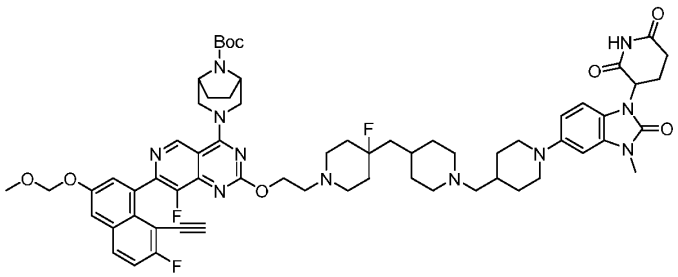
To a solution of tert-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-4-fluoro-piperidine-1-carboxylate (810 mg, 1 mmol) in dichloromethane (8 mL) was added 4 M HCl in 1,4-dioxane (8.0 mL), and the reaction mixture was stirred at 25 °C for 30 min. The reaction mixture was evaporated from petroleum ether (2 x 15 mL) to afford the title compound (686 mg, crude, HCl salt) as a white solid. LC/MS (ESI) *m/z*: 555.3 $[M+H]^+$.

Step 3: Preparation of tert-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-4-fluoro-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



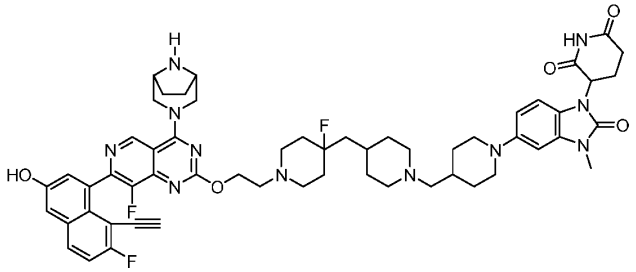
To a mixture of 3-[5-[4-[[4-[(4-fluoro-4-piperidyl)methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (686 mg, 1.1 mmol) and tert-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (992 mg, 1 mmol) in dichloromethane (8.0 mL), isopropanol (8.0 mL), and DMSO (3.0 mL) were added sodium acetate (1.5 g, 18 mmol) and 2-methylpyridine borane (529 mg, 5 mmol), and the reaction mixture was stirred at 25 °C for 12 h. The mixture was filtered and concentrated. The residue was diluted with sodium bicarbonate solution (15 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (15 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 6% methanol in dichloromethane) followed by by prep-HPLC (6% to 46% acetonitrile in water (HCl) over 36 min) to afford the title compound (220 mg, 12%) as a white solid. LC/MS (ESI) *m/z*: 1341.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.40 (s, 1H), 8.15 - 7.95 (m, 1H), 7.80 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.35 - 7.29 (m, 2H), 6.69 - 6.62 (m, 3H), 5.36 - 5.25 (m, 2H), 5.18 (dd, *J* = 5.6, 12.8 Hz, 1H), 4.80 - 4.58 (m, 3H), 4.49 - 4.32 (m, 2H), 4.21 (br d, *J* = 12.4 Hz, 1H), 3.87 - 3.70 (m, 1H), 3.58 - 3.53 (m, 2H), 3.52 (s, 3H), 3.41 (s, 3H), 3.34 - 3.22 (m, 2H), 3.03 - 2.91 (m, 5H), 2.88 - 2.80 (m, 1H), 2.79 - 2.65 (m, 4H), 2.63 - 2.58 (m, 3H), 2.46 - 2.34 (m, 3H), 2.27 - 2.19 (m, 4H), 2.02 - 1.96 (m, 5H), 1.92 - 1.85 (m, 5H), 1.72 (br s, 3H), 1.64 (br s, 1H), 1.58 (br s, 1H), 1.53 (s, 9H), 0.87 (t, *J* = 7.6 Hz, 18H), 0.56 (quin, *J* = 7.2 Hz, 3H).

Step 4: Preparation of tert-butyl 3-[2-[2-[4-[[1-[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-4-fluoro-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of tert-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-4-fluoro-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (340 mg, 0.2 mmol) in DMF (3.5 mL) was added cesium fluoride (578 mg, 3.8 mmol), and the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was filtered, and the filtrate was diluted with water (5.0 mL), then extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with water (6 x 5.0 mL) followed by brine (10 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (395 mg, crude) as a yellow foam. LC/MS (ESI) *m/z*: 1185.6 $[M+H]^+$.

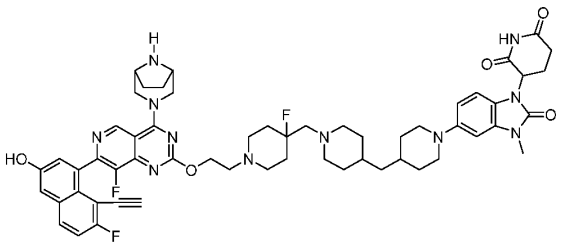
Step 5: Preparation of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-fluoro-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



To a solution of tert-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-4-fluoro-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (309 mg, 0.2 mmol) in dichloromethane (4.0 mL) was added 4 M HCl in 1,4-dioxane (4.0 mL), and the reaction mixture was stirred at 25 °C for 30 min. The reaction mixture suspended in petroleum ether (30 mL) and filtered. The filter cake was dissolved in tetrahydrofuran (5 mL) and triethylamine was then added to adjust the pH to 8. The mixture was purified by prep-HPLC (20% to 60% acetonitrile in water (ammonium bicarbonate) over 32 min) to afford the title compound (112.2 mg, 32%) as a yellow solid.

LC/MS (ESI) *m/z*: 1040.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 7.86 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.36 - 7.29 (m, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 6.80 (dd, *J* = 1.6, 9.2 Hz, 1H), 5.28 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.60 (br s, 4H), 3.77 - 3.63 (m, 4H), 3.59 (br d, *J* = 12.0 Hz, 2H), 3.40 (s, 3H), 3.37 (s, 1H), 3.01 - 2.83 (m, 7H), 2.83 - 2.74 (m, 2H), 2.74 - 2.65 (m, 2H), 2.52 - 2.42 (m, 2H), 2.32-2.30 (m, 2H), 2.19 - 2.11 (m, 1H), 2.11 - 1.99 (m, 2H), 1.94 - 1.83 (m, 6H), 1.82 - 1.74 (m, 4H), 1.73 - 1.69 (m, 1H), 1.68 - 1.65 (m, 1H), 1.65 - 1.61 (m, 1H), 1.61 - 1.57 (m, 1H), 1.52 (br d, *J* = 6.0 Hz, 1H), 1.28 - 1.28 (m, 1H), 1.48 - 1.26 (m, 4H).

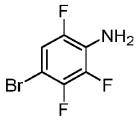
Example 45: Exemplary Synthesis of 3-{5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-4-fluoropiperidin-4-yl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 183**)



The title compound was made in an analogous manner to 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-fluoro-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione. (light yellow solid). LC/MS (ESI) *m/z*: 1040.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 7.88 - 7.84 (m, 1H), 7.35 - 7.30 (m, 2H), 7.21 - 7.20 (m, 1H), 6.99 - 6.96 (m, 1H), 6.87 - 6.86 (m, 1H), 6.81 - 6.78 (m, 1H), 5.30 - 5.25 (m, 1H), 4.69 - 4.57 (m, 4H), 3.73 - 3.67 (m, 4H), 3.58 - 3.54 (m, 2H), 3.40 (s, 3H), 3.37 (s, 1H), 2.95 - 2.87 (m, 7H), 2.81 - 2.75 (m, 2H), 2.70 - 2.65 (m, 2H), 2.52 - 2.44 (m, 4H), 2.18 - 2.09 (m, 3H), 1.90 - 1.79 (m, 9H), 1.70 - 1.61 (m, 3H), 1.55 - 1.46 (m, 1H), 1.39 - 1.34 (m, 3H), 1.25 - 1.19 (m, 4H).

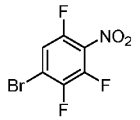
Example 46: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-4,7-difluoro-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 199**)

Step 1: Preparation of 4-bromo-2,3,6-trifluoro-aniline



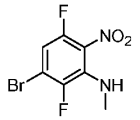
To a solution of 2,3,6-trifluoroaniline (12.5 g, 85 mmol) in *N,N*-dimethylformamide (200 mL) was added 1-bromopyrrolidine-2,5-dione (18.15 g, 102 mmol), and the mixture was allowed to stir at 20 °C for 2 h. The reaction mixture was diluted with water (1000 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were washed with brine (3 x 300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/0 to 20/1) to afford the title compound (37.3 g, 97%) as a dark red oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 - 7.30 (m, 1H), 5.79 - 5.69 (m, 2H).

Step 2: Preparation of 1-bromo-2,3,5-trifluoro-4-nitro-benzene



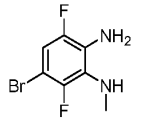
To a suspension of sodium perborate tetrahydrate (85.1 mL, 442 mmol) in acetic acid (100 mL) was added a solution of 4-bromo-2,3,6-trifluoro-aniline (10 g, 44 mmol) in acetic acid (100 mL) dropwise, and the reaction mixture was stirred at 80 °C for 12 h. The mixture was diluted with water (1000 mL) and extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were washed with brine (3 x 500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/0) to afford the title compound (3.1 g, 27%) as a red solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 – 8.15 (m, 1H).

Step 3: Preparation of 3-bromo-2,5-difluoro-*N*-methyl-6-nitroaniline



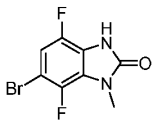
To a solution of 1-bromo-2,3,5-trifluoro-4-nitro-benzene (9.3 g, 36 mmol) in tetrahydrofuran (100 mL) were added methanamine hydrochloride (3.68 g, 54 mmol) and triethylamine (15.2 mL, 109 mmol) at 0 °C, and the reaction mixture was stirred at 20 °C for 12 h. The mixture was diluted with water (60 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/0 to 50/1) to afford the title compound (9 g, 92%) as a dark red oil.

Step 4: Preparation of 5-bromo-3,6-difluoro-N1-methylbenzene-1,2-diamine



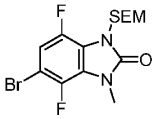
A mixture of 3-bromo-2,5-difluoro-*N*-methyl-6-nitroaniline (15 g, 56 mmol) and 3% platino-vanadium carbon (4 g) in tetrahydrofuran (300 mL) was loaded into a FLV1 flow chemistry reactor at 20 °C, and the mixture was stirred for 10 minutes at 20 °C. The backpressure regulator was set at 1.5 MPa, the flow rate of P1 was set at 0.5 mL/min, the flow rate of hydrogen was set at 30 mL/min, and the oven temperature was set at 60 °C. The reaction mixture was stirred at 60 °C for 2.5 minutes, then filtered and concentrated under reduced pressure to afford the title compound (8 g, 60%) as a yellow oil.

Step 5: Preparation of 6-bromo-4,7-difluoro-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one



To a solution of 5-bromo-3,6-difluoro-N1-methylbenzene-1,2-diamine (8.0 g, 34 mmol) in tetrahydrofuran (100 mL) were added 1,1′-carbonyldiimidazole (6.02 g, 37 mmol) and triethylamine (7.1 mL, 51 mmol), and the reaction mixture was stirred at 70 °C for 10 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (20% to 50% acetonitrile in water (trifluoroacetic acid) over 30 min) to afford the title compound (6.5 g, 73%) as a yellow solid. LC/MS (ESI) *m/z*: 264.9 $[M+H]^+$.

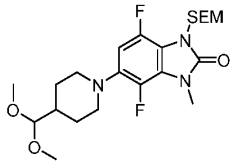
Step 6: Preparation of 5-bromo-4,7-difluoro-3-methyl-1-(2-trimethylsilylethoxymethyl)benzimidazol-2-one



To a solution of 5-bromo-4,7-difluoro-3-methyl-1H-benzimidazol-2-one (4.0 g, 15 mmol) in *N,N*-dimethylformamide (60 mL) was added sodium hydride (760 mg, 19 mmol, 60% in mineral oil), and the resulting mixture was stirred at 0 °C for 0.5 h under nitrogen atmosphere. 2-(Trimethyl silyl)ethoxymethyl chloride (4.0 mL, 23 mmol) was then added at 0 °C, and the resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with saturated ammonium chloride solution (60 mL) at 0 °C and extracted with ethyl acetate (200 mL). The combined organic extracts were concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1 to 15/1) to

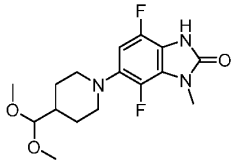
afford the title compound (4.7 g, 74%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (br d, J = 4.8, 1H), 5.36 (s, 2H), 3.66 - 3.60 (m, 5H), 0.95 - 0.91 (m, 2H), 0.02 (s, 9H).

Step 7: Preparation of 5-(4-(dimethoxymethyl)piperidin-1-yl)-4,7-difluoro-3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one



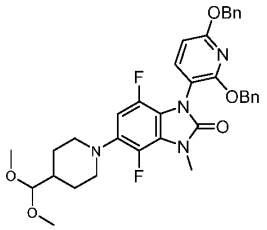
To a mixture of 5-bromo-4,7-difluoro-3-methyl-1-(2-trimethylsilylethoxymethyl)benzimidazol-2-one (5.5 g, 14 mmol), 4-(dimethoxymethyl)piperidine (4.45 g, 28 mmol), and cesium carbonate (9.11 g, 28 mmol) in 1,4-dioxane (90 mL) was added Pd-PEPPSI-IPent (680 mg, 0.7 mmol) at 25 °C under nitrogen atmosphere, and the reaction mixture was heated to 100 °C and stirred for 6 h under nitrogen atmosphere. The mixture was cooled to 25 °C, diluted with ethyl acetate (100 mL), then washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 10/1 then 4/1) to afford the title compound (5.7 g, 82%) as a white solid. LC/MS (ESI) *m/z*: 472.2 $[M+H]^+$.

Step 8: Preparation of 5-[4-(dimethoxymethyl)-1-piperidyl]-4,7-difluoro-3-methyl-1H-benzimidazol-2-one



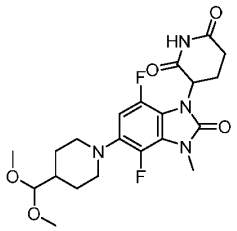
A mixture of 5-(4-(dimethoxymethyl)piperidin-1-yl)-4,7-difluoro-3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (5.6 g, 12 mmol) in tetrabutylammonium fluoride (1 M in THF, 60 mL) was heated to 80 °C and stirred for 72 h under nitrogen atmosphere. The mixture was cooled to 25 °C and concentrated. The residue was poured into ice-water (w/w = 1/1, 100 mL) and stirred for 15 min. The aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic extract was washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with t-butyl methyl ether (50 mL) to afford the title compound (2.8 g, 69%) as a yellow solid. LC/MS (ESI) *m/z*: 342.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.38 (s, 1H), 6.59 (br d, J = 6.4 Hz, 1H), 4.12 (d, J = 6.4 Hz, 1H), 3.40 (s, 3H), 3.28 (s, 6H), 3.26 (d, J = 14.4 Hz, 2H), 2.57 - 2.51 (m, 2H), 1.73 - 1.70 (m, 3H), 1.38 - 1.37 (m, 2H).

Step 9: Preparation of 1-(2,6-dibenzyloxy-3-pyridyl)-5-[4-(dimethoxymethyl)-1-piperidyl]-4,7-difluoro-3-methyl-benzimidazol-2-one



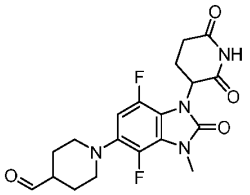
To a solution of 5-[4-(dimethoxymethyl)-1-piperidyl]-4,7-difluoro-3-methyl-1H-benzimidazol-2-one (2.0 g, 6 mmol) and 2,6-dibenzyloxy-3-iodo-pyridine (7.33 g, 18 mmol) in dimethyl sulfoxide (50 mL) were added cuprous oxide (168 mg, 1.2 mmol), N,N'-bis(2-furylmethyl)oxamide (582 mg, 2.3 mmol), and potassium phosphate (3.73 g, 17.58 mmol) under nitrogen atmosphere, and the reaction mixture was heated to 120 °C and stirred for 24 h under nitrogen atmosphere. The mixture was cooled to 25 °C and poured into ice-water (w/w = 1/1, 100 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL), and the combined organic extract was washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 10/1 then 3/1) to afford the title compound (1.6 g, 43%) as a yellow solid. LC/MS (ESI) *m/z*: 631.3 $[M+H]^+$.

Step 10: Preparation of 3-[5-[4-(dimethoxymethyl)-1-piperidyl]-4,7-difluoro-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



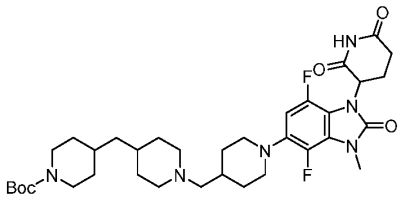
To a solution of 1-(2,6-dibenzyloxy-3-pyridyl)-5-[4-(dimethoxymethyl)-1-piperidyl]-4,7-difluoro-3-methyl-benzimidazol-2-one (1.4 g, 2 mmol) in tetrahydrofuran (15 mL) were added 10% palladium on carbon (0.3 g) and 20% palladium hydroxide on carbon (0.3 g) under nitrogen atmosphere. The suspension was degassed under vacuum and purged with hydrogen several times. The reaction mixture was then stirred under hydrogen (50 psi) at 50 °C for 16 h. The mixture was filtered and concentrated under reduced pressure. The resulting material was triturated with tert-butyl methyl ether (50 mL) to afford the title compound (740 mg, 73%) as a gray solid. LC/MS (ESI) *m/z*: 453.2 $[M+H]^+$.

Step 11: Preparation of 1-[1-(2,6-dioxo-3-piperidyl)-4,7-difluoro-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde



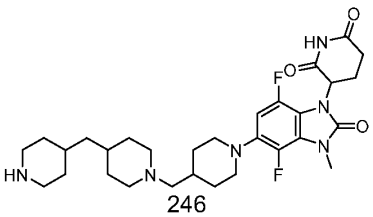
To a solution of 3-[5-[4-(dimethoxymethyl)-1-piperidyl]-4,7-difluoro-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (740 mg, 1.6 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (3 mL), and the reaction mixture was stirred at 25 °C for 2 h. The mixture was concentrated under reduced pressure, and the residue was triturated with methyl tert-butyl ether (30 mL) to afford the title compound (525 mg, crude) as a yellow solid. LC/MS (ESI) *m/z*: 407.1 $[M+H]^+$.

Step 12: Preparation of *tert*-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4,7-difluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate



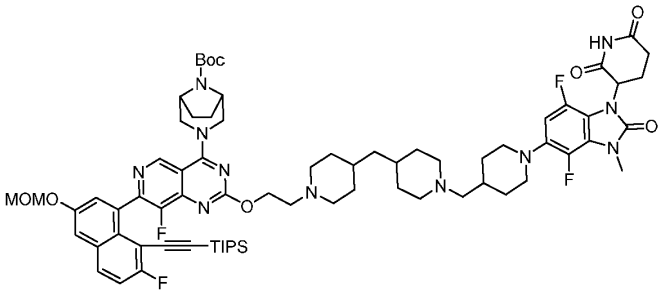
To a solution of 1-[1-(2,6-dioxo-3-piperidyl)-4,7-difluoro-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (200 mg, 0.5 mmol) in dichloromethane (3 mL) and dimethyl sulfoxide (3 mL) were added *N,N*-diisopropylethylamine (0.3 mL, 1 mmol), *tert*-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate (167 mg, 0.6 mmol), and sodium triacetoxyborohydride (209 mg, 1 mmol), and the reaction mixture was stirred at 25 °C for 2 h. The mixture was poured into water (20 mL) and extracted with dichloromethane (2 x 10 mL). The combined organic extract was washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (290 mg, crude) as a yellow solid. LC/MS (ESI) *m/z*: 673.4 $[M+H]^+$.

Step 13: Preparation of 3-[4,7-difluoro-3-methyl-2-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione



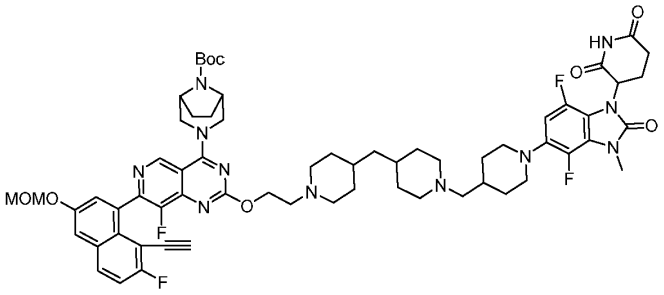
To a solution of *tert*-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4,7-difluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate (430 mg, 0.6 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (2.0 mL, 27 mmol), and the reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to afford the title compound (438 mg, crude, TFA salt) as a yellow gum. LC/MS (ESI) *m/z*: 573.5 $[M+H]^+$.

Step 14: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4,7-difluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



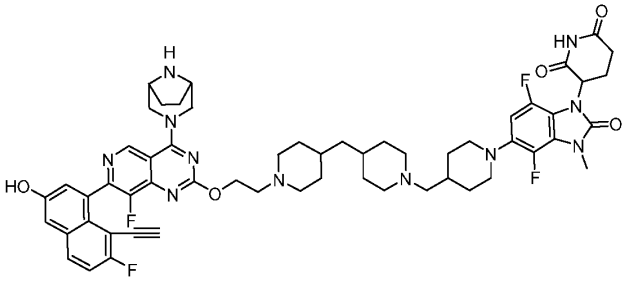
To a solution of 3-[4,7-difluoro-3-methyl-2-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione (438 mg, TFA salt) in dichloromethane (3 mL) and isopropanol (3 mL) were added *N,N*- diisopropylethylamine (0.3 mL, 2 mmol), tert-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (614 mg, 0.8 mmol), and sodium triacetoxyborohydride (270 mg, 1.3 mmol), and the reaction mixture was stirred at 25 °C for 2 h. The mixture was poured into water (30 mL) and extracted with dichloromethane (2 x 15 mL). The combined organic extract was washed with brine (2 x 15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (0 to 10% dichloromethane/methanol) to afford the title compound (410 mg, 47%) as a yellow solid. LC/MS (ESI) *m/z*: 1359.9 $[M+H]^+$.

Step 15: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4,7-difluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4,7-difluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (410 mg, 0.3 mmol) in *N,N*-dimethylformamide (10 mL) at 20 °C was added cesium fluoride (1.15 g, 7.5 mmol), and the reaction mixture was stirred for 2 h at 20 °C. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extract was washed with saturated sodium bicarbonate solution (20 mL) followed by brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford the title compound (250 mg, 69%) as a yellow solid. LC/MS (ESI) *m/z*: 1202.8 $[M+H]^+$.

Step 16: Preparation of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-4,7-difluoro-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione

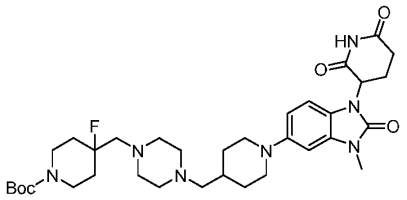


To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4,7-difluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (250 mg, 0.2 mmol) in dichloromethane (5 mL) was added 4 M HCl in 1,4-dioxane (2.5 mL) at 20 °C, and the reaction mixture was stirred for 0.5 h at 20 °C. The mixture was suspended in *tert*-butyl methyl ether (5 mL) and filtered to afford a yellow solid. This crude product was purified by prep-HPLC (8% to 38% acetonitrile in water (formic acid) over 10 min) to afford the title compound (162.8 mg, 66%, di-formic acid salt) as a

yellow solid. LC/MS (ESI) *m/z*: 1058.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (br s, 1H), 9.06 (s, 1H), 8.20 (s, 3H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.64 (br dd, *J* = 6.0, 12.4 Hz, 1H), 5.53 - 5.40 (m, 1H), 4.54 (br d, *J* = 12.4 Hz, 1H), 4.47 (br t, *J* = 5.6 Hz, 2H), 4.39 (br d, *J* = 1Step 2: Hz, 1H), 3.93 (s, 1H), 3.80 (br s, 3H), 3.72 (br t, *J* = 1Step 6: Hz, 4H), 3.49 (br s, 3H), 3.25 - 3.20 (m, 2H), 2.96 (br d, *J* = 9.2 Hz, 3H), 2.88 (br d, *J* = 10.8 Hz, 2H), 2.76 - 2.70 (m, 2H), 2.60 (br d, *J* = 10.8 Hz, 2H), 2.25 (br d, *J* = 6.4 Hz, 2H), 2.10 - 1.93 (m, 5H), 1.78 (br s, 6H), 1.67 - 1.55 (m, 5H), 1.36 - 1.23 (m, 4H), 1.16 - 1.03 (m, 6H).

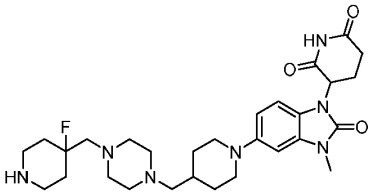
Example 51: Synthesis of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-fluoro-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 200**)

Step 1: Preparation of *tert*-butyl 4-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-4-fluoro-piperidine-1-carboxylate



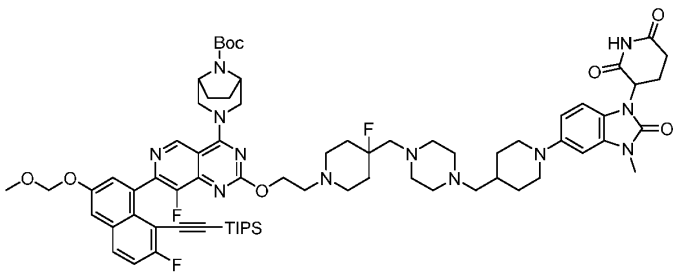
To a solution of (3-[3-methyl-2-oxo-5-[4-(piperazin-1-ylmethyl)-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione (400 mg, 0.9 mmol) and *tert*-butyl 4-fluoro-4-formyl-piperidine-1-carboxylate (419 mg, 1.8 mmol) in isopropanol (5 mL) and dichloromethane (5 mL) were added sodium acetate (744 mg, 9 mmol) and 2-picoline borane (291.4 mg, 2.7 mmol), and the reaction mixture was stirred at 20 °C for 15 h. The mixture was diluted with saturated sodium bicarbonate solution (30 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extract was washed with water (2 x 40 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 5 % methanol in dichloromethane) to afford the title compound (330 mg, 38%) as a white solid. LC/MS (ESI) *m/z*: 656.2 $[M+H]^+$.

Step 2: Preparation of 3-[5-[4-[[4-[(4-fluoro-4-piperidyl)methyl]piperazin-1-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



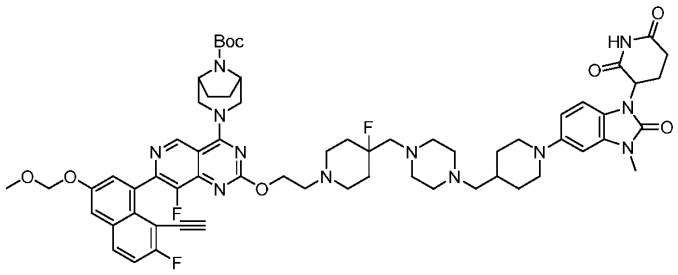
To a solution of *tert*-butyl 4-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-4-fluoro-piperidine-1-carboxylate (330 mg, 0.3 mmol) in dichloromethane (3 mL) was added 4 M HCl in 1,4-dioxane (1.7 mL), and the reaction mixture was stirred at 20 °C for 15 min. The mixture was triturated with petroleum ether (50 mL) to afford the title compound (205 mg, crude, HCl salt) as a white solid. LC/MS (ESI) *m/z*: 556.3 $[M+H]^+$.

Step 3: Preparation of *tert*-butyl 3-[2-[2-[4-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-4-fluoro-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



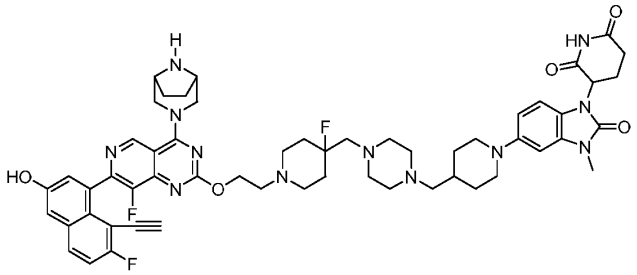
To a mixture of (3-[5-[4-[[4-[(4-fluoro-4-piperidyl)methyl]piperazin-1-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (205 mg, 0.3 mmol, HCl) and *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (360 mg, 0.4 mmol) in dichloromethane (5 mL) and isopropanol (5 mL) were added sodium acetate (284 mg, 3.5 mmol) and 2-picoline borane (185 mg, 1.7 mmol), and the reaction mixture was stirred at 20 °C for 12 h. Th mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (0 to 8 % methanol in dichloromethane) to afford the title compound (400 mg, 79%) as a yellow solid. LC/MS (ESI) *m/z*: 671.6 $[M/2+H]^+$.

Step 4: Preparation of *tert*-butyl 3-[2-[2-[4-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-4-fluoro-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[2-[4-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-4-fluoro-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg, 0.3 mmol) in DMF (3 mL) was added cesium fluoride (624 mg, 4.1 mmol), and the reaction mixture was stirred at 20 °C for 1 h. The mixture was filtered, washing with ethyl acetate (30 mL). The filtrate was diluted with water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extract was washed with water (3 x 30 mL) followed by brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (280 mg, crude) as a yellow solid. LC/MS (ESI) *m/z*: 593.6 $[M/2+H]^+$.

Step 5: Preparation of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-fluoro-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione

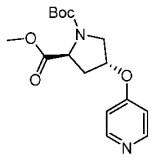


To a solution of *tert*-butyl 3-[2-[2-[4-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-4-fluoro-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (396 mg, 0.3 mmol) in dichloromethane (3 mL) was added 4 M HCl in 1,4-dioxane (2.5 mL), and the reaction mixture was stirred at 20 °C for 30 min. The mixture was suspended in petroleum ether (40 mL) and filtered. and the filter cake was dissolved in THF (30 mL). Triethylamine was added to adjust the pH to 9, and the resulting mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (16%-56% acetonitrile in water (ammonium bicarbonate) over 32 min) to afford the

title compound (143.0 mg, 40%) as a white solid. LC/MS (ESI) *m/z*: 1041.8 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 10.22 - 10.08 (m, 1H), 9.03 (s, 1H), 7.97 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 1.6 Hz, 1H), 6.61 (dd, *J* = 2.0, 8.8 Hz, 1H), 5.28 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.52 - 4.40 (m, 3H), 4.32 (br d, *J* = 11.6 Hz, 1H), 3.92 (s, 1H), 3.65 - 3.50 (m, 6H), 3.29 (s, 3H), 2.93 - 2.85 (m, 1H), 2.73 - 2.56 (m, 9H), 2.47 - 2.22 (m, 12H), 2.13 (br d, *J* = 7.2 Hz, 2H), 2.01 - 1.94 (m, 1H), 1.80 - 1.54 (m, 11H), 1.27 - 1.15 (m, 2H).

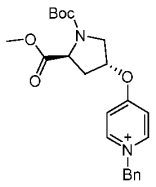
Example 47: Synthesis of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4,7-difluoro-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 201**)

Step 1: Preparation of 1-(tert-butyl) 2-methyl (2S,4R)-4-(pyridin-4-yloxy)pyrrolidine-1,2-dicarboxylate



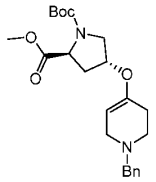
To a mixture of O1-tert-butyl O2-methyl (2S,4S)-4-hydroxypyrrolidine-1,2-dicarboxylate (90 g, 367 mmol), pyridin-4-ol (41.87 g, 440 mmol) and triphenylphosphine (144.4 g, 550 mmol) in toluene (900 mL) at 0 °C was added diisopropyl azodicarboxylate (99.9 mL, 514 mmol) dropwise, and the mixture was purged with nitrogen and stirred at 100 °C for 3 h under nitrogen atmosphere. The reaction mixture was diluted with water (3000 mL) and extracted with ethyl acetate (1000 mL x 3). The combined organic phase was washed with saturated brine (3000 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed-phase HPLC (10%-30% acetonitrile in water (formic acid) over 28 min) to afford the title compound (66 g, 56%) as a yellow solid. LC/MS (ESI) *m/z*: 323.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 - 8.44 (d, *J* = 4.8 Hz, 2H), 6.78 - 6.77 (d, *J* = 4.8 Hz, 2H), 3.87 - 3.77 (m, 4H), 2.59 - 2.55 (m, 1H), 2.33 - 2.26 (m, 1H), 1.70 (s, 3H), 1.46 - 1.43 (m, 9H).

Step 2: Preparation of 1-benzyl-4-(((3R,5S)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)pyrrolidin-3-yl)oxy)pyridin-1-ium



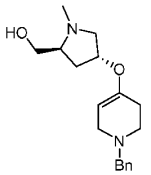
To a solution of 1-(tert-butyl) 2-methyl (2S,4R)-4-(pyridin-4-yloxy)pyrrolidine-1,2-dicarboxylate (10 g, 31 mmol) in acetonitrile (100 mL) was added benzyl bromide (4.42 mL, 37 mmol), and the mixture was degassed and purged with nitrogen, then stirred at 80 °C for 12 h under nitrogen atmosphere. The mixture was concentrated under reduced pressure to afford the title compound (15 g, crude) as a yellow oil. LC/MS (ESI) *m/z*: 413.49 $[M+H]^+$.

Step 3: Preparation of 1-(tert-butyl) 2-methyl (2S,4R)-4-((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)oxy)pyrrolidine-1,2-dicarboxylate



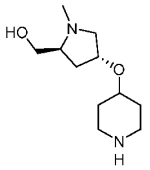
To a solution of 1-benzyl-4-(((3R,5S)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)pyrrolidin-3-yl)oxy)pyridin-1-ium (15 g, 30 mmol) in methanol (150 mL) at 0 °C was added sodium borohydride (3.48 g, 92 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with saturated ammonium chloride solution (50 mL) and water (10 mL), then extracted with ethyl acetate (25 mL x 2). The combined organic layers were washed with saturated sodium chloride (30 mL x 2), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (petroleum ether/ethyl acetate = 1:0 to 5:1) to afford the title compound (10.5 g, 83%) as a yellow oil. LC/MS (ESI) *m/z*: 416.23 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 - 7.27 (m, 4H), 7.27 - 7.20 (m, 1H), 4.61 (d, *J* = 3.6 Hz, 2H), 4.27 - 4.13 (m, 1H), 3.70 - 3.59 (m, 3H), 3.52 (s, 2H), 3.50 - 3.44 (m, 2H), 2.90 (s, 2H), 2.53 - 2.51 (m, 1H), 2.41 - 2.29 (m, 1H), 2.14 - 2.07 (m, 1H), 2.06 (d, *J* = 6.8 Hz, 2H), 1.99 (s, 1H), 1.49 - 1.25 (m, 9H).

Step 4: Preparation of [(2S,4R)-4-[(1-benzyl-3,6-dihydro-2H-pyridin-4-yl)oxy]-1-methyl-pyrrolidin-2-yl]methanol



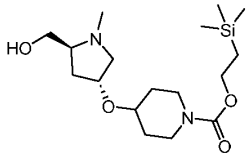
To a mixture of 1-(tert-butyl) 2-methyl (2S,4R)-4-((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)oxy)pyrrolidine-1,2-dicarboxylate (9.5 g, 23 mmol) in tetrahydrofuran (100 mL) was added lithium aluminum hydride (2.6 g, 68 mmol), and the mixture was stirred at 65 °C for 2 h under nitrogen atmosphere. The reaction mixture was quenched slowly with water (30 mL) followed by 1 M aqueous sodium hydroxide (30 mL). Sodium sulfate was then added, and the resulting mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and the residue was purified by prep-HPLC (20%-55% ethanol in hexane over 13min) to give the title compound (5.5 g, 80%) as a white oil. LC/MS (ESI) *m/z*: 302.42 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.36 - 7.27 (m, 4H), 7.27 - 7.19 (m, 1H), 4.51 (t, *J* = 3.2 Hz, 1H), 4.43 - 4.33 (m, 2H), 3.51 (s, 2H), 3.46 - 3.41 (m, 4H), 3.27 (dd, *J* = 5.6, 10.8 Hz, 2H), 2.88 (d, *J* = 3.2 Hz, 2H), 2.25 (s, 3H), 2.03 (t, *J* = 5.2 Hz, 2H), 1.85 - 1.75 (m, 2H).

Step 5: Preparation of [(2S,4R)-1-methyl-4-(4-piperidyloxy)pyrrolidin-2-yl]methanol



To a solution of [(2S,4R)-4-[(1-benzyl-3,6-dihydro-2H-pyridin-4-yl)oxy]-1-methyl-pyrrolidin-2-yl]methanol (2 g, 7 mmol) in tetrahydrofuran (20 mL) were added 10% palladium on carbon (500 mg, 0.7 mmol) and 20% palladium hydroxide (464.39 mg, 0.7 mmol). The suspension was degassed and purged with hydrogen several times, and the mixture was stirred under hydrogen (50 psi) at 50 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to give the title compound (1.2 g, 85%) as a yellow oil. LC/MS (ESI) *m/z*: 214.17 $[M+H]^+$.

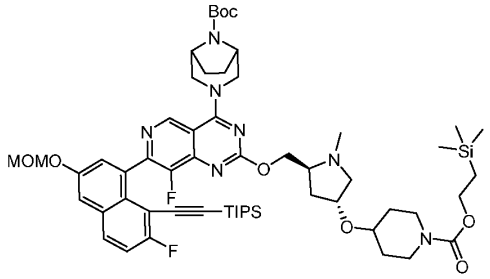
Step 6: Preparation of 2-trimethylsilylethyl 4-[(3R,5S)-5-(hydroxymethyl)-1-methyl-pyrrolidin-3-yl]oxypiperidine-1-carboxylate



To a solution of [(2S,4R)-1-methyl-4-(4-piperidyloxy)pyrrolidin-2-yl]methanol (1.9 g, 9 mmol) in dioxane (40 mL) were added triethylamine (3.7 mL, 27 mmol) and (2,5-dioxopyrrolidin-1-yl) 2-trimethylsilylethyl carbonate (2.30 g, 8.9 mmol), and the mixture was stirred at 25 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (25%-55% acetonitrile in water (formic acid) over 8min) to give the title compound (1.02 g, 32%) as a colorless oil. LC/MS (ESI) *m/z*: 359.3 $[M+H]^+$; ^1H NMR

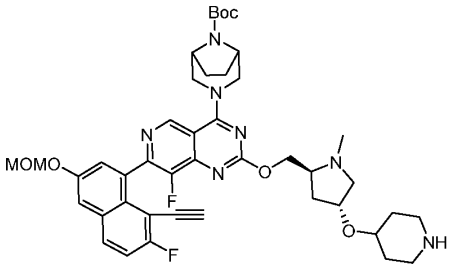
(400MHz, DMSO-d_6) δ 4.37 (s, 1H), 4.09 - 4.05 (m, 2H), 3.72 - 3.64 (m, 2H), 3.49 - 3.44 (m, 2H), 3.41 - 3.39 (m, 1H), 3.26 - 3.18 (m, 2H), 3.05 - 2.97 (m, 2H), 2.40 - 2.33 (m, 1H), 2.24 (s, 3H), 2.08 (dd, *J* = 6.4, 9.2 Hz, 1H), 1.80 - 1.69 (m, 4H), 1.31 - 1.24 (m, 2H), 0.96 - 0.90 (m, 2H), 0.06 - 0.00 (m, 9H).

Step 7: Preparation of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-[[(2S,4R)-1-methyl-4-[[1-(2-trimethylsilylethoxycarbonyl)-4-piperidyl]oxy]pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



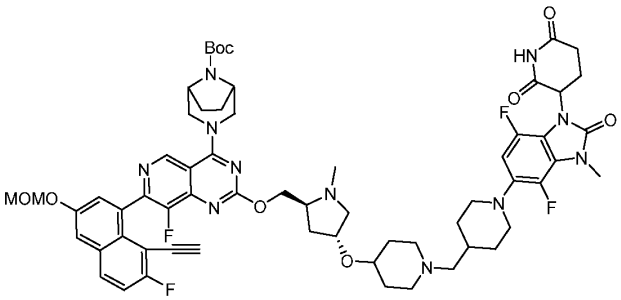
To a solution of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-methylsulfonyl-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (4.3 g, 5 mmol) and 2-trimethylsilylethyl 4-[(3R,5S)-5-(hydroxymethyl)-1-methyl-pyrrolidin-3-yl]oxypiperidine-1-carboxylate (1.91 g, 5 mmol) in tetrahydrofuran (50 mL) at 0 °C was added lithium tert-butoxide (2.2 M, 9.5 mL), and the reaction mixture was stirred at 25 °C for 1 h. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by prep-HPLC (55% to 85% acetonitrile in water (formic acid) over 20 min) to afford the title compound (2.6 g, 45%, formic acid salt) as a yellow gum. LC/MS (ESI) *m/z*: 1101.0 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.78 (dd, *J* = 5.6, 9.0 Hz, 1H), 7.51 (d, *J* = 2.5 Hz, 1H), 7.34 - 7.28 (m, 2H), 7.27 (s, 1H), 5.36 - 5.24 (m, 2H), 4.76 (s, 1H), 4.63 - 4.48 (m, 1H), 4.37 (dd, *J* = 6.3, 10.8 Hz, 2H), 4.30 - 4.18 (m, 3H), 3.79 (s, 3H), 3.51 (s, 3H), 3.42 - 3.33 (m, 1H), 3.18 - 3.05 (m, 2H), 3.02 - 2.90 (m, 1H), 2.49 (d, *J* = 2.0 Hz, 3H), 2.34 (*J* = 3.9, 6.1, 9.7 Hz, 1H), 2.03 - 1.94 (m, 3H), 1.86 - 1.74 (m, 2H), 1.57 - 1.51 (m, 9H), 0.95 - 0.78 (m, 18H), 0.55 (quin, *J* = 7.1 Hz, 3H), 0.10 -0.02 (m, 9H).

Step 8: Preparation of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,4R)-1-methyl-4-(4-piperidyloxy)pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-[[(2S,4R)-1-methyl-4-[[1-(2-trimethylsilylethoxycarbonyl)-4-piperidyl]oxy]pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2 g, 2 mmol) in *N,N*-dimethylformamide (20 mL) was added cesium fluoride (0.67 mL, 18 mmol), and the reaction mixture was stirred at 90 °C for 1 h. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (10%-40% acetonitrile in water (formic acid) over 11 min) to afford the title compound (1.3g, 89%, formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 800.5 $[M+H]^+$.

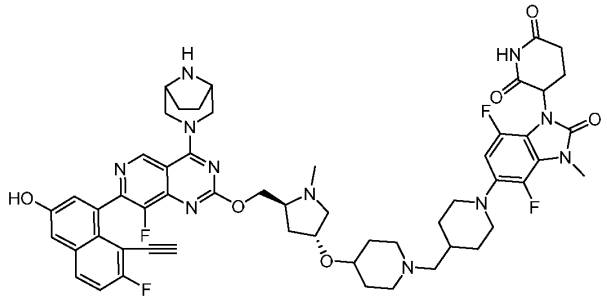
Step 9: Preparation of *tert*-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[1-(2,6-dioxo-3- piperidyl)-4,7-difluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a mixture of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,4R)-1-methyl-4-(4-piperidyloxy)pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.2 mmol) and 1-[1-(2,6-dioxo-3-piperidyl)-4,7-difluoro-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (100 mg, 0.2 mmol) in dichloromethane (2 mL) and isopropanol (1 mL) was added *N,N*-diisopropylethylamine (32 mg, 0.2 mmol), and the resulting mixture was stirred at 25 °C for 10 min. Sodium triacetoxyborohydride (158 mg, 0.7 mmol) was then added, and the reaction mixture was stirred at 25 °C for 0.5 h. The mixture was filtered and concentrated under reduced pressure to afford

the title compound (250 mg, 84%) as a yellow solid. LC/MS (ESI) *m/z*: 596.2 $[M/2+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 9.09 (s, 1H), 8.10 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.75 (d, *J* = 2.8 Hz, 1H), 7.55 (t, *J* = 9.2 Hz, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 6.70 - 6.60 (m, 1H), 5.53 - 5.41 (m, 1H), 5.37 (s, 2H), 4.61 - 4.50 (m, 1H), 4.46 - 4.35 (m, 2H), 4.34 - 4.22 (m, 3H), 4.17 - 4.09 (m, 1H), 4.00 - 3.97 (m, 1H), 3.71 - 3.59 (m, 2H), 3.49 (s, 3H), 3.44 (s, 3H), 3.28 - 3.19 (m, 4H), 3.06 - 2.85 (m, 2H), 2.84 - 2.70 (m, 2H), 2.65 - 2.57 (m, 3H), 2.37 (s, 3H), 2.25 - 2.16 (m, 2H), 2.15 - 2.07 (m, 2H), 1.91 (s, 4H), 1.89 - 1.70 (m, 9H), 1.67 - 1.57 (m, 1H), 1.46 (s, 11H), 1.33 - 1.21 (m, 2H).

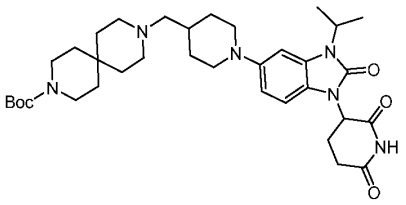
Step 4: Preparation of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4,7-difluoro-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione



To a solution of *tert*-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[1-(2,6-dioxo-3- piperidyl)-4,7-difluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (250 mg, 0.2 mmol) in dichloromethane (1 mL) was added 4 M HCl in 1,4-dioxane (1 mL), and the reaction mixture was stirred at 25 °C for 15 min. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (2% to 32% acetonitrile in water (formic acid) over 15 min) to afford the title compound (80.2 mg, 32%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1046.6 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 9.05 (s, 1H), 8.19 (s, 2H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.70 - 6.59 (m, 1H), 5.52 - 5.39 (m, 1H), 4.56 - 4.49 (m, 1H), 4.41 - 4.33 (m, 2H), 4.26 - 4.21 (m, 1H), 4.14 - 4.09 (m, 1H), 3.94 - 3.92 (m, 1H), 3.78 - 3.70 (m, 3H), 3.70 - 3.61 (m, 2H), 3.49 (s, 3H), 3.33 - 3.20 (m, 4H), 3.04 - 2.90 (m, 1H), 2.84 - 2.75 (m, 1H), 2.73 - 2.55 (m, 5H), 2.35 (s, 3H), 2.22 - 1.97 (m, 7H), 1.93 - 1.84 (m, 2H), 1.83 - 1.70 (m, 8H), 1.63 - 1.51 (m, 1H), 1.46 - 1.32 (m, 2H), 1.30 - 1.18 (m, 2H).

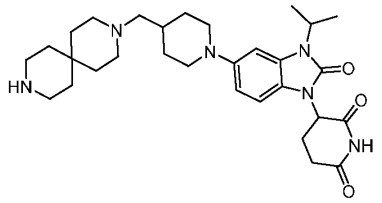
Example 48: Synthesis of 3-(5-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 202**)

Step 1: Preparation of *tert*-butyl 9-((1-(1-(2,6-dioxopiperidin-3-yl)-3-isopropyl-2-oxo-2,3-dihydro-1H-benzo[*d*]imidazol-5-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate



To a solution of 1-(1-(2,6-dioxopiperidin-3-yl)-3-isopropyl-2-oxo-2,3-dihydro-1H-benzo[d] imidazol-5-yl)piperidine-4-carbaldehyde (800 mg, 2 mmol) and *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (510 mg, 2 mmol) in dichloromethane (8 mL) and dimethyl sulfoxide (8 mL) was added acetic acid (0.2 mL, 4 mmol,) and the resulting mixture was stirred for 30 min. Sodium triacetoxyborohydride (851 mg, 4 mmol) was then added, and the reaction mixture was stirred at 25 °C for 2 h. The mixture was diluted with water (30 mL) and extracted with dichloromethane (2 x 30 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (0 to 100% ethyl acetate/petroleum ether then 0 to 15% dichloromethane/methanol) to afford the title compound (1 g, 78%) as a white solid. LC/MS (ESI) *m/z*: 637.4 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 - 8.18 (m, 1H), 6.81 (s, 1H), 6.67 (s, 2H), 5.20 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.67 (td, *J* = 7.2, 1Step 6: Hz, 1H), 3.56 - 3.47 (m, 3H), 3.43 - 3.34 (m, 4H), 2.95 - 2.88 (m, 1H), 2.86 - 2.74 (m, 3H), 2.73 - 2.64 (m, 4H), 2.63 (s, 2H), 2.61 - 2.56 (m, 1H), 2.25 - 2.17 (m, 1H), 2.04 (s, 2H), 1.95 (br d, *J* = 12.4 Hz, 2H), 1.83 (br s, 1H), 1.73 (br s, 3H), 1.55 (d, *J* = 7.2 Hz, 6H), 1.46 (s, 13H).

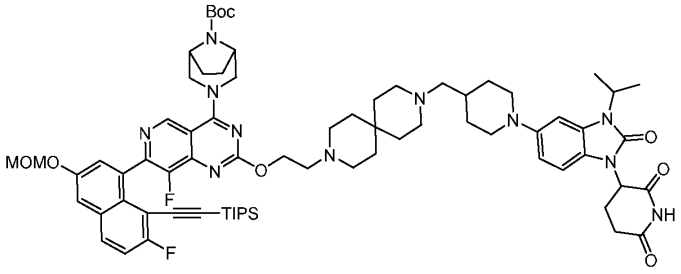
Step 2: Preparation of 3-(5-(4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-3-isopropyl-2-oxo-2,3-dihydro-1H-benzo[*d*]imidazol-1-yl)piperidine-2,6-dione



To a solution of *tert*-butyl 9-((1-(1-(2,6-dioxopiperidin-3-yl)-3-isopropyl-2-oxo-2,3-dihydro-1H-benzo[*d*]imidazol-5-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-

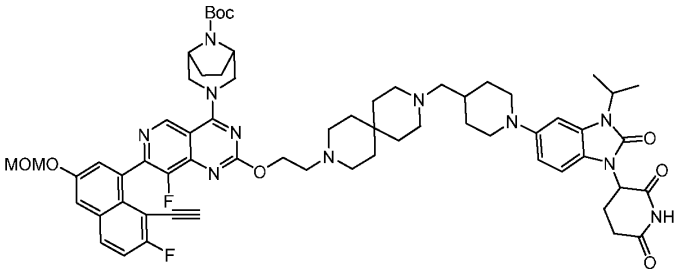
carboxylate (1 g, 1 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (5.0 mL, 67 mmol), and the reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to afford the title compound (1 g, 97%, TFA salt) as a pink oil. LC/MS (ESI) *m/z*: 537.5 $[M+H]^+$.

Step 3: Preparation of *tert*-butyl (1*R*,5*S*)-3-(2-(2-(9-((1-(1-(2,6-dioxopiperidin-3-yl)-3-isopropyl-2-oxo-2,3-dihydro-1H-benzo[*d*]imidazol-5-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethoxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



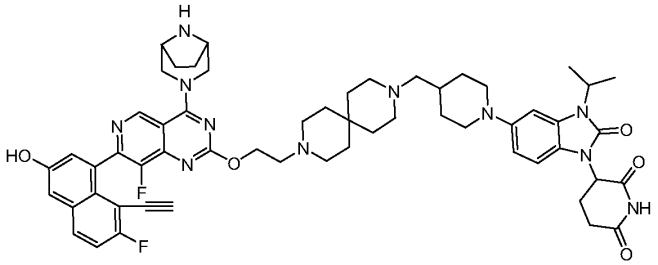
To a solution of 3-(5-(4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-3-isopropyl-2-oxo-2,3-dihydro-1H-benzo[*d*]imidazol-1-yl)piperidine-2,6-dione trifluoroacetate (1.0 g, 1.5 mmol) in dichloromethane (10 mL) and isopropanol (10 mL) was added *N,N*-diisopropylethylamine (0.5 mL, 3 mmol), and the resulting mixture was stirred for 15 min. Acetic acid (0.2 mL, 3 mmol) and *tert*-butyl (1*R*,5*S*)-3-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(2-oxoethoxy)pyrido [4,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.23 g, 1.5 mmol) were then added, and the mixture was stirred for 15 min. Sodium triacetoxyborohydride (651 mg, 3 mmol) was then added, and the reaction mixture was stirred at 25 °C for 2 h. The mixture was diluted with water (100 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (0 to 100% ethyl acetate/petroleum ether then 0 to 15% dichloromethane/methanol) to afford the title compound (1.4 g, 68%) as a yellow solid. LC/MS (ESI) *m/z*: 1323.0 $[M+H]^+$.

Step 4: Preparation of *tert*-butyl (1*R*,5*S*)-3-(2-(2-(9-((1-(1-(2,6-dioxopiperidin-3-yl)-3-isopropyl-2-oxo-2,3-dihydro-1H-benzo[*d*]imidazol-5-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethoxy)-7-(8-ethynyl-7-fluoro-3-(methoxy methoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1] octane-8-carboxylate



To a solution of *tert*-butyl (1*R*,5*S*)-3-(2-(2-(9-((1-(1-(2,6-dioxopiperidin-3-yl)-3-isopropyl-2-oxo-2,3-dihydro-1H-benzo[*d*]imidazol-5-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethoxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.4 g, 1 mmol) in *N,N*-dimethylformamide (15 mL) was added cesium fluoride (3.22 g, 21 mmol), and the reaction mixture was stirred at 25 °C for 12 h. The residue was diluted with water (100 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (12% to 42% acetonitrile in water (formic acid) over 15 min) to afford the title compound (620 mg, 50%, formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1166.8 $[M+H]^+$.

Step 5: Preparation of 3-(5-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione

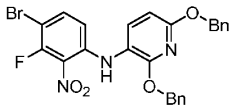


To a solution of *tert*-butyl (1*R*,5*S*)-3-(2-(2-(9-((1-(1-(2,6-dioxopiperidin-3-yl)-3-isopropyl-2-oxo-2,3-dihydro-1H-benzo[*d*]imidazol-5-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethoxy)-7-(8-ethynyl-7-fluoro-3-(methoxy methoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1] octane-8-carboxylate (620 mg, 0.5 mmol) in dichloromethane (7 mL) was added 4 M HCl in 1,4-dioxane (6 mL), and the reaction mixture was stirred at 25 °C for 15 min. The mixture was suspended in petroleum ether (30 mL), filtered, and the filter cake was dissolved in dimethyl sulfoxide (5 mL) and *N,N*-diisopropylethylamine to adjust the pH to 7. The resulting solution was purified by prep-HPLC

(1% to 28% acetonitrile in water (formic acid) over 15 min) to afford the title compound (235.6 mg, 38%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1023.6 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.06 (br s, 1H), 9.07 (s, 1H), 8.24 (s, 2H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.61 (dd, *J* = 1.6, 8.8 Hz, 1H), 5.26 (br dd, *J* = 5.6, 12.8 Hz, 1H), 4.65 - 4.52 (m, 2H), 4.48 (br t, *J* = 5.6 Hz, 2H), 4.40 (br d, *J* = 12.4 Hz, 1H), 3.94 (s, 1H), 3.83 (br s, 2H), 3.74 (br t, *J* = 1Step 6: Hz, 2H), 3.53 (br d, *J* = 11.6 Hz, 2H), 2.96 - 2.82 (m, 1H), 2.77 (br t, *J* = 5.2 Hz, 2H), 2.72 - 2.56 (m, 5H), 2.47 (br d, *J* = Step 2: Hz, 5H), 2.32 (br d, *J* = 6.4 Hz, 2H), 2.03 - 1.93 (m, 1H), 1.85 - 1.74 (m, 6H), 1.72 - 1.57 (m, 2H), 1.44 (br d, *J* = 6.8 Hz, 15H), 1.31 - 1.18 (m, 3H).

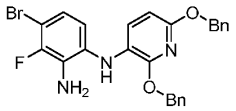
Example 49: Synthesis of 3-[5-[4-[[9-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-3,9-diazaspiro[5.5]undecan-3-yl]methyl]-1-piperidyl]-4-fluoro-3-isopropyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 203**)

Step 1: Preparation of 2,6-dibenzyloxy-N-(4-bromo-3-fluoro-2-nitro-phenyl)pyridin-3-amine



To a solution of 2,6-dibenzyloxypyridin-3-amine (4.9 g, 16 mmol) and 1-bromo-2,4-difluoro-3-nitro-benzene (3.81 g, 16 mmol) in DMSO (50 mL) was added DIEA (4.2 mL, 24 mmol), and the mixture was stirred at 110 °C for 18 h. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 x 70 mL). The combined organic extract was washed with water (6 x 20 mL) followed by brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 3% then up to 5% ethyl acetate in petroleum ether) to afford the title compound (5.09 g, 49%) as a dark brown solid. LC/MS (ESI) *m/z*: 524.2 $[M+H]^+$.

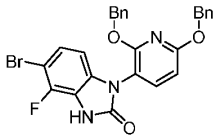
Step 2: Preparation of 4-bromo-N1-(2,6-dibenzyloxy-3-pyridyl)-3-fluoro-benzene-1,2-diamine



To a solution of 2,6-dibenzyloxy-N-(4-bromo-3-fluoro-2-nitro-phenyl)pyridin-3-amine (5 g, 9 mmol) in isopropanol (80 mL), THF (10 mL), and water (10 mL) were added ammonium chloride (4.08 g, 76 mmol) and iron (2.66 g, 48 mmol), and the reaction mixture was stirred at 80 °C for 3 h. The mixture was filtered, washing with ethyl acetate (3 x 100 mL). The filtrate was

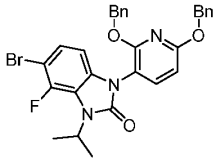
washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 3% then up to 5% ethyl acetate in petroleum ether) to afford the title compound (3.59 g, 64%) as a pink solid. LC/MS (ESI) *m/z*: 496.1 $[M+H]^+$.

Step 3: Preparation of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1H-benzimidazol-2-one



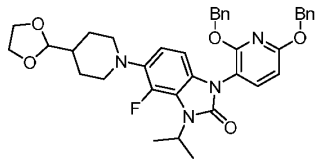
To a solution of 4-bromo-N1-(2,6-dibenzyloxy-3-pyridyl)-3-fluoro-benzene-1,2-diamine (3.6 g, 7.2 mmol) and triethylamine (3.01 mL, 22 mmol) in THF (60 mL) was added CDI (3.50 g, 22 mmol), and the reaction mixture was stirred at 70 °C for 16 h. The mixture was concentrated under reduced pressure, and the residue was diluted with water (50 mL) and extracted with chloromethane (3 x 50 mL). The combined organic extract was washed with water (3 x 20 mL) followed by brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was triturated with ethyl acetate/MTBE (1/1, 30 mL) to afford 2.7 g of product. The filtrate solution was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel (0 to 30% THF in petroleum ether over 16 min) to afford 0.78 g of product. In total, 3.48 g (93%) of the title compound was obtained as a pink solid. LC/MS (ESI) *m/z*: 522.0 $[M+H]^+$.

Step 4: Preparation of 5-bromo-1-(2,6-dibenzyloxy-3-pyridyl)-4-fluoro-3-isopropyl-benzimidazol-2-one



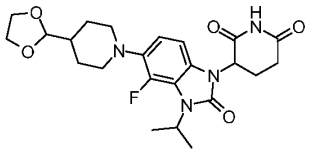
To a solution of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1H-benzimidazol-2-one (3.1 g, 6 mmol) in DMF (30 mL) were added cesium carbonate (4.85 g, 15 mmol) and 2-iodopropane (1.8 mL, 18 mmol), and the reaction mixture was stirred at 20 °C for 16 h. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 70 mL). The combined organic extract was washed with water (7 x 30 mL) followed by brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 15% ethyl acetate in petroleum ether over 8 min) to afford the title compound (3.01 g, 87%) as a yellow oily solid. LC/MS (ESI) *m/z*: 564.1 $[M+H]^+$.

Step 5: Preparation of 1-(2,6-dibenzyloxy-3-pyridyl)-5-[4-(1,3-dioxolan-2-yl)-1-piperidyl]-4-fluoro-3-isopropyl-benzimidazol-2-one



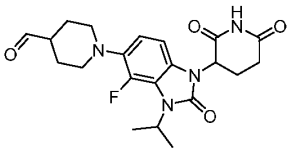
To a solution of 5-bromo-1-(2,6-dibenzyloxy-3-pyridyl)-4-fluoro-3-isopropyl-benzimidazol-2-one (1.0 g, 1.8 mmol) and 4-(1,3-dioxolan-2-yl)piperidine (559 mg, 3.6 mmol) in 1,4-dioxane (12 mL) were added t-BuONa (513 mg, 5.3 mmol) and BrettPhos Pd G3 (242 mg, 0.3 mmol) under nitrogen atmosphere, and the resulting mixture was degassed and purged with nitrogen (3X), then stirred at 90 °C for 12 h under nitrogen atmosphere. The mixture was suspended in dichloromethane (50 mL) and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 15% then up to 17% ethyl acetate in petroleum ether) to afford the title compound (460 mg, 30%) as a yellow solid. LC/MS (ESI) *m/z*: 639.5 $[M+H]^+$.

Step 6: Preparation of 3-[5-[4-(1,3-dioxolan-2-yl)-1-piperidyl]-4-fluoro-3-isopropyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



To a solution of 1-(2,6-dibenzyloxy-3-pyridyl)-5-[4-(1,3-dioxolan-2-yl)-1-piperidyl]-4-fluoro-3-isopropyl-benzimidazol-2-one (460 mg, 0.7 mmol) in THF (30 mL) was added 10% $Pd(OH)_2$ on carbon (0.19 g) under argon, and the resulting mixture was degassed and purged with hydrogen (3X), then stirred at 50°C for 16 h under hydrogen (50 psi). The mixture was filtered, washing with THF (100 mL), and the filtrate was concentrated under reduced pressure to afford the title compound (364 mg, 85%) as a white solid. LC/MS (ESI) *m/z*: 461.2 $[M+H]^+$.

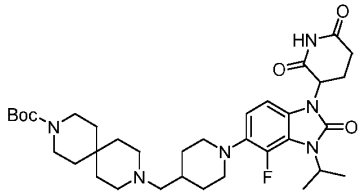
Step 7: Preparation of 1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde



To a solution of 3-[5-[4-(1,3-dioxolan-2-yl)-1-piperidyl]-4-fluoro-3-isopropyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (330 mg, 0.7 mmol) in acetone (4.0 mL) was added 3 M

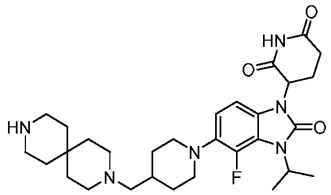
aqueous HCl solution (3.8 mL), and the mixture was stirred at 60 °C for 5 h. Then another 3 M aqueous HCl solution (2.5 mL) was added and stirred at 60 °C for 3 h. The mixture was concentrated under reduced pressure, then saturated sodium bicarbonate solution was added to adjust the pH to 8, and the mixture was extracted with methanol/dichloromethane (1:10, 3 x 50 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford the title compound (272 mg, 80%) as a yellow solid. LC/MS (ESI) *m/z*: 417.1 $[M+H]^+$.

Step 8: Preparation of tert-butyl 9-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate



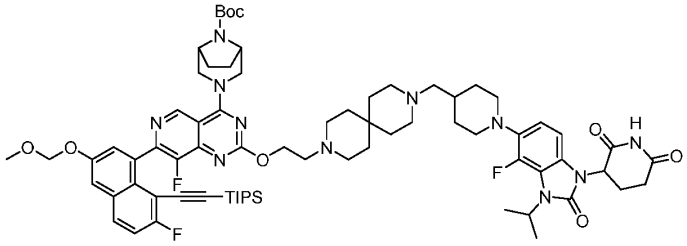
To a solution of 1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (400 mg, 1 mmol) and tert-butyl 3, 9-diazaspiro[5.5]undecane-3-carboxylate (318 mg, 1 mmol) in dichloromethane (5.0 mL) and isopropanol (5.0 mL) were added acetic acid (0.3 mL, 5 mmol) and 2-methylpyridine borane (411 mg, 3.8 mmol), and the reaction mixture was stirred at 25 °C for 12 h. Triethylamine was then added to adjust the pH to 8, and the resulting mixture was concentrated. The residue was purified by flash column chromatography on silica gel (0 to 6% methanol in dichloromethane) to afford the title compound (464 mg, 70%) as a white foam. LC/MS (ESI) *m/z*: 655.7 $[M+H]^+$.

Step 9: Preparation of 3-[5-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-4-fluoro-3-isopropyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



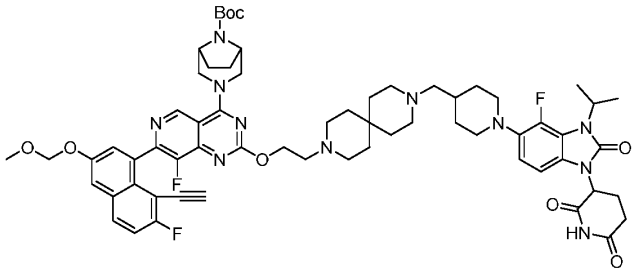
To a solution of tert-butyl 9-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate (464 mg, 0.7 mmol) in dichloromethane (5.0 mL) was added 4 M HCl in 1,4-dioxane (5.0 mL), and the reaction mixture was stirred at 25 °C for 20 min. The reaction mixture was evaporated from petroleum ether (15 mL x 2) to afford the title compound (470 mg, crude, 3 HCl salt) as a white solid. LC/MS (ESI) *m/z*: 555.5 $[M+H]^+$.

Step 10: Preparation of tert-butyl 3-[2-[2-[3-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To 3-[5-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-4-fluoro-3-isopropyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (440 mg, 0.4 mmol, 3 HCl) in dichloromethane (5.0 mL) and DMSO (2.5 mL) were added sodium acetate (341 mg, 4 mmol), tert-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (556 mg, 0.4 mmol), and $NaBH(OAc)_3$ (367 mg, 1.7 mmol), and the reaction mixture was stirred at 25 °C for 2 h. The mixture was diluted with saturated sodium bicarbonate solution (5.0 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with water (4 x 10 mL) followed by brine (15 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 6% methanol in dichloromethane over 15 min) to afford the title compound (588 mg, 52%) as a yellow foam. LC/MS (ESI) *m/z*: 1341.9 $[M+H]^+$.

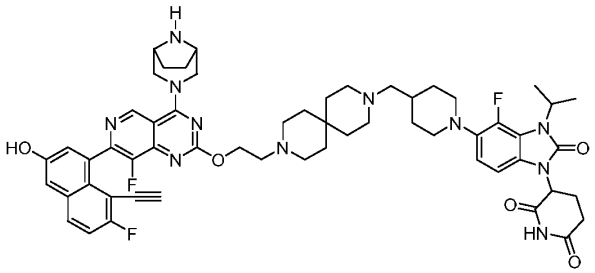
Step 11: Preparation of tert-butyl 3-[2-[2-[3-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of tert-butyl 3-[2-[2-[3-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-

yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (588 mg, 0.4 mmol) in DMF (6.0 mL) was added cesium fluoride (333 mg, 2 mmol), and the reaction mixture was stirred at 25 °C for 12 h. The mixture was diluted with ethyl acetate (20 mL), then washed with water (3 x 10 mL). The aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with water (5.0 mL x 6) followed by brine (2 x 15 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (488 mg, 54%) as a yellow foam. LC/MS (ESI) *m/z*: 1184.7 $[M+H]^+$.

Step 12: Preparation of 3-[5-[4-[[9-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-3,9-diazaspiro[5.5]undecan-3-yl]methyl]-1-piperidyl]-4-fluoro-3-isopropyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione

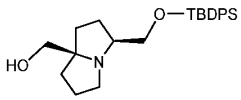


To a solution of tert-butyl 3-[2-[2-[3-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (488 mg, 0.2 mmol) in dichloromethane (4.0 mL) was added 4 M HCl in 1,4-dioxane (4.0 mL), and the reaction mixture was stirred at 25 °C for 15 min. The mixture was diluted with tetrahydrofuran (30 mL) and triethylamine to adjust the pH to 8. The resulting mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (30% to 70% acetonitrile in water (ammonium bicarbonate) over 32 min) to afford the title compound (138.6 mg, 32%) as a yellow solid. LC/MS (ESI) *m/z*: 1040.5 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 7.86 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.36 - 7.28 (m, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 6.90 - 6.80 (m, 2H), 5.28 (dd, *J* = 5.2, 12.4 Hz, 1H), 4.73 - 4.54 (m, 5H), 3.75 - 3.62 (m, 4H), 3.37 (s, 1H), 2.95 - 2.84 (m, 3H), 2.84 - 2.71 (m, 3H), 2.71 - 2.65 (m, 2H), 2.62 (br s, 4H), 2.46 (br s, 4H), 2.32 (br d, *J* = 6.4 Hz, 2H), 2.18 - 2.11 (m, 1H), 1.87 (br d, *J* = 12.8 Hz, 4H), 1.83 - 1.77 (m, 2H), 1.75 - 1.66 (m, 1H), 1.57 (br s, 8H), 1.51 (br d, *J* = 6.8 Hz, 6H), 1.48 (br s, 1H), 1.46 - 1.38 (m, 2H).

Example 50: Synthesis of 3-[5-[4-[[4-[[(3S,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-

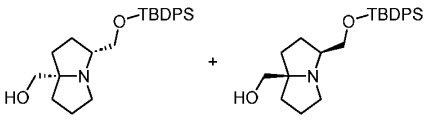
1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 204**)

Step 7: Preparation of *cis*-[3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol



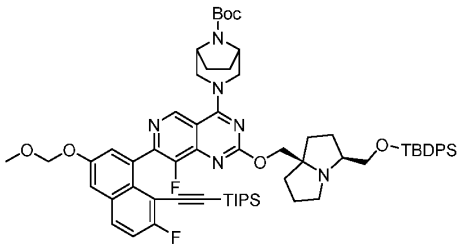
To a stirred solution of methyl 3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizine-8-carboxylate (1.0 g, 2 mmol) in tetrahydrofuran (15 mL) was added lithium aluminium hydride (104 mg, 2.7 mmol), and the reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with water (0.1 mL), aqueous sodium hydroxide solution (0.1 mL, 15 wt%), and water (0.3 mL) sequentially at 0 °C. The mixture was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 50% ethyl acetate in petroleum ether over 10 min) to afford the title compound (477 mg, 48%) as a white oil. LC/MS (ESI) *m/z*: 410.3 $[M+H]^+$.

Step 8: Preparation of [(3R,8S)-3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol & [(3S,8R)-3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol



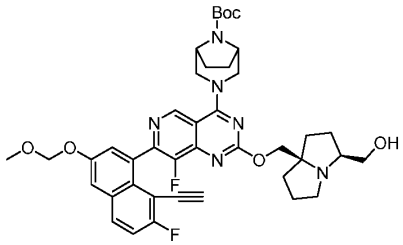
cis-[3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (500 mg) was purified by SFC (column: DAICEL CHIRALCEL OX (250mm*30mm,10um); [0.1%NH_3H_2O-IPA], 35%) to afford the first eluted enantiomer [(3R,8S)-3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (240 mg, 46%) as colorless oil, and then the later eluted enantiomer [(3S,8R)-3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (265 mg, 49%) as colorless oil. LC/MS (ESI) *m/z*: 410.3 $[M+H]^+$.

Step 9: Preparation of tert-butyl 3-[2-[[(3S,8R)-3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a mixture of tert-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-methylsulfonyl-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 0.6 mmol), 4A molecular sieves (500 mg), and [(3S,8R)-3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (249 mg, 0.6 mmol) in tetrahydrofuran (6 mL) at 0°C was added t-BuONa (146 mg, 1.5 mmol) under nitrogen atmosphere, and the reaction mixture was stirred at 0 °C for 30 min. The mixture was diluted with 0.2 M aqueous HCl solution (8 mL) and extracted with dichloromethane (3 x 40 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 20% ethyl acetate in petroleum ether over 18 min) to afford the title compound (294 mg, 39%) as a yellow oil. LC/MS (ESI) m/z: 1151.5 $[M+H]^+$.

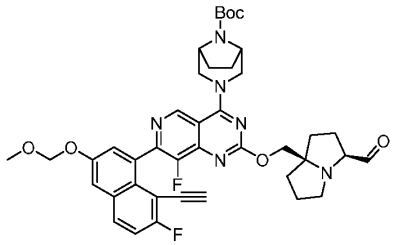
Step 10: Preparation of tert-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3S,8R)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of tert-butyl 3-[2-[[(3S,8R)-3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (294 mg, 0.3 mmol) in DMF (4 mL) was added cesium fluoride (310 mg, 2 mmol), and the reaction mixture was stirred at 30 °C for 12 h. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to

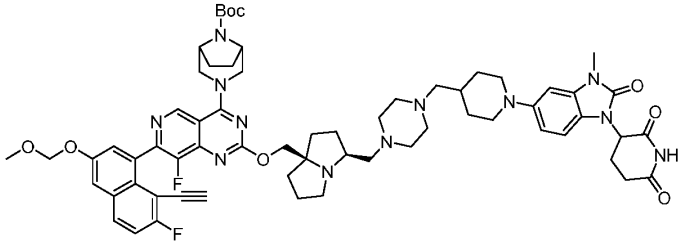
2% then up to 7% methanol in dichloromethane) to afford the title compound (167 mg, 78%) as a yellow solid. LC/MS (ESI) m/z: 757.3 $[M+H]^+$.

Step 11: Preparation of tert-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3S,8R)-3-formyl-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



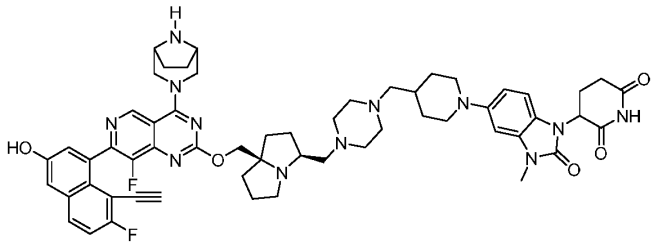
To a mixture of DMSO (413 µL) and dichloromethane (2 mL) at -67°C was added a solution of oxalyl dichloride (290 µL, 3.3 mmol) in dichloromethane (3 mL) dropwise under nitrogen atmosphere, and the mixture was stirred for 15 min. tert-Butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3S,8R)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 0.7 mmol) in dichloromethane (4 mL) was then added dropwise, and the resulting mixture was stirred at -67 °C for 30 min. Triethylamine (2.3 mL) was then, and the reaction mixture was stirred at -67 °C for 20 min under nitrogen atmosphere. The mixture was diluted with saturated sodium bicarbonate solution (10 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extract was washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (498 mg, crude) in dichloromethane (3 mL) as a yellow solution. LC/MS (ESI) *m/z*: 773.2 $[M+H_3O]^+$.

Step 12: Preparation of *tert*-butyl 3-[2-[[(3S,8R)-3-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a mixture of 3-[3-methyl-2-oxo-5-[4-(piperazin-1-ylmethyl)-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione (275 mg, 0.6 mmol) and tert-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3S,8R)-3-formyl-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (376 mg, 0.5 mmol) in dichloromethane (15 mL) was added $NaBH(OAc)_3$ (264 mg, 1.3 mmol), and the reaction mixture was stirred at 25 °C for 12 h. The mixture was diluted with sodium bicarbonate (10 mL) and extracted with dichloromethane (3 x 40 mL). The combined organic extract was washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 7% methanol in dichloromethane) to afford the title compound (255 mg, 43%) as a yellow solid. LC/MS (ESI) m/z: 1179.5 $[M+H]^+$.

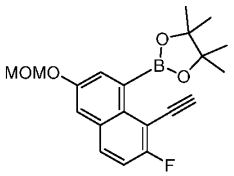
Step 13: Preparation of 3-[5-[4-[[4-[[(3S,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



To a solution of tert-butyl 3-[2-[[(3S,8R)-3-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (255 mg, 0.2 mmol) in dichloromethane (2.0 mL) was added 4 M HCl in 1,4-dioxane (2.0 mL), and the mixture was stirred at 25°C for 10 min. The reaction mixture was suspended in petroleum ether (6 mL) and filtered. The sticky filter cake was diluted with THF (50 mL) and triethylamine to adjust the pH to 8. The mixture was filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (18% to 58% acetonitrile in water (ammonium bicarbonate) over 32 min) to afford the title compound (114.0 mg, 50%) as a yellow solid. LC/MS (ESI) m/z: 1035.7 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.01 (d, *J* = 2.4 Hz, 1H), 7.85 (ddd, *J* = 3.2, 5.6, 9.2 Hz, 1H), 7.37 - 7.26 (m, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.87 (s, 1H), 6.80 (br d, *J* = 8.4 Hz, 1H), 5.28 (dd, *J* = 5.6, 12.4 Hz, 1H), 4.69 - 4.55 (m, 2H), 4.32 - 4.20 (m, 2H), 3.75 - 3.64 (m, 4H), 3.57 (br d, *J* = 11.6 Hz, 2H), 3.43 - 3.35 (m, 4H), 3.14 - 2.97 (m, 2H), 2.95 - 2.74 (m, 4H), 2.73 - 2.31 (m, 12H), 2.27 - 2.06 (m, 5H), 1.99 - 1.65 (m, 13H), 1.44 - 1.27 (m, 2H).

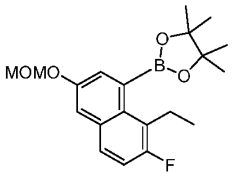
Example 51: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 205**)

Step 1: Preparation of 2-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



To a solution of 2-[2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl-triisopropyl-silane (5.0 g, 10 mmol) in *N,N*-dimethylformamide (50 mL) was added cesium fluoride (29.64 g, 195 mmol), and the reaction mixture was stirred at 25 °C for 12 h. The mixture was diluted with water (60 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (2 x 40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1 then 4:1) to afford the title compound (3.3 g, 95%) as a light yellow solid. LC/MS (ESI) *m/z*: 356.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.48 (t, J = 9.2 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 5.32 (s, 2H), 5.01 (s, 1H), 3.42 (s, 3H), 1.37 (s, 12H).

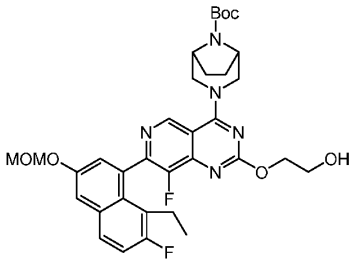
Step 2: Preparation of 2-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



A mixture of 2-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3 g, 9 mmol) and platinum/aluminium oxide (0.3 g) in tetrahydrofuran (30 mL) and ethyl acetate (30 mL) was added into a FLV1 flow chemistry reactor at 20 °C, and the mixture was stirred for 10 min at 20 °C. The backpressure regulator was set to 0.5 MPa, the flow rate of P1 was at 0.5 mL/min, the hydrogen flow rate was 20 mL/min, and the reaction mixture was stirred at 40 °C for 20 min. The reaction solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1 to 4:1) to afford the title compound (1.5 g, 45%) as a light yellow gum. ^{1}H NMR

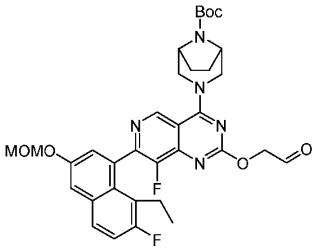
(400 MHz, $CDCl_3$) δ 7.66 - 7.51 (m, 1H), 7.47 - 7.33 (m, 2H), 7.25 - 7.13 (m, 1H), 5.41 - 5.26 (m, 2H), 3.64 - 3.51 (m, 3H), 3.25 - 3.06 (m, 2H), 1.58 - 1.44 (m, 12H), 1.32 - 1.25 (m, 3H).

Step 3: Preparation of *tert*-butyl 3-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-(2-hydroxyethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



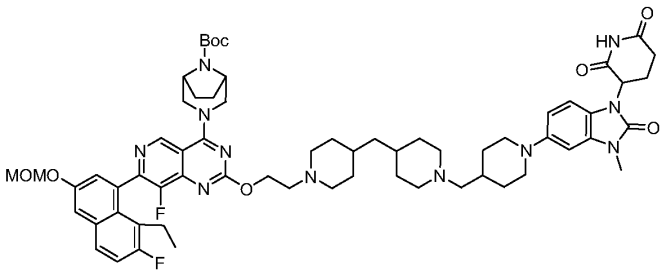
A mixture of 2-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (524 mg, 1.45 mmol), *tert*-butyl 3-[7-chloro-8-fluoro-2-(2-hydroxyethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (600 mg, 1.3 mmol), potassium phosphate (842 mg, 4 mmol), and CataCXium A Pd G3 (97 mg, 0.1 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was purged and degassed with nitrogen (3X), and the mixture was stirred at 90 °C for 16 h. The mixture was cooled to 25 °C, diluted with water (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extract was washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1 then 4:1) to afford the title compound (520 mg, 60%) as a light yellow solid. LC/MS (ESI) *m/z*: 652.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 7.89 (dd, J = 6.0, 9.2 Hz, 1H), 7.67 (d, J = 2.8 Hz, 1H), 7.43 (t, J = 9.2 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 5.34 (s, 2H), 4.91 (t, J = 5.6 Hz, 1H), 4.63 - 4.47 (m, 2H), 4.40 (br t, J = 4.8 Hz, 2H), 4.29 (br d, J = 12.4 Hz, 2H), 3.77 - 3.70 (m, 3H), 3.62 (br d, J = 12.8 Hz, 1H), 3.44 - 3.39 (m, 3H), 2.45 - 2.31 (m, 1H), 2.16 (ddd, J = 2.8, 7.2, 14.4 Hz, 1H), 1.83 (br s, 2H), 1.69 (br d, J = 8.4 Hz, 2H), 1.46 (s, 9H), 0.73 (t, J = 7.6 Hz, 3H).

Step 4: Preparation of *tert*-butyl 3-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of dimethyl sulfoxide (156 mg, 2 mmol) in dichloromethane (3 mL) was added oxalyl dichloride (0.1 mL, 1 mmol) in dichloromethane (3 mL) dropwise at -65 °C, and the mixture was stirred at -65 °C for 30 min. *tert*-Butyl 3-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-(2-hydroxyethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (520 mg, 0.8 mmol) in dichloromethane (3 mL) was then added dropwise, and the mixture was stirred at -65 °C for 0.5 h. Triethylamine (0.5 mL, 4 mmol) was then added, and the reaction mixture was stirred at -65 °C for 30 min, then warmed to 25 °C and stirred for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford the title compound (500 mg, crude) as a yellow solid. LC/MS (ESI) *m/z*: 650.2 $[M+H]^+$.

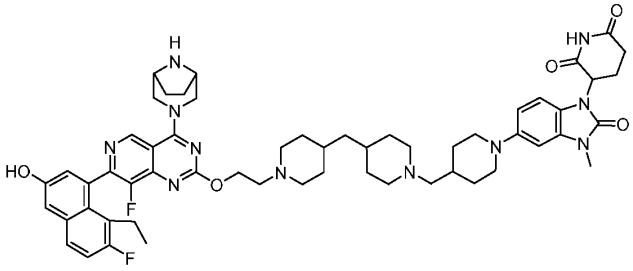
Step 5: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 3-[3-methyl-2-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione trifluoroacetate (450 mg, 0.7 mmol) in dichloromethane (5 mL) and isopropanol (5 mL) were added *N,N*-diisopropylethylamine (0.2 mL, 1 mmol) and *tert*-butyl 3-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (899 mg, 1.4 mmol), and the resulting mixture was stirred at 25 °C for 0.5 h. Sodium triacetoxyborohydride (439.69 mg, 2 mmol) was then added, and the reaction mixture was stirred at 25 °C for 0.5 h. The mixture was diluted with water (30 mL) and extracted with dichloromethane (2 x 30 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (0 to 100% ethyl acetate/petroleum ether) to afford the title compound (590 mg, 73%) as a white solid. LC/MS (ESI) *m/z*: 1170.9 $[M+H]^+$.

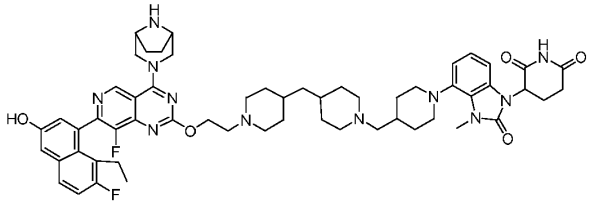
Step 6: Preparation of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-

yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione



To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (460 mg, 0.4 mmol) in dichloromethane (5 mL) was added 4 M HCl in 1,4-dioxane (5 mL), and the mixture was stirred at 25 °C for 0.5 h. The reaction mixture was suspended in petroleum ether (30 mL) and filtered under nitrogen atmosphere. The filtered cake was diluted with dimethyl sulfoxide (4 mL) and *N*,*N*-diisopropylethylamine to adjust the pH to 7. The resulting solution was purified by prep-HPLC (0% to 30% acetonitrile in water (formic acid) over 12 min) to afford the title compound (181.7 mg, 42%, formic acid salt) as a white solid. LC/MS (ESI) *m/z*: 1026.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (br s, 1H), 9.13 (s, 1H), 8.26 (s, 3H), 7.77 (dd, J = 6.0, 9.2 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.03 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 2.0, 8.8 Hz, 1H), 5.29 (dd, J = 5.2, 12.8 Hz, 1H), 4.63 - 4.39 (m, 4H), 3.92 - 3.66 (m, 4H), 3.57 (br d, J = 11.6 Hz, 2H), 3.03 - 2.84 (m, 5H), 2.80 - 2.57 (m, 6H), 2.42 - 2.26 (m, 3H), 2.21 - 1.93 (m, 6H), 1.84 - 1.72 (m, 6H), 1.70 - 1.55 (m, 5H), 1.40 - 1.02 (m, 10H), 0.73 (t, J = 7.6 Hz, 3H).

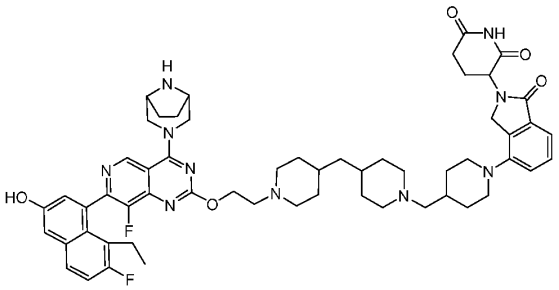
Example 52: Synthesis of 3-{4-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 172**)



The title compound was made in an analogous manner to 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-

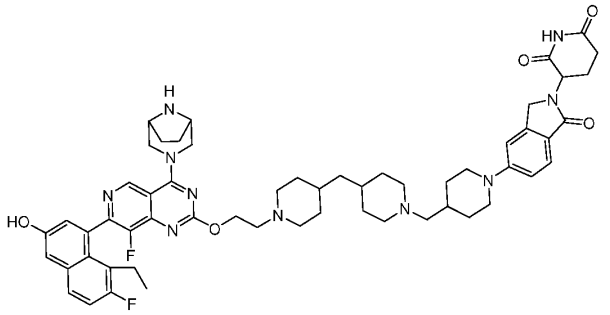
d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione. (white solid, formic acid salt). LC/MS (ESI) *m/z*: 1026.7 $[M+H]^+$; ^{1}H NMR (DMSO-d_6) δ (br s, 1H), 9.13 (s, 1H), 8.26 (s, 3H), 7.77 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.82 (d, *J* = 2.0 Hz, 1H), 6.62 (dd, *J* = 2.0, 8.8 Hz, 1H), 5.29 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.63 - 4.39 (m, 4H), 3.92 - 3.66 (m, 4H), 3.57 (br d, *J* = 11.6 Hz, 2H), 3.03 - 2.84 (m, 5H), 2.80 - 2.57 (m, 6H), 2.42 - 2.26 (m, 3H), 2.21 - 1.93 (m, 6H), 1.84 - 1.72 (m, 6H), 1.70 - 1.55 (m, 5H), 1.40 - 1.02 (m, 10H), 0.73 (t, *J* = 7.6 Hz, 3H).

Example 53: Synthesis of 3-{4-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 137**)



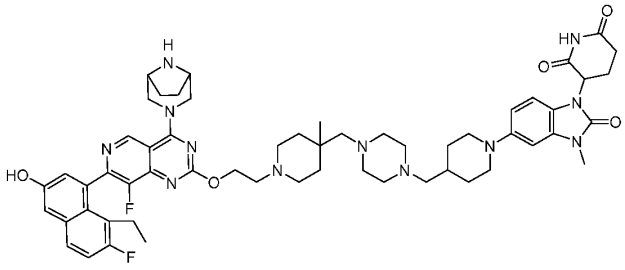
The title compound was made in an analogous manner to 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione. (white solid, formic acid salt). LC/MS (ESI) *m/z*: 1011.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.13 (s, 1H), 8.17 (s, 2H), 7.80 - 7.72 (m, 1H), 7.42 (t, J=7.6 Hz, 1H), 7.37 - 7.32 (m, 2H), 7.29 (d, J=7.6 Hz, 1H), 7.15 (d, J=8.0 Hz, 1H), 7.02 (d, J=2.4 Hz, 1H), 5.15 - 5.08 (m, 1H), 4.62 – 4.47 (m, 5H), 4.45 – 4.39 (m, 1H), 4.31 – 4.25 (m, 1H), 3.96 – 3.88 (m, 2H), 2.86 - 2.72 (m, 3H), 3.42 - 3.31 (m, 2H), 3.05 - 2.89 (m, 5H), 2.82 - 2.76 (m, 2H), 2.74 - 2.65 (m, 2H), 2.63 - 2.55 (m, 1H), 2.39 - 2.30 (m, 3H), 2.19 - 2.07 (m, 5H), 2.04 - 1.95 (m, 1H), 1.88 - 1.72 (m, 7H), 1.66 - 1.58 (m, 4H),1.42 - 1.17 (m, 6H), 1.15 - 1.05(m, 4H), 0.72 (t, J=7.2 Hz, 3H).

Example 54: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 86**)



The title compound was made in an analogous manner to 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione. (white solid, formic acid salt). LC/MS (ESI) *m/z*: 1011.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 9.14 - 9.06 (m, 1H), 8.19 (s, 3H), 7.76 (dd, J = 6.0, 9.2 Hz, 1H), 7.49 (d, J = 9.2 Hz, 1H), 7.39 - 7.30 (m, 2H), 7.09 - 6.99 (m, 3H), 5.03 (dd, J = 5.2, 13.2 Hz, 1H), 4.51 - 4.40 (m, 4H), 4.33 - 4.28 (m, 1H), 4.16 (s, 1H), 3.85 (br d, J = 12.8 Hz, 4H), 2.96 - 2.88 (m, 3H), 2.87 - 2.75 (m, 5H), 2.73 - 2.66 (m, 2H), 2.61 - 2.55 (m, 1H), 2.41 - 2.31 (m, 2H), 2.20 - 2.08 (m, 3H), 2.06 - 1.84 (m, 6H), 1.80 - 1.64 (m, 7H), 1.58 (br d, J = 11.6 Hz, 4H), 1.39 - 1.21 (m, 3H), 1.20 - 0.99 (m, 8H), 0.72 (t, J = 7.2 Hz, 3H).

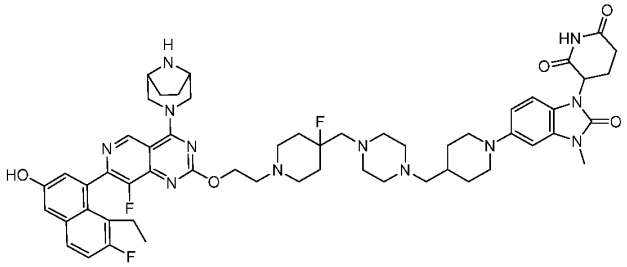
Example 55: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-4-methylpiperidin-4-yl)methyl]piperazin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 180**)



The title compound was made in an analogous manner to 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione. (yellow solid, formic acid salt.) LC/MS (ESI) *m/z*: 1041.3 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (br s, 1H), 9.12 (s, 1H), 8.22 (s, 2H), 7.77 (dd, J = 6.0, 9.2 Hz, 1H), 7.39 - 7.31 (m, 2H), 7.02 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 2.0, 8.8 Hz, 1H), 5.29 (dd, J =

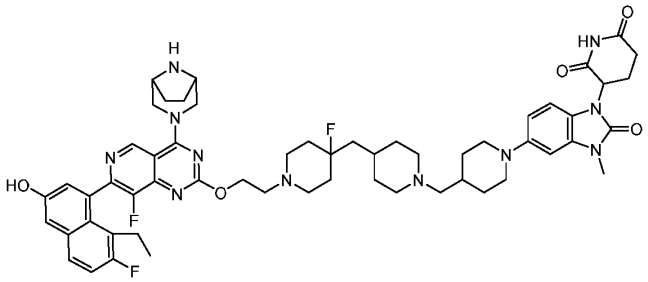
5.2, 12.8 Hz, 1H), 4.55 - 4.39 (m, 4H), 3.77 - 3.66 (m, 3H), 3.56 (br d, J = 11.6 Hz, 2H), 3.30 (s, 3H), 3.00 - 2.67 (m, 2H), 2.55 (s, 4H), 2.47 (br d, J = 4.0 Hz, 7H), 2.41 - 2.27 (m, 8H), 2.20 - 2.03 (m, 6H), 2.01 - 1.94 (m, 1H), 1.79 - 1.68 (m, 6H), 1.63 - 1.54 (m, 1H), 1.51 - 1.42 (m, 2H), 1.22 (br d, J = 8.0 Hz, 4H), 0.85 (s, 3H), 0.73 (t, J = 7.2 Hz, 3H).

Example 56: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-4-fluoropiperidin-4-yl)methyl]piperazin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 181**)



The title compound was made in an analogous manner to 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione. (pink solid). LC/MS (ESI) *m/z*: 1045.8 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.10 (s, 1H), 8.22 - 8.17 (m, 2H), 7.76 (dd, J = 6.0, 9.2 Hz, 1H), 7.38 - 7.31 (m, 2H), 7.02 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 6.61 (dd, J = 2.0, 8.8 Hz, 1H), 5.28 (dd, J = 5.2, 12.8 Hz, 1H), 4.51 - 4.41 (m, 4H), 3.70 - 3.60 (m, 5H), 3.56 (d, J = 12.0 Hz, 3H), 3.29 (s, 3H), 2.92 - 2.83 (m, 1H), 2.76 - 2.65 (m, 5H), 2.64 - 2.55 (m, 4H), 2.46 (s, 3H), 2.40 (s, 2H), 2.36 - 2.28 (m, 6H), 2.13 (d, J = 7.2 Hz, 3H), 2.02 - 1.94 (m, 1H), 1.82 - 1.71 (m, 5H), 1.68 (s, 4H), 1.62 - 1.51 (m, 2H), 1.22 (d, J = 10.0 Hz, 2H), 0.72 (t, J = 7.6 Hz, 3H).

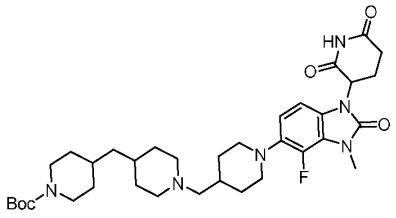
Example 57: Exemplary Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-4-fluoropiperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 182**)



The title compound was made in an analogous manner to 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione. (white solid, formic acid salt.) LC/MS (ESI) *m/z*: 1045.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (br s, 1H), 9.12 (s, 1H), 8.27 (s, 2H), 7.77 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.44 - 7.30 (m, 2H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.92 (br d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 1.6 Hz, 1H), 6.62 (br d, *J* = 8.8 Hz, 1H), 5.29 (br dd, *J* = 5.2, 12.8 Hz, 1H), 4.59 - 4.46 (m, 3H), 3.85 - 3.66 (m, 3H), 3.57 (br d, *J* = 11.6 Hz, 2H), 3.30 (s, 3H), 2.99 - 2.82 (m, 3H), 2.81 - 2.69 (m, 4H), 2.66 - 2.56 (m, 3H), 2.41 - 2.26 (m, 4H), 2.19 - 2.10 (m, 1H), 2.08 - 1.98 (m, 2H), 1.82 - 1.62 (m, 10H), 1.57 - 1.43 (m, 3H), 1.24 (q, *J* = 10.8 Hz, 3H), 0.73 (br t, *J* = 7.2 Hz, 2H).

Example 58: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 206**)

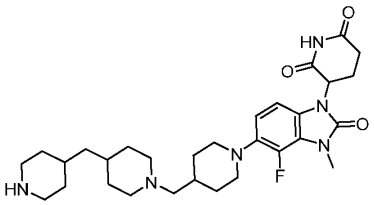
Step 1: Preparation of *tert*-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate



To a solution of tert-butyl 4-(piperidin-4-ylmethyl)piperidine-1-carboxylate acetate (344 mg, 1 mmol) in dichloromethane (4 mL) and dimethyl sulfoxide (3 mL) were added *N,N*-diisopropylethylamine (0.15 mL, 0.9 mmol), acetic acid (70 mg, 1 mmol), 1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (300 mg, 0.8 mmol), and sodium triacetoxyborohydride (409 mg, 1.9 mmol), and the reaction mixture was stirred at 25 °C for 2 h. The mixture was filtered and concentrated under reduced pressure, and

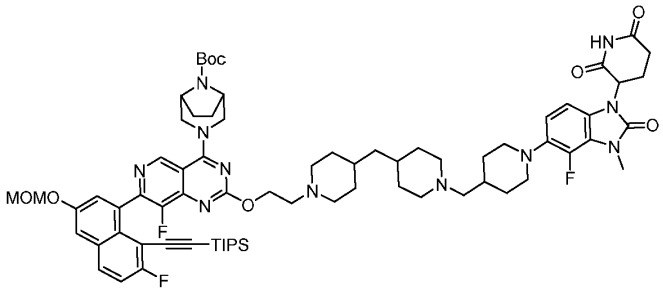
the residue was purified by prep-TLC (dichloromethane/methanol = 10/1) to afford the title compound (400 mg, 79%) as a yellow solid. LC/MS (ESI) *m/z*: 655.6 $[M+H]^+$.

Step 2: Preparation of 3-[4-fluoro-3-methyl-2-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione



To a solution of *tert*-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate (400 mg, 0.6 mmol) in dichloromethane (6 mL) was added trifluoroacetic acid (2.0 mL, 27 mmol), and the reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure, and the residue was purified by prep-HPLC (0% to 25% acetonitrile in water (trifluoroacetic acid) over 15 min) to afford the title compound (320 mg, 78%, TFA salt) as a yellow solid.

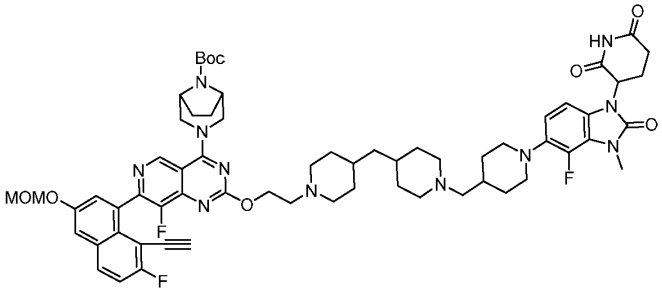
Step 3: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl] methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 3-[4-fluoro-3-methyl-2-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione trifluoroacetate (230 mg, 0.3 mmol) in dichloromethane (3 mL) and isopropanol (3 mL) were added *N,N*-diisopropylethylamine (0.7 mL, 0.4 mmol), sodium triacetoxyborohydride (219 mg, 1 mmol), and *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (303 mg, 0.4 mmol), and the reaction mixture was stirred at 25 °C for 1 h. The mixture was filtered and concentrated under reduced pressure, and the residue was purified by prep-TLC

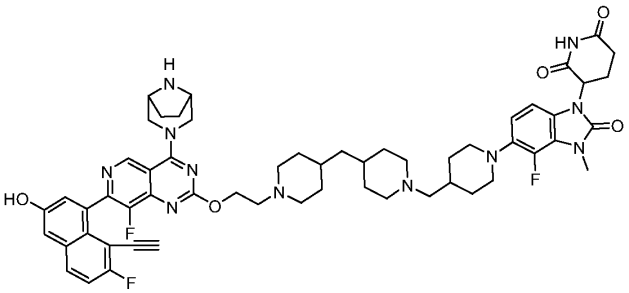
(dichloromethane/methanol = 7/1) to afford the title compound (300 mg, 65%) as a yellow oil. LC/MS (ESI) *m/z*: 1342.1 $[M+H]^+$.

Step 4: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl] methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (270 mg, 0.2 mmol) in *N,N*-dimethylformamide (15 mL) was added cesium fluoride (918 mg, 6 mmol), and the reaction mixture was stirred at 25 °C for 10 h. The mixture was filtered and concentrated under reduced pressure, and the residue was purified by prep-HPLC (23% to 43% acetonitrile in water (formic acid) over 10 min) to afford the title compound (230 mg, 96%, formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1184.9 $[M+H]^+$.

Step 5: Preparation of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione

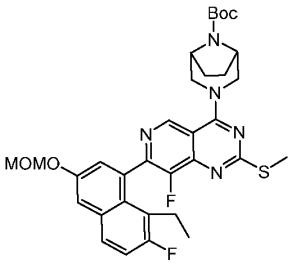


To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-

fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (170 mg, 0.1 mmol) in dichloromethane (6 mL) was added 4 M HCl in 1,4-dioxane (1.9 mL), and the reaction mixture was stirred at 25 °C for 0.25 h. The mixture was filtered and concentrated under reduced pressure, and the residue was purified by prep-HPLC (1% to 30% acetonitrile in water (formic acid) over 10 min) to afford the title compound (62.8 mg, 39%, formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1040.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1 H), 9.06 (s, 1 H), 8.21 (s, 2 H), 7.98 (dd, *J* = 9.2, 6.0 Hz, 1 H), 7.47 (t, *J* = 9.2 Hz, 1 H), 7.40 (d, *J* = 2.4 Hz, 1 H), 7.18 (d, *J* = 2.4 Hz, 1 H), 6.88 - 6.80 (m, 1 H), 6.73 (t, *J* = 8.0 Hz, 1 H), 5.33 (br dd, *J* = 12.8, 5.6 Hz, 1 H), 4.54 - 4.43 (m, 3 H), 4.36 (br d, *J*=11.6 Hz, 1 H), 3.94 (s, 1 H), 3.73 - 3.60 (m, 4 H), 3.47 (d, *J* = 1.2 Hz, 3 H), 3.21 (br d, *J* = 11.2 Hz, 2 H), 2.97 - 2.81 (m, 5 H), 2.74 - 2.57 (m, 6 H), 2.43 (br dd, *J*=3.6, 2.0 Hz, 1 H), 2.20 (br d, *J* = 7.2 Hz, 2 H), 2.06 – 1.96 (m, 3 H), 1.90 (br t, *J* = 10.4 Hz, 2 H), 1.81 - 1.70 (m, 6 H), 1.59 (br d, *J* = 11.2 Hz, 5 H), 1.35 - 1.22 (m, 4 H), 1.10 (br d, *J* = 6.8 Hz, 6 H).

Example 59: Synthesis of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 207**)

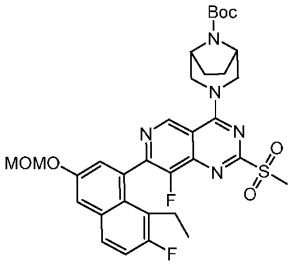
Step 1: Preparation of tert-butyl 3-[7-[8-ethyl-7-fluoro-3-(methoxy methoxy)-1-naphthyl]-8-fluoro-2-methylsulfanyl-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a mixture of *tert*-butyl 3-(7-chloro-8-fluoro-2-methylsulfanyl-pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 1.1 mmol) and 2-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (450 mg, 1.3 mmol) in dioxane (10 mL) and water (1 mL) were added potassium phosphate (724 mg, 3.4 mmol) and methanesulfonato(diadamantyl-n-butylphosphino)-2'-amino-1,1'-biphenyl-2-yl)palladium(II) (83 mg, 0.1 mmol), and the mixture was degassed and purged with nitrogen several times. The reaction mixture was stirred at 90 °C for 12 hours under nitrogen atmosphere. The mixture was filtered through a pad of celite, the filtrate solution was diluted with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure.

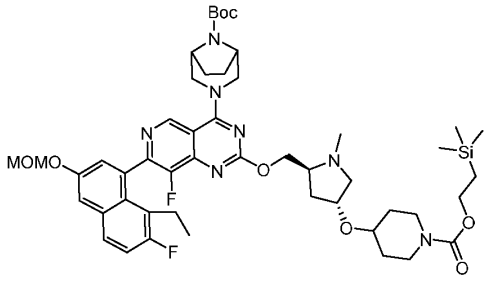
The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/0 to 1/1) to afford the title compound (627 mg, 89%) as a yellow gum. **LC/**MS (ESI) m/z: 638.3 $[M+1]^+$.

Step 2: Preparation of *tert*-butyl 3-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-methylsulfonyl-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a mixture of *tert*-butyl 3-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-methylsulfanylpyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (627 mg, 0.98 mmol) in *N,N*-dimethylformamide (6mL) was added molecular sieves (4A, 627 mg), and the mixture was stirred for 4 h, followed by the addition of Oxone (1.81 g, 3 mmol). The reaction mixture was stirred at 25 °C for 12 hours. The mixture was filtered, the filtrate solution was diluted with water (30 mL) and extracted with ethyl acetate (30 mL × 2). The combined organic layers were washed with brine (30 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/0 to 1/1) to afford the title compound (365 mg, 58%) as a yellow gum. LC/MS (ESI) *m/z*: 670.2 $[M+1]^+$.

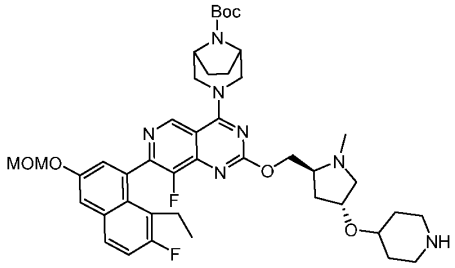
Step 3: Preparation of *tert*-butyl 3-[7-[8-ethyl-7-fluoro-3-(methoxy methoxy)-1-naphthyl]-8-fluoro-2-[[(2S,4R)-1-methyl-4-[[1-(2-trimethylsilyl ethoxycarbonyl)-4-piperidyl]oxy]pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a mixture of 2-trimethylsilylethyl 4-[(3R,5S)-5-(hydroxymethyl)-1-methyl-pyrrolidin-3-yl]oxypiperidine-1-carboxylate (221 mg, 0.6 mmol) and 4A molecular sieves (6 mL) at 0 °C was added lithium tert-butoxide (1 M, 1.63 mL) followed by *tert*-butyl 3-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-methylsulfonyl-pyrido[4,3-d]pyrimidin-4-yl]-3,8-

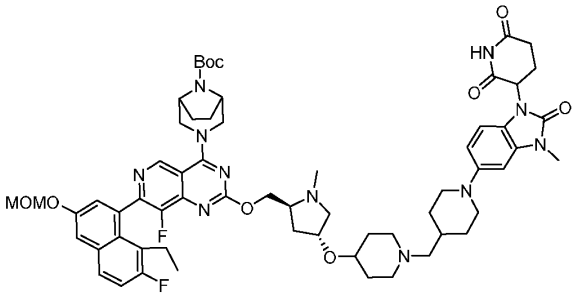
diazabicyclo[3.2.1]octane-8-carboxylate (365 mg, 0.5 mmol), and the reaction mixture was stirred at 0 °C for 1 h. The mixture was diluted with ethyl acetate (20 mL) and washed with saturated ammonium chloride (3 x 20 mL). The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by prep-HPLC (45% -75% acetonitrile in water (formic acid) over 10 min) to afford the title compound (157 mg, 30%) as a brown gum. LC/MS (ESI) *m/z*: 948.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 7.86 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.64 (d, *J* = 2.8 Hz, 1H), 7.40 (t, *J* = 9.6 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 5.30 (s, 2H), 4.60 - 4.35 (m, 3H), 4.29 - 4.18 (m, 3H), 4.00 - 3.95 (m, 1H), 3.69 - 3.54 (m, 4H), 3.50 - 3.42 (m, 1H), 3.40 - 3.36 (m, 3H), 3.26 - 3.14 (m, 2H), 3.03 - 2.93 (m, 2H), 2.81 - 2.72 (m, 1H), 2.36 - 2.27 (m, 4H), 2.18 - 2.09 (m, 2H), 1.83 - 1.69 (m, 5H), 1.67 - 1.60 (m, 2H), 1.42 (s, 9H), 1.31 - 1.20 (m, 3H), 0.88 (d, *J* = 8.0 Hz, 2H), 0.69 (t, *J* = 7.2 Hz, 3H), -0.03 (s, 9H).

Step 4: Preparation of *tert*-butyl 3-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,4R)-1-methyl-4-(4-piperidyloxy)pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



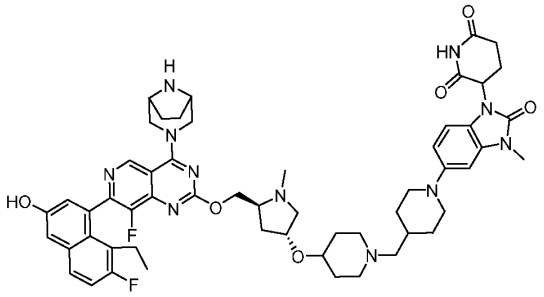
To a solution of *tert*-butyl 3-[7-[8-ethyl-7-fluoro-3-(methoxy methoxy)-1-naphthyl]-8-fluoro-2-[[(2S,4R)-1-methyl-4-[[1-(2-trimethylsilyl ethoxycarbonyl)-4-piperidyl]oxy]pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (157 mg, 0.2 mmol) in *N,N*-dimethylformamide (2 mL) at 25 °C was added cesium fluoride (251 mg, 2 mmol), and the reaction mixture was stirred at 90 °C for 1 h. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x 10 mL) followed by dichloromethane (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (128 mg, crude) as a yellow gum. LC/MS (ESI) *m/z*: 804.3 $[M+H]^+$.

Step 5: Preparation of *tert*-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,4R)-1-methyl-4-(4-piperidyloxy)pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate formate (160 mg, 0.2 mmol) in dichloromethane (3 mL) and isopropanol (3 mL) were added *N,N*-diisopropylethylamine (29 mg, 0.2 mmol), acetic acid (17 mg, 0.3 mmol), 1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (77 mg, 0.2 mmol), and sodium triacetoxyborohydride (120 mg, 0.6 mmol), and the reaction mixture was stirred at 25 °C for 2 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (dichloromethane/methanol = 4/1) to afford the title compound (150 mg, 68%) as a yellow solid. LC/MS (ESI) *m/z*: 1158.9 $[M+H]^+$.

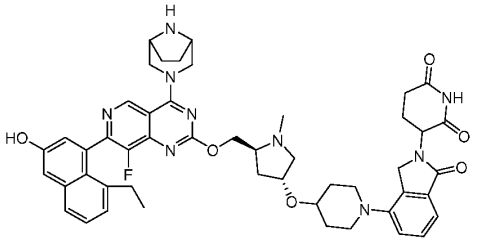
Step 6: Preparation of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione



To a solution of *tert*-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (145 mg, 0.1 mmol) in dichloromethane (3 mL) was added 4 M hydrochloric acid in 1,4-dioxane (2 mL), and the reaction mixture was stirred at 25 °C for 0.25 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (1% to 25% acetonitrile in water (formic acid) over 10 min) to afford

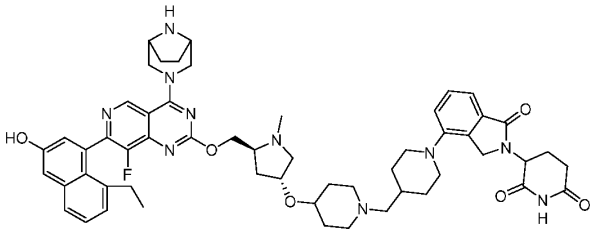
the title compound (64.2 mg, 46%, formic acid salt) as a white solid. LC/MS (ESI) *m/z*: 1014.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.11 (s, 1H), 8.19 (s, 2H), 7.77 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.40 - 7.31 (m, 2H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.62 (dd, *J* = 2.0, 8.4 Hz, 1H), 5.29 (dd, *J* = 5.2, 1Step 2: Hz, 1H), 4.51 - 4.35 (m, 3H), 4.27 (dt, *J* = 6.0, 11.6 Hz, 1H), 4.16 - 4.08 (m, 1H), 3.70 - 3.54 (m, 9H), 3.50 - 3.37 (m, 5H), 3.25 (m, 2H), 2.94 - 2.86 (m, 1H), 2.82 - 2.75 (m, 1H), 2.73 - 2.65 (m, 3H), 2.64 - 2.57 (m, 3H), 2.55 (s, 1H), 2.35 (s, 3H), 2.21 - 2.11 (m, 4H), 2.05 - 1.95 (m, 3H), 1.91 - 1.87 (m, 1H), 1.79 (br t, *J* = 12.4 Hz, 4H), 1.68 (br d, *J* = 6.8 Hz, 3H), 1.46 - 1.37 (m, 2H), 1.28 - 1.18 (m, 2H), 0.73 (t, *J* = 7.2 Hz, 3H).

Example 60: Synthesis of 3-[4-(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)-1-oxo-2,3-dihydro-1H-isoindol-2-yl]piperidine-2,6-dione (**Compound 118**)



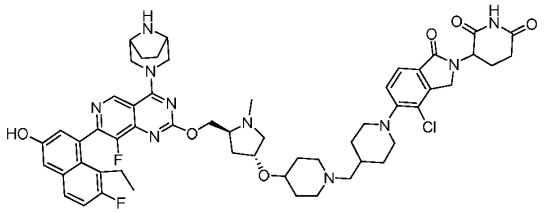
The title compound was made in an analogous manner to 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 884.6 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.09 (s, 1H), 8.18 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.45 - 7.33 (m, 2H), 7.32 - 7.26 (m, 2H), 7.14 (dd, J = 7.6, 14.4 Hz, 2H), 6.97 (d, J = 2.4 Hz, 1H), 5.10 (dd, J = 5.2, 13.2 Hz, 1H), 4.48 - 4.36 (m, 4H), 4.33 - 4.23 (m, 2H), 4.22 - 4.13 (m, 1H), 3.66 (d, J = 1.2 Hz, 1H), 3.61 - 3.57 (m, 3H), 3.54 - 3.47 (m, 5H), 2.95 - 2.77 (m, 5H), 2.68 - 2.59 (m, 1H), 2.36 (s, 3H), 2.29 - 2.17 (m, 3H), 2.01 - 1.89 (m, 5H), 1.69 - 1.54 (m, 6H), 0.81 (t, J = 7.6 Hz, 3H).

Example 61: Synthesis of 3-(4-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 139**)



The title compound was made in an analogous manner to 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (white solid). LC/MS (ESI) *m/z*: 981.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.00 - 10.96 (m, 1H), 9.10 (s, 1H), 8.15 (s, 2H), 7.67 (d, J = 8.0 Hz, 1H), 7.47 - 7.34 (m, 2H), 7.31 - 7.26 (m, 2H), 7.13 (t, J = 7.6 Hz, 2H), 6.96 (d, J = 2.4 Hz, 1H), 5.11 (dd, J = 5.2, 13.2 Hz, 1H), 4.52 - 4.43 (m, 2H), 4.41 - 4.35 (m, 2H), 4.31 - 4.24 (m, 2H), 4.14 - 4.09 (m, 1H), 3.70 (d, J = 11.6 Hz, 4H), 3.65 - 3.62 (m, 1H), 3.36 (s, 2H), 3.24 (d, J = 5.6 Hz, 2H), 2.94 - 2.88 (m, 1H), 2.81 - 2.77 (m, 1H), 2.73 - 2.67 (m, 4H), 2.61 - 2.56 (m, 2H), 2.35 (s, 3H), 2.30 - 2.23 (m, 2H), 2.22 - 2.19 (m, 1H), 2.16 (d, J = 7.6 Hz, 2H), 2.04 - 1.96 (m, 3H), 1.92 - 1.85 (m, 2H), 1.83 - 1.76 (m, 4H), 1.74 - 1.67 (m, 4H), 1.66 - 1.58 (m, 1H), 1.43 - 1.34 (m, 2H), 1.29 - 1.19 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H).

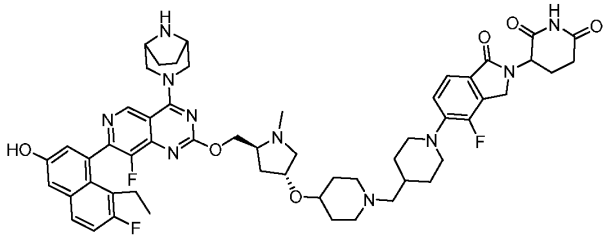
Example 62: Synthesis of 3-(4-chloro-5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 177**)



The title compound was made in an analogous manner to 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (white solid, formic acid salt). LC/MS (ESI) *m/z*: 1033.7 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.12 (s, 1H), 8.18 (s, 2H), 7.76 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.42 - 7.30 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 5.09 (dd, *J* = 5.2, 13.2 Hz, 1H), 4.53 (br t, *J* = 15.2 Hz, 3H), 4.45 - 4.35 (m, 3H), 4.32 - 4.27 (m, 2H), 4.22 (s,

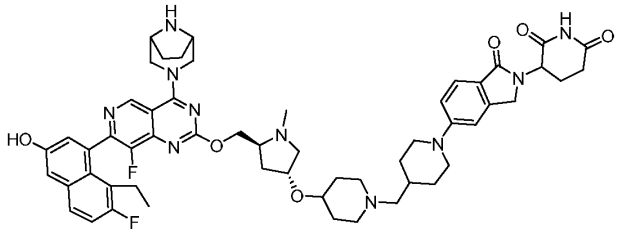
1H), 4.16 - 4.09 (m, 2H), 3.87 (br d, *J* = 10.8 Hz, 2H), 3.80 (br d, *J* = 13.2 Hz, 1H), 3.73 (br d, *J* = 13.6 Hz, 1H), 3.42 - 3.31 (m, 3H), 3.26 (br dd, *J* = 6.0, 9.2 Hz, 1H), 2.96 - 2.86 (m, 1H), 2.82 (br t, *J* = 5.2 Hz, 1H), 2.78 - 2.66 (m, 4H), 2.59 (br d, *J* = 16.8 Hz, 1H), 2.44 (br dd, *J* = 4.8, 13.6 Hz, 1H), 2.36 (s, 4H), 2.28 - 2.18 (m, 3H), 2.16 - 2.05 (m, 3H), 1.98 (br dd, *J* = 5.2, 10.4 Hz, 1H), 1.89 (br d, *J* = 5.2 Hz, 1H), 1.85 - 1.76 (m, 7H), 1.72 - 1.59 (m, 1H), 1.51 - 1.37 (m, 2H), 1.29 (q, *J* = 10.4 Hz, 2H), 0.72 (t, *J* = 7.2 Hz, 3H).

Example 63: Synthesis of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 178**)



The title compound was made in an analogous manner to 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (white solid, formic acid salt). LC/MS (ESI) *m/z*: 1017.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (br s, 1H), 9.11 (s, 1H), 8.21 (s, 1H), 7.76 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.39 - 7.29 (m, 2H), 7.14 (t, J = 8.0 Hz, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 5.07 (br dd, *J* = 5.2, 13.3 Hz, 1H), 4.47 (br d, *J* = 16.8 Hz, 3H), 4.41 - 4.37 (m, 1H), 4.34 - 4.23 (m, 4H), 4.14 - 4.10 (m, 1H), 3.80 - 3.65 (m, 5H), 3.47 (br s, 2H), 3.35 - 3.19 (m, 2H), 2.98 - 2.84 (m, 1H), 2.83 - 2.64 (m, 5H), 2.63 - 2.55 (m, 1H), 2.48 - 2.38 (m, 1H), 2.35 (s, 3H), 2.22 - 2.16 (m, 3H), 2.15 - 2.10 (m, 1H), 2.05 (br t, *J* = 9.6 Hz, 2H), 2.00 - 1.94 (m, 1H), 1.92 - 1.84 (m, 2H), 1.83 - 1.63 (m, 8H), 1.49 - 1.34 (m, 2H), 1.32 - 1.15 (m, 2H), 0.72 (t, *J* = 7.6 Hz, 3H)

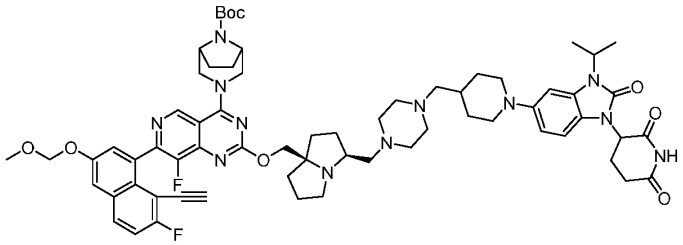
Example 64: Synthesis of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 85**)



The title compound was made in an analogous manner to 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (white solid, formic acid salt). LC/MS (ESI) *m/z*: 1000.8 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 9.13 (s, 1H), 8.17 (s, 2H), 7.82 - 7.70 (m, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.09 - 6.96 (m, 3H), 5.04 (dd, *J* = 5.2, 13.2 Hz, 1H), 4.62 - 4.47 (m, 2H), 4.44 - 4.36 (m, 1H), 4.34 - 4.25 (m, 2H), 4.23 - 4.09 (m, 2H), 3.95 - 3.67 (m, 7H), 3.39 - 3.23 (m, 2H), 2.96 - 2.70 (m, 6H), 2.59 (d, *J* = 16.4 Hz, 1H), 2.43 - 2.29 (m, 6H), 2.28 - 2.04 (m, 7H), 1.96 - 1.88 (m, 2H), 1.85 - 1.72 (m, 9H), 1.53 - 1.34 (m, 2H), 1.21 - 1.09 (m, 2H), 0.77 - 0.67 (m, 3H)

Example 65: Synthesis of 3-[5-[4-[[4-[[(3S,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-3-isopropyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 208**)

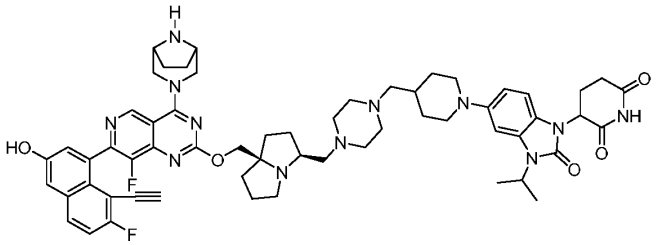
Step 1: Preparation of *tert*-butyl 3-[2-[[(3S,8R)-3-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 3-[3-isopropyl-2-oxo-5-[4-(piperazin-1-ylmethyl)-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione (257.6 mg, 0.6 mmol) and tert-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3S,8R)-3-formyl-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-

carboxylate (415 mg, 0.6 mmol) in dichloromethane (15 mL) and DMSO (2.0 mL) was added $NaBH(OAc)_3$ (291 mg, 1.4 mmol), and the reaction mixture was stirred at 25 °C for 12 h. The mixture was quenched with sodium bicarbonate (10 mL) and stirred at 25 °C for 30 min. The mixture was concentrated under reduced pressure, and the residue was extracted with ethyl acetate (3 x 40 mL). The combined organic extract was washed with water (7 x 10 mL) followed by brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 7% methanol in dichloromethane over 20 min) to afford the title compound (379.8 mg, 57%) as a yellow solid. LC/MS (ESI) m/z: 1207.9 $[M+H]^+$.

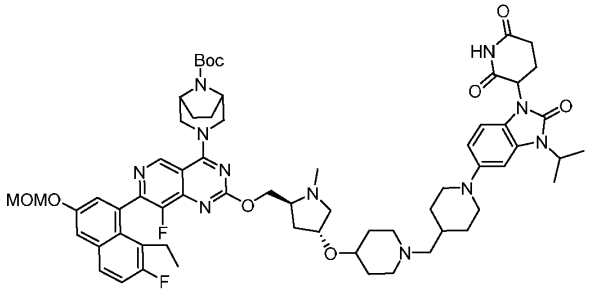
Step 2: Preparation of 3-[5-[4-[[4-[[(3S,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-3-isopropyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



To a solution of tert-butyl 3-[2-[[(3S,8R)-3-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (370 mg, 0.3 mmol) in dichloromethane (2.5 mL) was added 4 M HCl in 1,4-dioxane (2.5 mL), and the reaction mixture was stirred at 25°C for 10 min. The reaction mixture was diluted with petroleum ether (3 x 20 mL), removing the supernatant each time. The remaining material was then diluted with THF (50 mL) and the pH adjusted to 8 by addition of triethylamine. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by preparative HPLC (24% to 64% acetonitrile in water (ammonium bicarbonate) over 32 min) to afford the title compound (124.7 mg, 38%) as a yellow solid. LC/MS (ESI) m/z: 1063.6 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.00 (d, *J* = 2.4 Hz, 1H), 7.84 (m, *J* = 2.4, 6.0, 9.0 Hz, 1H), 7.35 - 7.27 (m, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.02 - 6.89 (m, 2H), 6.78 (br d, *J* = 8.4 Hz, 1H), 5.26 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.68 - 4.55 (m, 3H), 4.33 - 4.18 (m, 2H), 3.75 - 3.60 (m, 4H), 3.52 (br d, *J* = 11.6 Hz, 2H), 3.36 (s, 1H), 3.13 - 2.96 (m, 2H), 2.94 - 2.73 (m, 4H), 2.72 - 2.63 (m, 3H), 2.62 - 2.34 (m, 9H), 2.27 - 2.06 (m, 5H), 1.96 - 1.62 (m, 13H), 1.54 (dd, *J* = 1.2, 6.8 Hz, 6H), 1.44 - 1.29 (m, 2H).

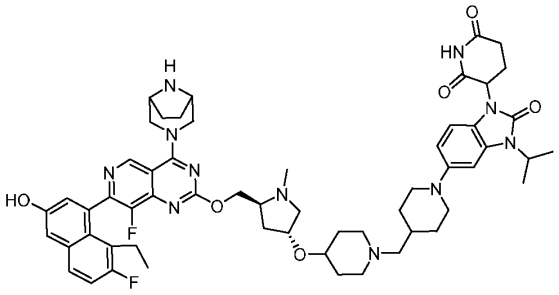
Example 66: Synthesis of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 209**)

Step 1: Preparation of *tert*-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,4R)-1-methyl-4-(4-piperidyloxy)pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate formate (160 mg, 0.2 mmol) in dichloromethane (3 mL) and isopropanol (3 mL) were added *N,N*-diisopropylethylamine (29.2 mg, 0.2 mmol), acetic acid (17 mg, 0.3 mmol), 1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (90 mg, 0.2 mmol), and sodium triacetoxyborohydride (120 mg, 0.6 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (dichloromethane/methanol = 4/1) to afford the title compound (140 mg, 62%) as a yellow solid. LC/MS (ESI) *m/z*: 1187.0 $[M+H]^+$.

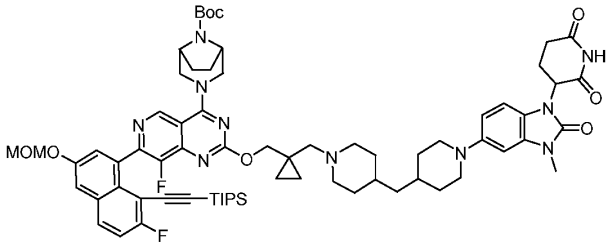
Step 2: Preparation of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione



To a solution of *tert*-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (135 mg, 0.1 mmol) in dichloromethane (3 mL) was added 4 M HCl in 1,4-dioxane (0.4 mL), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (1% to 25% acetonitrile in water (formic acid) over 10 min) to afford the title compound (51.1 mg, 30%) as a white solid. LC/MS (ESI) *m/z*: 1042.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.11 (s, 1H), 8.21 (s, 1H), 7.77 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.39 - 7.30 (m, 2H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.95 - 6.84 (m, 2H), 6.66 - 6.57 (m, 1H), 5.26 (br dd, *J* = 5.6, 12.8 Hz, 1H), 4.58 - 4.58 (m, 1H), 4.58 (td, *J* = 6.8, 14.0 Hz, 1H), 4.49 - 4.35 (m, 3H), 4.27 (td, *J* = 5.6, 11.8 Hz, 1H), 4.12 - 4.11 (m, 1H), 4.16 - 4.09 (m, 1H), 3.70 - 3.58 (m, 5H), 3.54 (br d, *J* = 12.0 Hz, 3H), 3.32 - 3.23 (m, 3H), 2.87 (br dd, *J* = 4.8, 16.8 Hz, 1H), 2.79 (br t, *J* = 5.2 Hz, 1H), 2.74 - 2.65 (m, 3H), 2.64 - 2.57 (m, 3H), 2.55 (s, 1H), 2.35 (s, 3H), 2.20 - 2.12 (m, 4H), 2.00 - 1.99 (m, 1H), 1.99 (br d, *J* = 8.0 Hz, 3H), 1.88 (dt, *J* = 4.8, 8.0 Hz, 2H), 1.79 (br t, *J* = 12.0 Hz, 4H), 1.72 - 1.63 (m, 4H), 1.63 - 1.52 (m, 1H), 1.45 (d, *J* = 6.8 Hz, 8H), 1.23 (br d, *J* = 10.4 Hz, 2H), 0.73(t, *J* = 7.2 Hz, 3H).

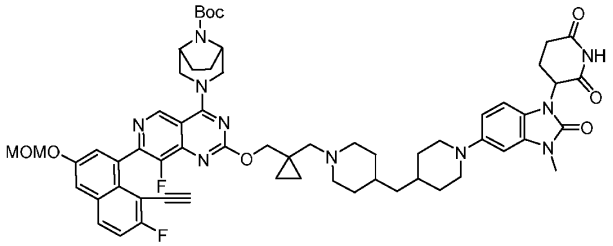
Example 67: Synthesis of 3-{5-[4-({1-[(1-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}cyclopropyl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 210**)

Step 1: Preparation of *tert*-butyl 3-[2-[[1-[[4-[[1-[1-(2,6-dioxo-3- piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]cyclopropyl]methoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



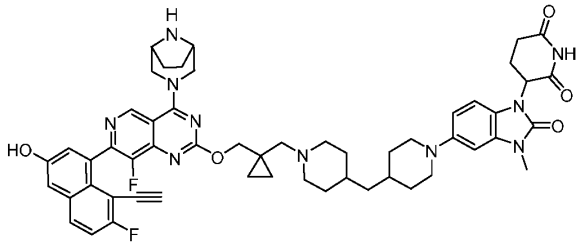
To a mixture of 3-[3-methyl-2-oxo-5-[4-(4-piperidylmethyl)-1-piperidyl]benzimidazol-1-yl] piperidine-2,6-dione trifluoroacetate (400 mg, 0.7 mmol) and *tert*-butyl 3-[8-fluoro-7 -[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-[(1-formylcyclopropyl)methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (669 mg, 0.8 mmol) in dichloromethane (10 mL) and isopropanol (10 mL) were added *N,N*-diisopropylethylamine (0.4 mL, 2.2 mmol) and 2-methylpyridine borane (232 mg, 2.17 mmol) under nitrogen atmosphere, and the mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by prep-HPLC (30% to 60% acetonitrile in water (formic acid) over 15 min) to afford the title compound (180 mg, 20%) as a white solid. LC/MS (ESI) *m/z*: 1266.0 $[M+H]^+$.

Step 2: Preparation of *tert*-butyl 3-[2-[[1-[[4-[[1-[1-(2,6-dioxo-3- piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]cyclopropyl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To *tert*-butyl 3-[2-[[1-[[4-[[1-[1-(2,6-dioxo-3- piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]cyclopropyl]methoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (180 mg, 0.1 mmol) in *N,N*-dimethylformamide (5 mL) was added cesium fluoride (432 mg, 2.8 mmol), and the reaction mixture was stirred at 20 °C for 1 h. The mixture was filtered and concentrated under reduced pressure, and the residue was purified by prep-HPLC (25% to 55% acetonitrile in water (formic acid) over 7 min) to afford the title compound (132 mg, 84%) as a white solid. LC/MS (ESI) *m/z*: 1110.0 $[M+H]^+$.

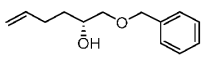
Step 3: Preparation of 3-{5-[4-({1-[(1-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}cyclopropyl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione



To a solution of *tert*-butyl 3-[2-[[1-[[4-[[1-[1-(2,6-dioxo-3- piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]cyclopropyl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (132 mg, 0.1 mmol) in dichloromethane (2 mL) was added 4 M HCl in 1,4-dioxane (2 mL), and the reaction mixture was stirred at 20 °C for 15 min. The mixture was suspended in petroleum ether (10 mL) and filtered. The filter cake was purified by prep-HPLC (0% to 30% acetonitrile in water (formic acid) over 12 min) to afford the title compound (56.8 mg, 43%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 965.5 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.04 (s, 1H), 8.20 (s, 2H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.61 (dd, *J* = 1.6, 8.8 Hz, 1H), 5.28 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.57 - 4.48 (m, 1H), 4.35 - 4.25 (m, 3H), 3.93 (s, 1H), 3.67 (s, 4H), 3.63 - 3.49 (m, 5H), 3.01 - 2.81 (m, 4H), 2.66 - 2.53 (m, 4H), 2.33 (s, 2H), 2.02 - 1.94 (m, 1H), 1.88 (t, *J* = 11.2 Hz, 2H), 1.75 - 1.66 (m, 6H), 1.59 (d, *J* = 11.2 Hz, 2H), 1.42 (s, 1H), 1.33 (d, *J* = Step 2: Hz, 1H), 1.26 - 1.18 (m, 2H), 1.15 - 0.98 (m, 5H), 0.64 (s, 2H), 0.41 (s, 2H).

Example 68: Synthesis of 3-(5-{4-[(4-{[(2S,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-2-yl]methyl}piperazin-1-yl)methyl]piperidin-1-yl}-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 211**)

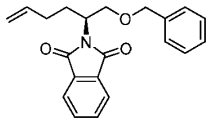
Step 1: Preparation of (2*R*)-1-benzyloxyhex-5-en-2-ol



To a mixture of (2*R*)-2-(benzyloxymethyl)oxirane (38.4 mL, 253 mmol) in THF (500 mL) was added CuI (4.81 g, 25 mmol), and the resulting mixture was cooled to 0 °C. Allyl(chloro)magnesium (2.0 M, 500 mL) was then added dropwise, and the reaction mixture was stirred at 0 °C for 1 h. The reaction was diluted with aqueous saturated ammonium chloride

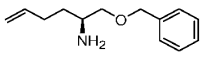
(500 mL) at 0 °C and extracted with ethyl acetate (500 mL x 3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (46.36 g, crude) as a colorless oil. LC/MS (ESI) *m/z*: 207.1 $[M+H]^+$.

Step 2: Preparation of 2-[(1*S*)-1-(benzyloxymethyl)pent-4-enyl]isoindoline-1,3-dione



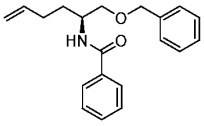
To a mixture of (2*R*)-1-benzyloxyhex-5-en-2-ol (29.36 g, 142 mmol), isoindoline-1,3-dione (25.0 g, 170 mmol), and PPh_3 (44.0 g, 168 mmol) in THF (300 mL) at 0 °C was added DIAD (33.0 mL, 170 mmol), and the reaction mixture was stirred at 20 °C for 15 h. The mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography (0-10% ethyl acetate in petroleum ether) to afford the title compound (36.47 g, 63%) as a colorless oil. LC/MS (ESI) *m/z*: 336.1 $[M+H]^+$.

Step 3: Preparation of (2*S*)-1-benzyloxyhex-5-en-2-amine



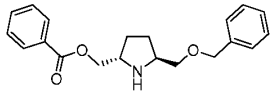
To 2-[(1*S*)-1-(benzyloxymethyl)pent-4-enyl]isoindoline-1,3-dione (54.66 g, 163 mmol) in ethanol (550 mL) was added hydrazine monohydrate (16.28 mL, 335 mmol), and the reaction mixture was stirred at 80 °C for 15 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with saturated ammonium bicarbonate solution (250 mL) and extracted with dichloromethane (500 mL). The organic layer was washed with saturated ammonium bicarbonate solution (250 mL x 2), brine (250 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford (2*S*)-1-benzyloxyhex-5-en-2-amine (31.54 g, crude) as a colorless oil. LC/MS (ESI) *m/z*: 206.0 $[M+H]^+$.

Step 4: Preparation of *N*-[(1*S*)-1-(benzyloxymethyl)pent-4-enyl]benzamide



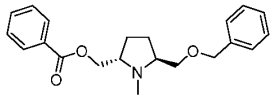
To (2*S*)-1-benzyloxyhex-5-en-2-amine (31.54 g, 154 mmol) in dichloromethane (300 mL) was added triethylamine (64.0 mL, 461 mmol), and the resulting mixture was cooled to 0 °C. Benzoyl chloride (17.85 mL, 154 mmol) was then added dropwise, and the reaction mixture was stirred at 20 °C for 15 h. The mixture was washed with water (300 mL x 2), then brine (300 mL x 2), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-25% ethyl acetate in petroleum ether) to afford the title compound (44.11 g, 76%) as a white solid. LC/MS (ESI) *m/z*: 310.0 $[M+H]^+$.

Step 5: Preparation of [(2*S*,5*S*)-5-(benzyloxymethyl)pyrrolidin-2-yl]methyl benzoate



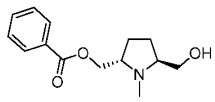
To *N*-[(1*S*)-1-(benzyloxymethyl)pent-4-enyl]benzamide (44.11 g, 117 mmol) in acetonitrile (1500 mL) and water (500 mL) was added iodine (89.45 g, 352 mmol), and the reaction mixture was stirred at 20 °C for 15 h. The mixture was diluted with saturated aqueous Na_2SO_3 solution (500 mL), then extracted with ethyl acetate (1 L x 3). The combined organic extract was washed with brine (1 L x 2), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with ethyl acetate to afford the title compound (36.33 g, 90%) as a white solid. LC/MS (ESI) *m/z*: 326.0 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 9.43 - 9.32 (m, 1H), 8.07 (br d, *J* = 7.2 Hz, 2H), 7.76 - 7.64 (m, 1H), 7.62 - 7.50 (m, 2H), 7.45 - 7.24 (m, 5H), 4.57 (s, 2H), 4.54 - 4.38 (m, 2H), 4.04 - 3.94 (m, 1H), 3.91 - 3.83 (m, 1H), 3.74 - 3.63 (m, 2H), 2.23 - 2.09 (m, 2H), 1.86 - 1.67 (m, 2H).

Step 6: Preparation of [(2*S*,5*S*)-5-(benzyloxymethyl)-1-methyl-pyrrolidin-2-yl]methyl benzoate



To a mixture of [(2*S*,5*S*)-5-(benzyloxymethyl)pyrrolidin-2-yl]methyl benzoate (29.5 g, 86 mmol) and 37% formaldehyde (19.2 mL, 258 mmol) in *i*-PrOH (300 mL) and dichloromethane (300 mL) were added acetic acid (19.7 mL, 344 mmol) and 2-methylpyridine borane (46.0 g, 431 mmol), and the reaction mixture was stirred at 20 °C for 15 h. The mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography (0-10% methanol in DCM) to afford the title compound (47.64 g, crude) as a colorless oil. LC/MS (ESI) *m/z*: 340.0 $[M+H]^+$

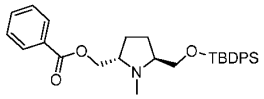
Step 7: Preparation of [(2*S*,5*S*)-5-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methyl benzoate



To a solution of [(2*S*,5*S*)-5-(benzyloxymethyl)-1-methyl-pyrrolidin-2-yl]methyl benzoate (30 g, 57 mmol) in CH_2Cl_2 (300 mL) under nitrogen at -78 °C was added BBr_3 (25.5 mL, 265 mmol), and the reaction mixture was stirred at -78 °C for 2 h under nitrogen. The mixture was diluted with water (200 mL) and concentrated under reduced pressure to remove CH_2Cl_2. The residue was extracted with MTBE (500 mL x 3), and the pH of the aqueous layer was adjusted to 8 by addition of saturated sodium bicarbonate solution. The resulting aqueous mixture was then extracted with CH_2Cl_2/CH_3OH (500 mL x 3, V/ V = 10: 1), and the combined organic extract was washed with brine (500 mL x 2), dried over sodium sulfate, filtered, and

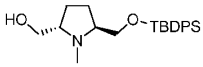
concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-4% then up to 10% CH_3OH in CH_2Cl_2) to afford the title compound (9.25 g, 60%) as a yellow oil. LC/MS (ESI) *m/z*: 249.9 $[M+H]^+$.

Step 8: Preparation of [(2*S*,5*S*)-5-[[tert-butyl(diphenyl)silyl]oxymethyl]-1-methyl-pyrrolidin-2-yl]methyl benzoate



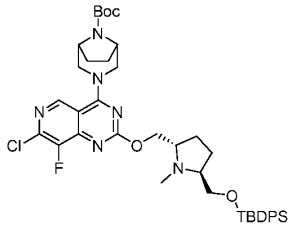
To [(2*S*,5*S*)-5-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methyl benzoate (9.25 g, 34 mmol) in CH_2Cl_2 (150 mL) were added imidazole (2.79 g, 41 mmol) and TBDPSCl (9.68 mL, 38 mmol), and the reaction mixture was stirred at 20 °C for 15 h. The mixture was filtered, and the filtrate was washed with water (100 mL x 3) followed by brine (100 mL x 3), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-20% then up to 50% ethyl acetate in petroleum ether) to afford the title compound (16.5 g, 97%) as a colorless oil. LC/MS (ESI) *m/z*: 488.0 $[M+H]^+$.

Step 9: Preparation of [(2*S*,5*S*)-5-[[tert-butyl(diphenyl)silyl]oxymethyl]-1-methyl-pyrrolidin-2-yl]methanol



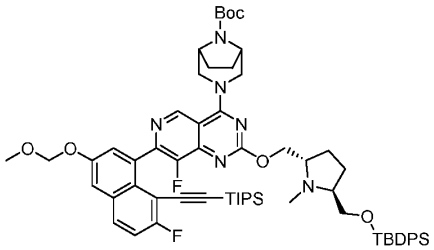
To [(2*S*,5*S*)-5-[[tert-butyl(diphenyl)silyl]oxymethyl]-1-methyl-pyrrolidin-2-yl]methyl benzoate (16.5 g, 33 mmol) in THF (100 mL) was added lithium hydroxide hydrate (6.96 g, 166 mmol) in water (60 mL), and the reaction mixture was stirred at 25 °C for 72 h. The mixture was extracted with EtOAc (100 mL x 3), and the combined organic extract was washed with brine (100 mL x 2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-4% then up to 10% CH_3OH in CH_2Cl_2) to afford the title compound (11.8 g, 89%) as a yellow oil. LC/MS (ESI) *m/z*: 384.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 - 7.63 (m, 4H), 7.50 - 7.36 (m, 6H), 3.76 - 3.62 (m, 3H), 3.45 (dd, *J* = 1.6, 10.8 Hz, 1H), 3.27 (br d, *J* = 4.0 Hz, 1H), 3.00 (td, *J* = 2.8, 5.6 Hz, 1H), 2.45 (s, 3H), 2.11 - 2.00 (m, 1H), 1.96 - 1.85 (m, 1H), 1.84 - 1.74 (m, 2H), 1.07 (s, 9H).

Step 10: Preparation of *tert*-butyl 3-[2-[[(2S,5S)-5-[[tert-butyl(diphenyl)silyl]oxymethyl]-1-methyl-pyrrolidin-2-yl]methoxy]-7-chloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



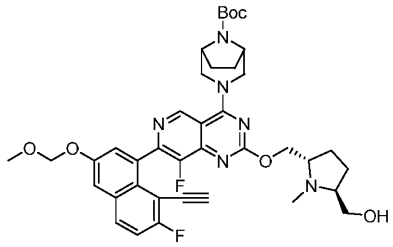
To a solution of *tert*-butyl 3-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.0 g, 2 mmol) and [(2S,5S)-5-[[tert-butyl(diphenyl)silyl]oxymethyl]-1-methyl-pyrrolidin-2-yl]methanol (895 mg, 2 mmol) in dioxane (20 mL) was added 4 A molecular sieves (1 g), and the resulting mixture was stirred at 40 °C for 20 minutes under nitrogen. The mixture was then cooled to 0 °C. Sodium tert-butoxide (561 mg, 5.8 mmol) was then added, and the reaction mixture was stirred at 0 °C for 40 min. The mixture was diluted with saturated aqueous NH_4Cl solution (30 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-21% tetrahydrofuran in petroleum ether) to afford the title compound (1.25 g, 69%) as a yellow oil. LC/MS (ESI) *m/z*: 775.2 $[M+H]^+$.

Step 11: Preparation of tert-butyl 3-[2-[[(2S,5S)-5-[[tert-butyl(diphenyl)silyl]oxymethyl]-1-methyl-pyrrolidin-2-yl]methoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



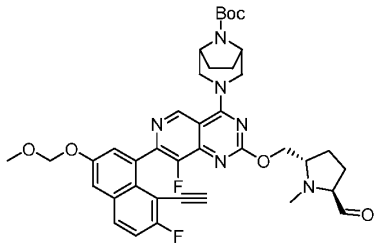
To a stirred solution of tert-butyl 3-[2-[[(2S,5S)-5-[[tert-butyl(diphenyl)silyl]oxymethyl]-1-methyl-pyrrolidin-2-yl]methoxy]-7-chloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.39 g, 2 mmol) and 2-[2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl-triisopropyl-silane (1.01 g, 2 mmol) in 1,4-dioxane (20 mL) and water (2 mL) were added K_3PO_4 (1.14 g, 5 mmol) and CataCXium A Pd G3 (130 mg, 0.2 mmol), and the reaction mixture was stirred at 85 °C under nitrogen for 16 h. The crude reaction mixture was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 20% ethyl acetate in petroleum ether over 25 min) to afford the title compound (1.57 g, 78%) as a yellow solid. LC/MS (ESI) *m/z*: 1125.9 $[M+H]^+$.

Step 12: Preparation of tert-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,5S)-5-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of tert-butyl 3-[2-[[(2S,5S)-5-[[tert-butyl(diphenyl)silyl]oxymethyl]-1-methyl-pyrrolidin-2-yl]methoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.57 g, 1.4 mmol) in DMF (15 mL) was added cesium fluoride (2.12 g, 14 mmol), and the mixture was stirred at 40 °C for 16 h. The reaction mixture was filtered and washed with ethyl acetate (30 mL). The filtrate was diluted with water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extract was washed with water (3 x 30 mL) followed by brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 15% methanol in dichloromethane) to afford the title compound (0.825 g, 81%) as a yellow solid. LC/MS (ESI) *m/z*: 731.3 $[M+H]^+$.

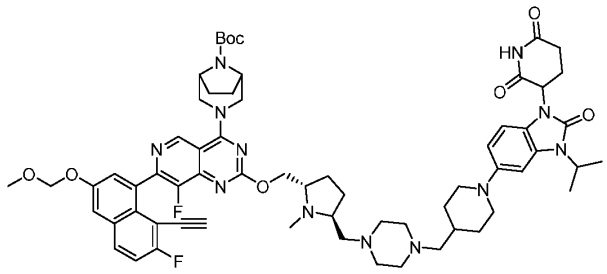
Step 13: Preparation of tert-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,5S)-5-formyl-1-methyl-pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To DMSO (352 mg, 4.5 mmol) in dichloromethane (5 mL) at -67 °C was added oxalyl dichloride (429 mg, 3.4 mmol) in dichloromethane (1 mL) dropwise under nitrogen atmosphere, and the resulting mixture was stirred for 15 min. tert-Butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,5S)-5-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (412 mg, 0.6 mmol) in dichloromethane (1.5 mL) was then added dropwise, and the mixture was stirred at -67 °C for 30 min. Triethylamine (2.4 mL, 17 mmol) was then added dropwise, and the

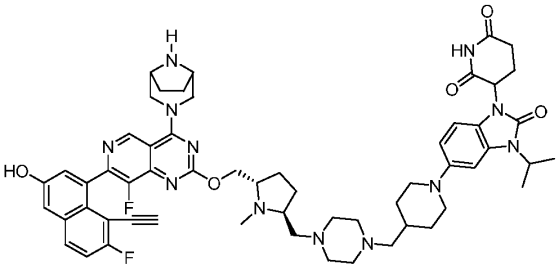
reaction mixture was stirred at -67 °C for 15 min under nitrogen atmosphere. The reaction mixture was diluted with water (30 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (410 mg, crude) as a yellow oil. LC/MS (ESI) *m/z*: 747.3 $[M+H_3O]^+$.

Step 14: Preparation of tert-butyl 3-[2-[[(2S,5S)-5-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



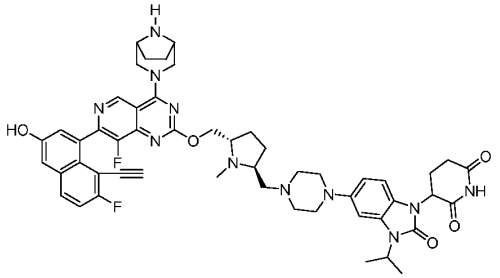
To a mixture of tert-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,5S)-5-formyl-1-methyl-pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (410 mg, 0.6 mmol) and 3-[3-isopropyl-2-oxo-5-[4-(piperazin-1-ylmethyl)-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione (298 mg, 0.6 mmol, HCl salt) in dichloromethane (15 mL) was added $NaBH(OAc)_3$ (298 mg, 1.4 mmol), and the reaction mixture was stirred at 25 °C for 16 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with water (3 x 50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 10% methyl alcohol in dichloromethane) to afford the title compound (370 mg, 55.67%) as a yellow solid. LC/MS (ESI) *m/z*: 1181.9 $[M+H]^+$.

Step 15: Preparation of 3-(5-{4-[(4-{[(2S,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-2-yl]methyl}piperazin-1-yl)methyl]piperidin-1-yl}-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione



To a solution of tert-butyl 3-[2-[[(2S,5S)-5-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (370 mg, 0.3 mmol) in dichloromethane (3 mL) was added 4 M HCl in 1,4-dioxane (3 mL), and the mixture was stirred at 25 °C for 10 min. The reaction mixture was suspended in petroleum ether (10 mL), filtered, and washed with petroleum ether (2 x 10 mL). The filter cake was dissolved with THF (10 mL) and triethylamine to adjust the pH to 8. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (18%-58% acetonitrile in water (ammonium bicarbonate) over 32 min) to afford the title compound (123.2 mg, 39%) as an off-white solid. LC/MS (ESI) *m/z*: 1037.7 $[M+H]^+$; ^{1}H NMR (CD_3OD) δ 9.01 (s, 1H), 7.86 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.00 - 6.94 (m, 2H), 6.80 (dd, *J* = 1.6, 9.2 Hz, 1H), 5.27 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.68 - 4.55 (m, 5H), 4.54 - 4.46 (m, 1H), 3.76 - 3.64 (m, 4H), 3.53 (br d, *J* = 11.6 Hz, 2H), 3.49 - 3.39 (m, 2H), 3.38 (s, 1H), 3.22 - 3.21 (m, 1H), 3.26 - 2.86 (m, 6H), 2.56 - 2.39 (m, 7H), 2.34 - 2.21 (m, 3H), 2.20 - 2.04 (m, 4H), 1.94 - 1.76 (m, 8H), 1.75 - 1.66 (m, 2H), 1.54 (d, *J* = 6.8 Hz, 6H), 1.45 - 1.31 (m, 2H).

Example 69: Synthesis of 3-[5-(4-{[(2S,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-2-yl]methyl}piperazin-1-yl)-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl]piperidine-2,6-dione (**Compound 176**)

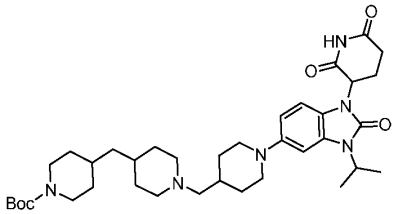


The title compound was made in an analogous manner to 3-(5-{4-[(4-{[(2S,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-2-yl]methyl}piperazin-1-

yl)methyl]piperidin-1-yl}-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (white solid). LC/MS (ESI) *m/z*: 940.4 $[M+H]^+$; ^1H NMR (CD_3OD) δ 9.02 (s, 1H), 7.86 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.36 - 7.28 (m, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 6.76 (br d, *J* = 8.8 Hz, 1H), 5.26 (dd, *J* = 5.6, 12.4 Hz, 1H), 4.68 - 4.56 (m, 5H), 4.54 - 4.48 (m, 1H), 3.75 - 3.65 (m, 4H), 3.49 - 3.41 (m, 1H), 3.38 (s, 1H), 3.14 (br t, *J* = 4.0 Hz, 4H), 2.94 - 2.86 (m, 1H), 2.82 - 2.74 (m, 2H), 2.71 - 2.64 (m, 8H), 2.36 (dd, J = 7.6, 12.4 Hz, 1H), 2.17 - 2.08 (m, 3H), 1.90 - 1.74 (m, 6H), 1.57 - 1.51 (m, 6H)

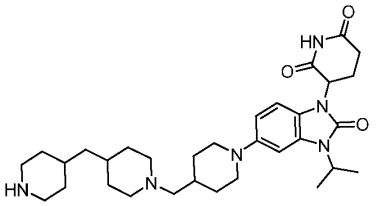
Example 70: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 212**)

Step 1: Preparation of *tert*-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate



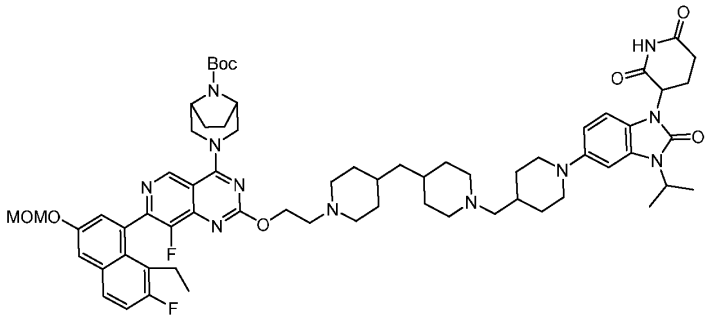
To a solution of *tert*-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate acetate (662 mg, 1.9 mmol) and 1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl] piperidine-4-carbaldehyde (700 mg, 1.8 mmol) in dimethyl sulfoxide (2 mL) and dichloromethane (5 mL) were added sodium triacetoxyborohydride (745 mg, 3.5 mmol) and *N,N*-diisopropylethylamine (0.6 mL, 3 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 40 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with ethyl acetate/methyl tert-butyl ether (1/10, 60 mL) to afford the title compound (1 g, 86%) as green solid. LC/MS (ESI) *m/z*: 665.4 $[M+H]^+$.

Step 2: Preparation of 3-[3-isopropyl-2-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione



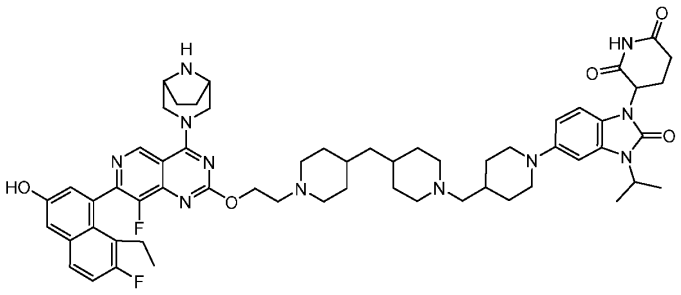
To a solution of *tert*-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate (1.0 g, 1.5 mmol) in dichloromethane (12 mL) was added trifluoroacetic acid (3.0 mL, 40 mmol), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was triturated with ethyl acetate/methyl tert-butyl ether (1/10, 60 mL) to afford the title compound (1.1 g, 92%, 2 TFA salt) as a dark green solid. LC/MS (ESI) *m/z*: 565.5 $[M+H]^+$.

Step 3: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3- piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 3-[3-isopropyl-2-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione di-trifluoroacetate (200 mg, 0.25 mmol) and *tert*-butyl 3-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (213 mg, 0.3 mmol) in isopropanol (5 mL) and dichloromethane (5 mL) were added sodium triacetoxyborohydride (107 mg, 0.5 mmol) and *N,N*-diisopropylethylamine (0.13 mL, 0.8 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with water (15 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (25% -55% acetonitrile in water (trifluoroacetic acid) over 15 min) to afford the title compound (150 mg, 50%) as a white solid. LC/MS (ESI) *m/z*: 1198.8 $[M+H]^+$.

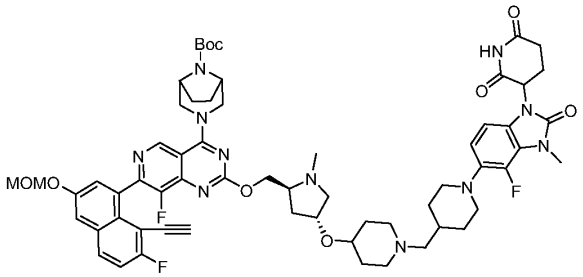
Step 4: Preparation of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione



To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3- piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150 mg, 0.1 mmol) in dichloromethane (5 mL) was added 4 M HCl in 1,4-dioxane (0.3 mL), and the mixture was stirred at 25 °C for 15 min. The reaction mixture was triturated with ethyl acetate/methyl tert-butyl ether (1/10, 100 mL) to obtain a yellow solid. This crude material was purified by prep-HPLC (1% to 30% acetonitrile in water (formic acid) over 10 min) to afford the title compound (56.4 mg, 37%, tri-formic acid salt) as a white solid. LC/MS (ESI) *m/z*: 1054.8 $[M+H]^+$; ^{1}HNMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1 H), 9.13 - 9.08 (m, 1 H), 8.19 (s, 3 H), 7.81 - 7.74 (m, 1 H), 7.39 - 7.32 (m, 2 H), 7.02 (d, *J* = 2.4 Hz, 1 H), 6.94 - 6.86 (m, 2 H), 6.62 (br d, *J* = 8.0 Hz, 1 H), 5.32 - 5.22 (m, 1 H), 4.62 - 4.54 (m, 1 H), 4.51 - 4.41 (m, 4 H), 3.65 (br s, 4 H), 3.54 (br d, *J* = 10.4 Hz, 4 H), 2.98 - 2.90 (m, 3 H), 2.89 - 2.83 (m, 3 H), 2.72 - 2.66 (m, 3 H), 2.64 - 2.56 (m, 3 H), 2.41 - 2.32 (m, 2 H), 2.18 (br d, *J* = 6.8 Hz, 2 H), 2.03 – 1.95 (m, 3 H), 1.93 - 1.86 (m, 2 H), 1.77 (br d, *J* = 12.4 Hz, 2 H), 1.70 - 1.65 (m, 3 H), 1.62 - 1.55 (m, 5 H), 1.44 (br d, *J* = 6.8 Hz, 6 H), 1.33 - 1.21 (m, 4 H), 1.14 - 1.04 (m, 6 H), 0.73 (br t, *J* = 7.6 Hz, 3 H).

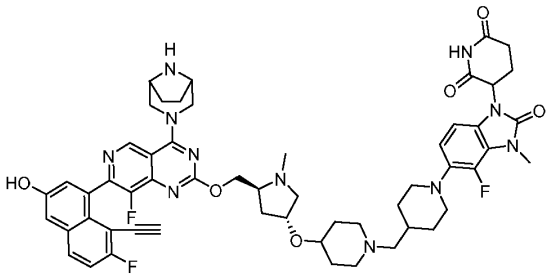
Example 71: Synthesis of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 213**)

Step 1: Preparation of *tert*-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[1-(2,6-dioxo-3- piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,4R)-1-methyl-4-(4-piperidyloxy)pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate formate (100 mg, 0.1 mmol) in dichloromethane (2 mL) and isopropanol (2 mL) were added *N,N*-diisopropylethylamine (22.9 mg, 0.2 mmol), 1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (51 mg, 0.1 mmol), and sodium triacetoxyborohydride (63 mg, 0.3 mmol), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (dichloromethane/methanol = 4/1) to afford the title compound (90 mg, 64%) as a yellow solid. LC/MS (ESI) *m/z*: 1172.9 $[M+H]^+$.

Step 2: Preparation of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione

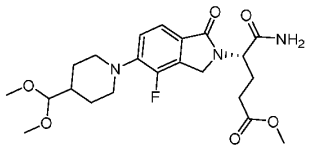


To a solution of *tert*-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[1-(2,6-dioxo-3- piperidyl)-4-fluoro-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.07 mmol) in dichloromethane (6 mL) was added 4 M HCl in 1,4-dioxane (3 mL), and the mixture was stirred at 25 °C for 0.2 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (1% to 30% acetonitrile in water (formic acid) over 10 min) to afford the title compound (49.8 mg, 66%, formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1028.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1 H), 9.07 (s, 1 H), 8.17 (s,

2 H), 8.04 – 7.93 (m, 1 H), 7.52 - 7.37 (m, 2 H), 7.19 (br d, *J* = 2.0 Hz, 1 H), 6.64 - 6.91 (m, 2 H), 5.33 (br dd, *J* = 12.8, 4.8 Hz, 1 H), 4.61 - 4.51 (m, 1 H), 4.44 - 4.35 (m, 2 H), 4.30 - 4.25 (m, 1 H), 4.25 - 4.22 (m, 1 H), 4.13 - 4.12 (m, 1 H), 4.17 - 4.09 (m, 1 H), 3.95 (br s, 1 H), 3.83 (br s, 2 H), 3.76 - 3.69 (m, 2 H), 3.35 - 3.21 (m, 8 H), 2.93 - 2.85 (m, 1 H), 2.83 - 2.78 (m, 1 H), 2.71 (br dd, *J* = 4.4, 2.8 Hz, 2 H), 2.63 (br s, 3 H), 2.55 (s, 8 H), 2.37 (s, 3 H), 2.25 - 2.17 (m, 3 H), 2.11 – 1.98 (m, 3 H), 1.91 - 1.87 (m, 2 H), 1.65 - 1.57 (m, 1 H), 1.49 - 1.36 (m, 2 H), 1.29 - 1.24 (m, 1 H), 1.21 (br d, *J* = 6.4 Hz, 3 H).

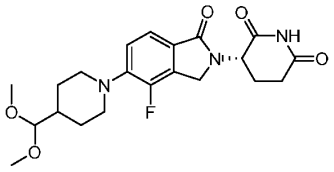
Example 72: Synthesis of (3S)-3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 214**)

Step 1: Preparation of methyl (S)-5-amino-4-(5-(4-(dimethoxymethyl)piperidin-1-yl)-4-fluoro-1-oxoisoindolin-2-yl)-5-oxopentanoate



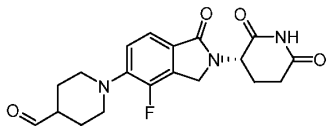
To a mixture of methyl 4-[4-(dimethoxymethyl)-1-piperidyl]-3-fluoro-2-formyl-benzoate (600 mg, 1.8 mmol) and methyl (4S)-4,5-diamino-5-oxo-pentanoate hydrochloride (417 mg, 2 mmol) in methanol (10 mL) was added sodium acetate (725 mg, 8.8 mmol), and the mixture was stirred at 20 °C for 0.5 h. Sodium cyanoborohydride (222 mg, 3.5 mmol) was then added, and the reaction mixture was stirred at 35 °C for 11 h. The reaction was concentrated under reduced pressure, and the resulting residue was diluted with ethyl acetate (100 mL) and washed with brine (60 mL x 2). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 3:1 to 1:100) to afford the title compound (500 mg, 59%) as a light yellow solid. LC/MS (ESI) m/z: 452.3 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.40 (br s, 1H), 5.48 (br s, 1H), 4.97 - 4.78 (m, 1H), 4.59 - 4.36 (m, 2H), 4.11 (d, *J* = 7.2 Hz, 1H), 3.69 - 3.56 (m, 5H), 3.39 (s, 6H), 2.75 (br t, *J* = 11.8 Hz, 2H), 2.52 - 2.29 (m, 3H), 2.19 (dt, *J* = 5.4, 9.8 Hz, 1H), 1.92 - 1.80 (m, 3H), 1.61 - 1.44 (m, 2H).

Step 2: Preparation of (S)-3-(5-(4-(dimethoxymethyl)piperidin-1-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione



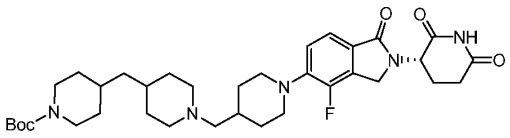
To a solution of methyl methyl (S)-5-amino-4-(5-(4-(dimethoxymethyl)piperidin-1-yl)-4-fluoro-1-oxoisoindolin-2-yl)-5-oxopentanoate (500 mg, 1 mmol) in tetrahydrofuran (10 mL) at -20 °C was added lithium *tert*-butoxide solution (1 M, 2.2 mL), and the reaction mixture was stirred at -20 °C for 4 h. 2 M aqueous sulfuric acid solution was added to adjust the pH to 5 while keepojping the temperature at -20 °C. Saturated sodium bicarbonate solution was added to adjust the pH to 8, and the resulting mixture was diluted with brine (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with ethyl acetate (20 mL) to afford the title compound (290 mg, 62%) as a white solid. LC/MS (ESI) *m/z*: 420.1 $[M+H]^+$.

Step 3: Preparation of (S)-1-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)piperidine-4-carbaldehyde



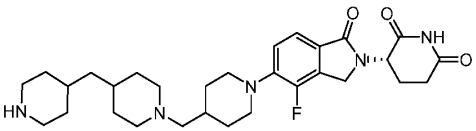
To a mixture of (S)-3-(5-(4-(dimethoxymethyl)piperidin-1-yl)-4-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (290 mg, 0.7 mmol) in acetone (8 mL) and water (0.8 mL) was added p-toluenesulfonic acid monohydrate (23 mg, 0.1 mmol), and the reaction mixture was stirred at 70 °C for 2 h. The mixture was cooled to 25 °C and filtered, washing with acetone (2 x 50 mL). The filtrate solution was concentrated under reduced pressure to afford the title compound (130 mg, 50%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.65 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.26 - 7.12 (m, 1H), 5.08 (dd, J = 5.2, 1Step 6: Hz, 1H), 4.55 - 4.42 (m, 1H), 4.38 - 4.26 (m, 1H), 3.48 - 3.37 (m, 3H), 2.98 - 2.85 (m, 3H), 2.64 - 2.55 (m, 1H), 2.48 - 2.34 (m, 1H), 2.05 - 1.93 (m, 3H), 1.74 - 1.57 (m, 2H).

Step 4: Preparation of *tert*-butyl (S)-4-((1-((1-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)piperidin-4-yl)methyl)piperidin-4-yl)methyl)piperidine-1-carboxylate



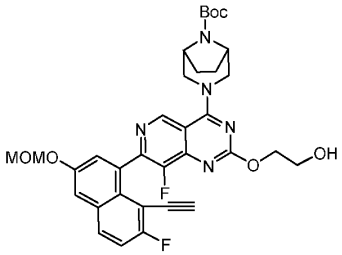
To a solution of (S)-1-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)piperidine-4-carbaldehyde (130 mg, 0.3 mmol) in dichloromethane (3 mL) and dimethyl sulfoxide (0.8 mL) was added *tert*-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate (98 mg, 0.3 mmol), and the resulting mixture was stirred at 0 °C for 10 min. Sodium triacetoxyborohydride (221 mg, 1 mmol) was then added, and the reaction mixture was stirred at 0 °C for 0.5 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-TLC (dichloromethane:methanol = 10:1) to afford the title compound (160 mg, 71%) as a white solid. LC/MS (ESI) *m/z*: 640.5 $[M+H]^+$.

Step 5: Preparation of (S)-3-(4-fluoro-1-oxo-5-(4-((4-(piperidin-4-ylmethyl)piperidin-1-yl)methyl)piperidin-1-yl)isoindolin-2-yl)piperidine-2,6-dione



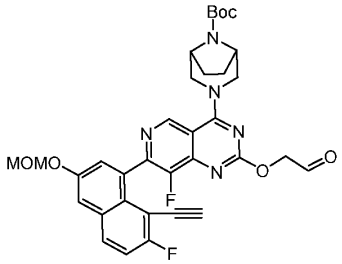
To *tert*-butyl (S)-4-((1-((1-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)piperidin-4-yl)methyl)piperidin-4-yl)methyl)piperidine-1-carboxylate (160 mg, 0.3 mmol) in dichloromethane (2 mL) at 25 °C was added trifluoroacetic acid (1.0 mL, 13 mmol), and the reaction mixture was stirred for 15 min. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (1% to 30% acetonitrile in water (formic acid) over 10 min) to afford the title compound (100 mg, 74%) as a white solid. LC/MS (ESI) *m/z*: 540.3 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 7.55 - 7.42 (m, 1H), 7.26 - 7.05 (m, 1H), 5.08 (dd, *J* = 5.2, 1Step 6: Hz, 1H), 4.58 - 4.39 (m, 1H), 4.38 - 4.26 (m, 1H), 3.60 - 3.48 (m, 4H), 3.31 - 3.18 (m, 3H), 3.06 - 2.97 (m, 2H), 2.94 - 2.75 (m, 7H), 2.64 - 2.54 (m, 1H), 2.42 - 2.37 (m, 1H), 2.07 - 1.92 (m, 2H), 1.89 - 1.73 (m, 6H), 1.68 - 1.53 (m, 2H), 1.46 - 1.31 (m, 4H), 1.29 - 1.09 (m, 4H).

Step 6: Preparation of tert-butyl 3-[7-[8-ethynyl-7-fluoro-3- (methoxymethoxy)-1-naphthyl]-8-fluoro-2-(2-hydroxyethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



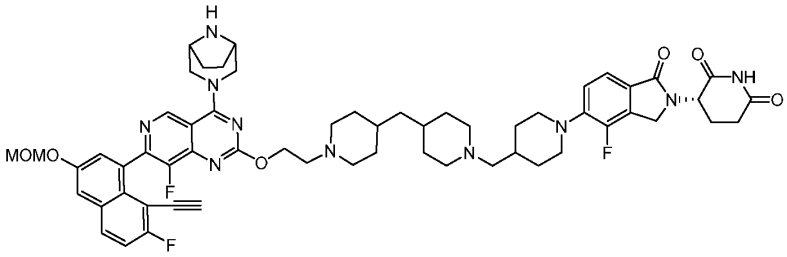
To a solution of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-hydroxyethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2 g, 2 mmol) in N,N-dimethylformamide (20 mL) was added cesium fluoride (11.5 g, 76 mmol). The mixture was stirred at 25 °C for 0.5 hour. The reaction mixture was diluted with water (100 mL) and extracted with dichloromethane (80 mL × 2). The combined organic phase was washed with brine (80 mL × 2), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (dichloromethane:methanol = 10:1) to afford *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-(2-hydroxyethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.5 g, 93%) as a yellow solid.

Step 7: Preparation of tert-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl] -8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



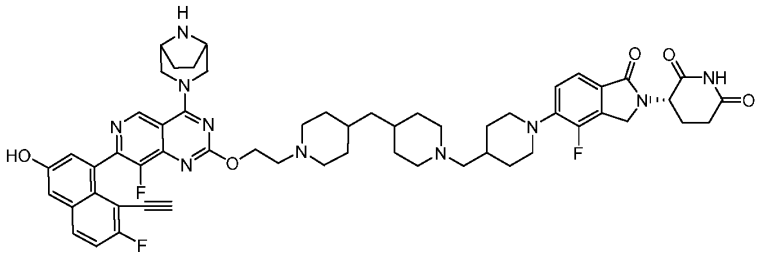
To a solution of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-(2-hydroxyethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.30 mmol) in dichloromethane (2 mL) were added Dess-Martin reagent (196 mg, 0.46 mmol) and sodium bicarbonate (51 mg, 0.61 mmol). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was diluted with saturated aqueous sodium bicarbonate: saturated aqueous sodium thiosulfate: water (1:1:1, 45 mL) and extracted with dichloromethane(15 mL × 2). The combined organic phase was washed with brine (30 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-TLC (petroleum ether:ethyl acetate = 0:1) to afford *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (118 mg, 59%) as a yellow solid. LC/MS (ESI) *m/z*: 646.3 $[M+1]^+$.

Step 8: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-[(3S)-2,6-dioxo-3- piperidyl]-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of (S)-3-(4-fluoro-1-oxo-5-(4-((4-(piperidin-4-ylmethyl)piperidin-1-yl)methyl)piperidin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (100 mg, 0.2 mmol) and *N*-methylmorpholine (18 mg, 0.18 mmol) in dichloromethane (2 mL) and dimethyl sulfoxide (0.2 mL) was added *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl] -8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (119 mg, 0.2 mmol), and the resulting mixture was stirred at 0 °C for 10 min. Sodium triacetoxyborohydride (117 mg, 0.6 mmol) was then added, and the reaction mixture was stirred at 0 °C for 0.5 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over sodium sulfate anhydrous, filtered, and concentrated under reduced pressure. The residue was purified by prep-TLC (dichloromethane/methanol = 10:1) to afford the title compound (100 mg, 46%) as a white solid. LC/MS (ESI) *m/z*: 585.6 $[M/2+H]^+$.

Step 9: Preparation of (3S)-3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione

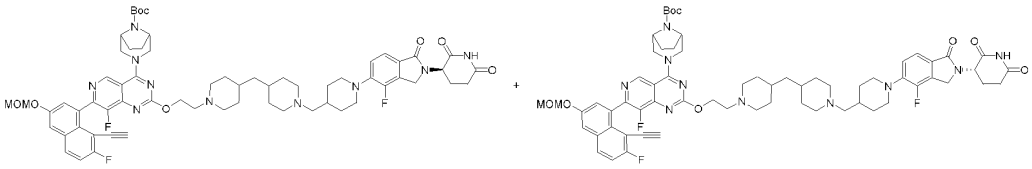


To *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-[(3S)-2,6-dioxo-3- piperidyl]-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.08 mmol) in dichloromethane (2 mL) at 25 °C was added 4 M HCl in 1,4-dioxane (0.5 mL), and the reaction mixture was stirred for 15 min. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (1% to 30% acetonitrile in water (formic acid) over 10 min) to afford the title

compound (61.3 mg, 63%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1007.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.07 (s, 1H), 8.15 (s, 2H), 7.98 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.50 - 7.43 (m, 2H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.20 - 7.13 (m, 2H), 5.08 (dd, *J* = 5.2, 13.6 Hz, 1H), 4.61 - 4.35 (m, 6H), 4.34 - 4.27 (m, 1H), 3.94 (s, 1H), 3.87 - 3.82 (m, 2H), 3.76 - 3.69 (m, 2H), 3.49 - 3.46 (m, 2H), 2.99 - 2.87 (m, 5H), 2.80 - 2.72 (m, 4H), 2.60 - 2.54 (m, 1H), 2.44 - 2.37 (m, 1H), 2.32 - 2.25 (m, 2H), 2.10 - 1.93 (m, 5H), 1.83 - 1.76 (m, 6H), 1.75 - 1.67 (m, 1H), 1.65 - 1.56 (m, 4H), 1.35 - 1.23 (m, 4H), 1.18 - 1.04 (m, 6H).

Example 73: Synthesis of (3R)-3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 163**)

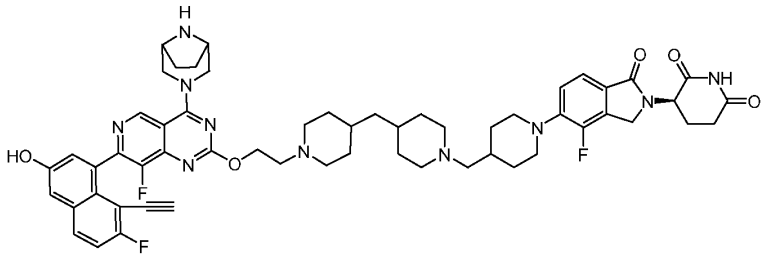
Step 1: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-[(3R)-2,6-dioxo-3-piperidyl]-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and *tert*-butyl 3-[2-[2-[4-[[1-[[1- [2-[(3S)-2,6-dioxo-3-piperidyl]-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



Tert-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2 g) was purified by chiral SFC (40% to 40% acetonitrile/isopropanol (0.1% NH_4OH) in CO_2), then further purified by prep-HPLC (30% to 60% acetonitrile in water (formic acid) over 10 min). *tert*-Butyl 3-[2-[2-[4-[[1-[[1-[2-[(3R)-2,6-dioxo-3-piperidyl]-4-fluoro-1-oxo- isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (900 mg, 45%) was obtained as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.09 (s, 1H), 8.23 - 8.17 (m, 1H), 8.14 - 8.06 (m, 1H), 7.79 - 7.71 (m, 1H), 7.55 (t, *J* = 8.8 Hz, 1H), 7.50 - 7.43 (m, 1H), 7.40 - 7.31 (m, 1H), 7.19 - 7.09 (m, 1H), 5.37 (s, 2H), 5.07 (dd, *J* = 4.8, 12.8 Hz, 1H), 4.61 - 4.36 (m, 6H), 4.35 - 4.26 (m, 3H), 3.98 (s, 1H), 3.69 - 3.60 (m, 2H), 3.49 - 3.39 (m, 5H), 3.01 - 2.88 (m,

3H), 2.87 - 2.81 (m, 2H), 2.79 - 2.67 (m, 4H), 2.63 - 2.54 (m, 1H), 2.43 - 2.37 (m, 1H), 2.26 - 2.15 (m, 2H), 2.06 - 1.73 (m, 11H), 1.63 - 1.55 (m, 4H), 1.46 (s, 9H), 1.36 - 1.23 (m, 4H), 1.15 - 0.99 (m, 6H). *tert*-Butyl 3-[2-[2-[4-[[1-[[1- [2-[(3S)-2,6-dioxo-3-piperidyl]-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (900 mg, 45%) was obtained as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.09 (s, 1H), 8.18 (s, 1H), 8.14 - 8.06 (m, 1H), 7.78 - 7.73 (m, 1H), 7.55 (t, J = 8.8 Hz, 1H), 7.50 - 7.43 (m, 1H), 7.40 - 7.31 (m, 1H), 7.19 - 7.09 (m, 1H), 5.38 (s, 2H), 5.07 (dd, J = 4.8, 12.8 Hz, 1H), 4.61 - 4.36 (m, 6H), 4.33 - 4.26 (m, 3H), 3.98 (s, 1H), 3.69 - 3.60 (m, 2H), 3.49 - 3.39 (m, 5H), 2.99 - 2.69 (m, 9H), 2.59 (d, J = 16.0 Hz, 1H), 2.42 - 2.33 (m, 1H), 2.24 - 2.17 (m, 2H), 2.06 - 1.72 (m, 11H), 1.64 - 1.55 (m, 4H), 1.46 (s, 9H), 1.34 - 1.20 (m, 4H), 1.17 - 1.02 (m, 6H).

Step 2: Preparation of (3R)-3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione

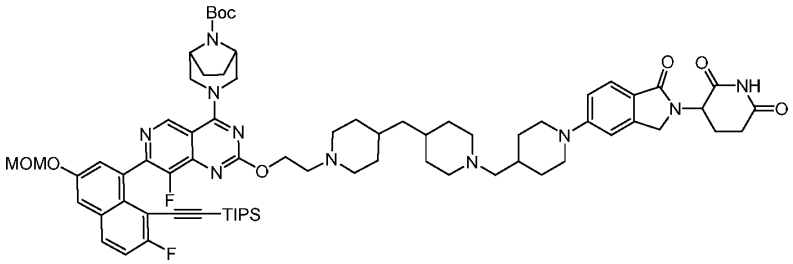


To *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-[(3R)-2,6-dioxo-3-piperidyl]-4-fluoro-1-oxo- isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (900 mg, 0.8 mmol) in dichloromethane (10 mL) was added 4 M HCl in 1,4-dioxane (2 mL) at 25 °C, and the mixture was stirred for 15 min. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (0% to 20% acetonitrile in water (formic acid) over 30 min) to afford the title compound (352.9 mg, 42%, formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1025.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.05 (s, 1H), 8.25 - 8.23 (m, 1H), 8.23 - 8.23 (m, 1H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.50 - 7.42 (m, 2H), 7.41 - 7.37 (m, 1H), 7.23 - 7.08 (m, 2H), 5.07 (dd, J = 5.2, 1Step 2: Hz, 1H), 4.55 - 4.50 (m, 2H), 4.47 - 4.44 (m, 2H), 4.37 - 4.35 (m, 1H), 4.33 - 4.28 (m, 2H), 3.92 (s, 1H), 3.75 - 3.71 (m, 2H), 3.70 - 3.61 (m, 2H), 3.50 - 3.43 (m, 2H), 2.99 - 2.81 (m, 5H), 2.80 - 2.67 (m, 4H), 2.63 - 2.55 (m, 1H), 2.47 - 2.35 (m, 1H), 2.20

(d, *J* = 6.8 Hz, 2H), 2.07 - 1.86 (m, 5H), 1.83 - 1.72 (m, 6H), 1.71 - 1.64 (m, 1H), 1.58 (d, *J* = 12.0 Hz, 4H), 1.36 - 1.19 (m, 4H), 1.17 - 1.01 (m, 6H).

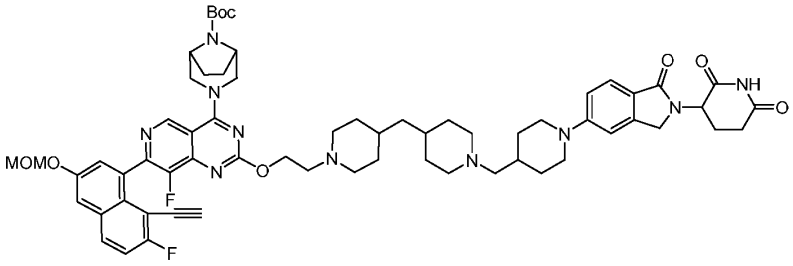
Example 74: Synthesis of (3S)-3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 215**)

Step 1: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3- piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



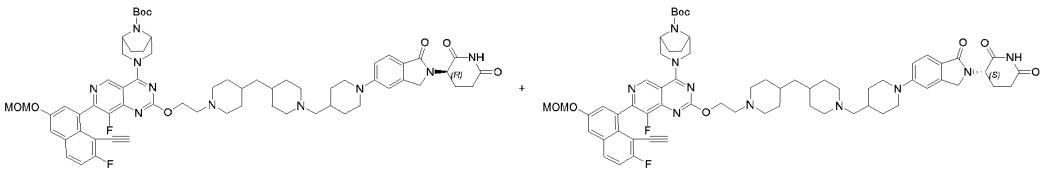
To a mixture of *tert*-butyl-3-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.6 g, 3 mmol), 3-[1-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl] methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione trifluoroacetate (2.3 g, 4 mmol) and *N,N*-diisopropylethylamine (1.6 mL, 9.7 mmol) in dimethyl sulfoxide (6 mL) and dichloromethane (10 mL) was added sodium triacetoxyborohydride (1.37 g, 6.5 mmol), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by prep-HPLC (45% to 75% acetonitrile in water (formic acid) over 15 min) to afford the title compound (1.7 g, 40%) as a white solid. LC/MS (ESI) *m/z*: 1308.9 $[M+H]^+$.

Step 2: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3- piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3- piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.7 g, 1.3 mmol) in *N,N*-dimethylformamide (20 mL) was added cesium fluoride (5.92 g, 39 mmol), and the mixture was stirred at 25 °C for 2 h. Trifluoroacetic acid was added to the reaction mixture to adjust the pH to 2-3, the mixture was filtered, and concentrated. The residue was purified by reversed-phase HPLC (30% to 60% acetonitrile in water (formic acid) over 12 min) to afford the title compound (1.3 g, 86%) as a yellow solid. LC/MS (ESI) *m/z*: 576.7 $[M/2+H]^+$.

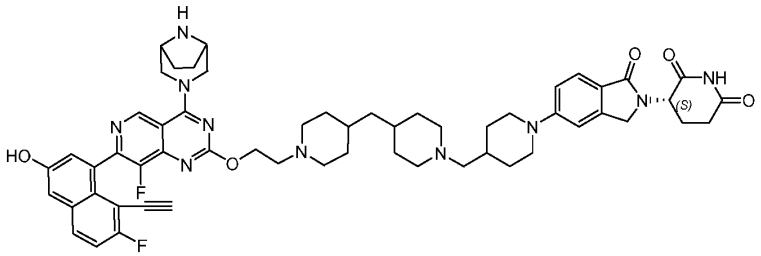
Step 3: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-[(3R)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5- yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5- yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



tert-Butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3- piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg) was purified by chiral SFC (75% to 75% acetonitrile/isopropanol (0.1% NH_3H_2O) in CO_2). The crude product was further purified by prep-HPLC (23% to 53% acetonitrile in water (formic acid) over 10 min, then 15% to 45% acetonitrile in water (formic acid) over 10 min) to afford *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-[(3R)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5- yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-

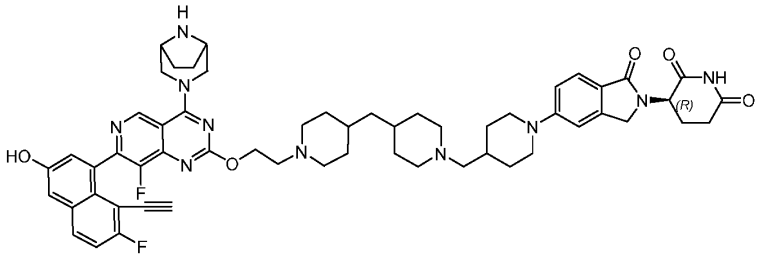
d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150 mg, 37%) as a pale yellow solid and *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5- yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 50%) as a pale yellow solid. LC/MS (ESI) *m/z*: 1151.8 $[M+H]^+$.

Step 4: Preparation of (3S)-3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione



To a mixture of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5- yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.2 mmol) in dichloromethane (2 mL) at 25 °C was added 4 M HCl in 1,4-dioxane (0.6 mL), and the mixture was stirred for 15 min. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (1% to 30% acetonitrile in water (formic acid) over 10 min) to afford the title compound (55.2 mg, 28%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1007.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 9.06 (s, 1H), 8.24 - 8.18 (m, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.54 - 7.45 (m, 2H), 7.40 (d, J = 2.4 Hz, 1H), 7.21 - 7.17 (m, 1H), 7.07 - 7.00 (m, 2H), 5.04 (dd, J = 6.0, 9.2 Hz, 1H), 4.59 - 4.37 (m, 4H), 4.34 - 4.27 (m, 1H), 4.22 - 4.14 (m, 1H), 3.93 (d, J = 0.8 Hz, 1H), 3.89 - 3.77 (m, 4H), 3.76 - 3.65 (m, 2H), 3.02 - 2.68 (m, 9H), 2.62 - 2.54 (m, 1H), 2.43 - 2.31 (m, 1H), 2.28 - 2.14 (m, 2H), 2.13 - 1.89 (m, 5H), 1.87 - 1.68 (m, 7H), 1.59 (d, J = 10.8 Hz, 4H), 1.38 - 1.25 (m, 2H), 1.24 - 1.02 (m, 8H).

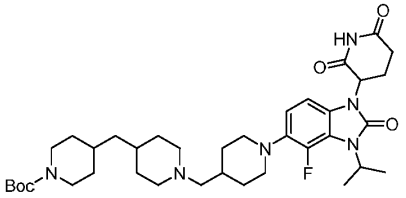
Example 75: Synthesis of (3R)-3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 216**)



To a mixture of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-[(3R)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5- yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150 mg, 0.1 mmol) in dichloromethane (2 mL) at 25 °C was added 4 M HCl in 1,4-dioxane (0.5 mL), and the mixture was stirred for 15 min. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (1% to 30% acetonitrile in water (formic acid) over 10 min) to afford the title compound (37.8 mg, 27%, formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1107.7 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 9.05 (s, 1H), 8.24 - 8.18 (m, 1H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.53 - 7.43 (m, 2H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.06 - 6.99 (m, 2H), 5.04 (dd, J = 5.2, 1Step 2: Hz, 1H), 4.54 - 4.42 (m, 3H), 4.39 - 4.34 (m, 1H), 4.33 - 4.28 (m, 1H), 4.22 - 4.16 (m, 1H), 3.93 (d, *J* = 0.8 Hz, 1H), 3.85 (d, *J* = 12.4 Hz, 2H), 3.72 - 3.61 (m, 4H), 2.98 - 2.88 (m, 3H), 2.87 - 2.75 (m, 4H), 2.73 - 2.66 (m, 2H), 2.62 - 2.56 (m, 1H), 2.41 - 2.31 (m, 1H), 2.15 (d, *J* = 6.0 Hz, 2H), 2.08 - 1.84 (m, 5H), 1.81 - 1.66 (m, 7H), 1.58 (d, *J* = 10.8 Hz, 4H), 1.35 - 1.25 (m, 2H), 1.22 - 1.02 (m, 8H).

Example 76: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 217**)

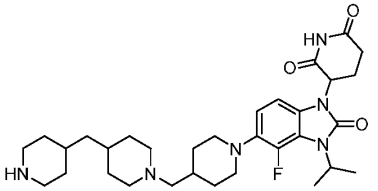
Step 1: Preparation of tert-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate



To a solution of 1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (297 mg, 0.35 mmol, HCl salt) and tert-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate (262 mg, 0.9 mmol) in dichloromethane (4.0 mL) and

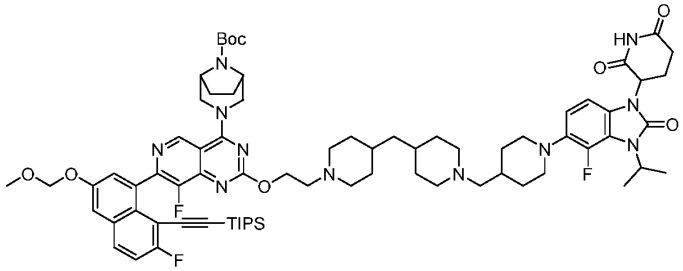
isopropanol (4.0 mL) were added acetic acid (0.41 mL, 7 mmol) and 2-methylpyridine borane (305 mg, 2.9 mmol), and the reaction mixture was stirred at 25 °C for 12 h. The mixture was neutralized with triethylamine to adjust the pH to 7, then the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 7% methanol in dichloromethane) to afford to afford the title compound (305 mg, 59%) as a white foam. LC/MS (ESI) *m/z*: 683.5 $[M+H]^+$.

Step 2: Preparation of 3-[4-fluoro-3-isopropyl-2-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione



To a solution of tert-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate (305 mg, 0.4 mmol) in dichloromethane (4.0 mL) was added 4 M HCl in 1,4-dioxane (4.0 mL), and the reaction mixture was stirred at 25 °C for 20 min. The mixture was concentrated under reduced pressure to afford the title compound (260 mg, crude, HCl salt) as a white solid. LC/MS (ESI) *m/z*: 583.4 $[M+H]^+$.

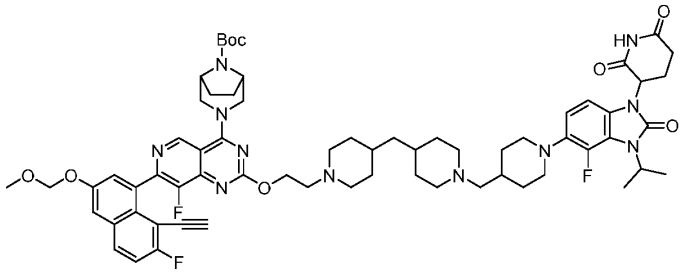
Step 3: Preparation of tert-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a mixture of 3-[4-fluoro-3-isopropyl-2-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione (260 mg, 0.4 mmol) and tert-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (501 mg, 0.6 mmol) in dichloromethane (5.0 mL) and isopropanol (5.0 mL) were added sodium acetate (366 mg, 4 mmol) and 2-methylpyridine borane (191 mg, 1.8 mmol), and the reaction mixture was

stirred at 25 °C for 12 h. The mixture was filtered and concentrated under reduced pressure, then neutralized with triethylamine to adjust the pH to 7. The resulting mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (0 to 8% methanol in dichloromethane) to afford to afford the title compound (400 mg, 51%) as a yellow foam. LC/MS (ESI) *m/z*: 1369.5 $[M+H]^+$.

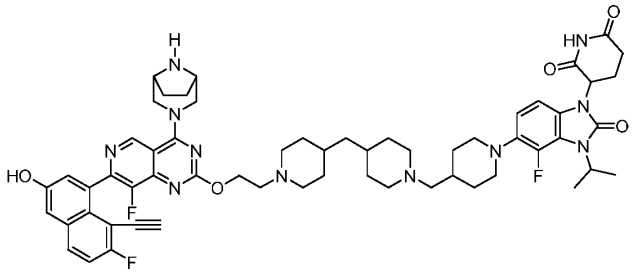
Step 4: Preparation of tert-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of tert-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg, 0.2 mmol) in DMF (4.0 mL) was added cesium fluoride (222 mg, 1.5 mmol), and the mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with water (8 x 10 mL) followed by brine (2 x 30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (2% to 42% acetonitrile in water (formic acid) over 36 min) to afford the title compound (132 mg, 37%) as a yellow solid. LC/MS (ESI) *m/z*: 1212.6 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 11.10 (s, 1H), 9.09 (s, 1H), 8.19 - 8.07 (m, 2H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.55 (t, *J* = 9.2 Hz, 1H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.22 (s, 1H), 5.37 (s, 2H), 5.36 - 5.32 (m, 1H), 4.72 (td, *J* = 6.8, 1Step 5: Hz, 1H), 4.55 (br d, *J* = 12.8 Hz, 1H), 4.49 - 4.38 (m, 3H), 4.30 (br s, 2H), 3.65 (br t, *J* = 11.6 Hz, 3H), 3.44 (s, 8H), 3.06 (br d, *J* = 17.2 Hz, 5H), 2.93 (br d, *J* = 8.8 Hz, 2H), 2.83 (br d, *J* = 10.4 Hz, 3H), 2.73 (br d, *J* = 4.0 Hz, 1H), 2.68 - 2.66 (m, 2H), 2.60 (br d, *J* = 16.0 Hz, 1H), 2.35 - 2.31 (m, 1H), 2.18 (br d, *J* = 6.4 Hz, 2H), 1.90 - 1.81 (m, 4H), 1.74 (br d, *J* = 10.8 Hz, 4H), 1.58 (br d, *J* = 11.2 Hz, 4H), 1.47 (s, 9H), 1.41 (br d, *J* = 7.2 Hz, 6H), 1.09 (br d, *J* = 6.4 Hz, 6H).

Step 5: Preparation of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-

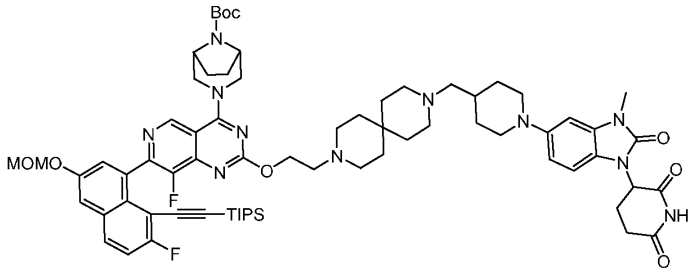
yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione



To a solution of tert-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (132 mg, 0.1 mmol) in dichloromethane (2.0 mL) was added 4 M HCl in 1,4-dioxane (2 mL), and the mixture was stirred at 25 °C for 20 min. The reaction mixture was suspended in petroleum ether (15 mL), filtered, and the filter cake was dissolved in tetrahydrofuran (5 mL) and triethylamine to adjust the pH to 8. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (32% to 72% acetonitrile in water (ammonium bicarbonate) over 36 min) to afford the title compound (42.1 mg, 35%) as a yellow solid. LC/MS (ESI) *m/z*: 1068.7 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 7.86 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.40 - 7.27 (m, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 6.94 - 6.77 (m, 2H), 5.29 (dd, *J* = 5.6, 12.8 Hz, 1H), 4.70 - 4.49 (m, 6H), 3.77 - 3.63 (m, 4H), 3.37 (s, 1H), 3.14 - 3.06 (m, 2H), 3.02 - 2.95 (m, 2H), 2.93 - 2.83 (m, 3H), 2.82 - 2.78 (m, 1H), 2.77 - 2.73 (m, 1H), 2.71 (br s, 1H), 2.69 - 2.65 (m, 1H), 2.33 (br dd, *J* = 1.6, 4.4 Hz, 2H), 2.22 - 2.12 (m, 3H), 2.09 - 1.97 (m, 2H), 1.91 - 1.84 (m, 4H), 1.80 (br d, *J* = 9.6 Hz, 2H), 1.75 - 1.65 (m, 5H), 1.51 (br d, *J* = 7.2 Hz, 6H), 1.48 - 1.39 (m, 4H), 1.32 - 1.13 (m, 7H).

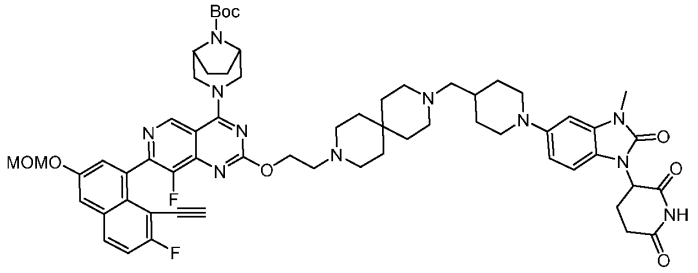
Example 77: Synthesis of 3-(5-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 218**)

Step 1: Preparation of *tert*-butyl 3-[2-[2-[3-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



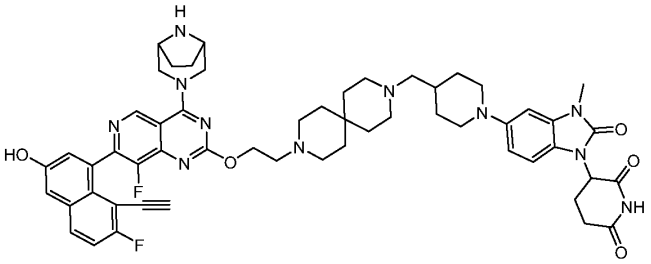
To a solution of *tert*-butyl *tert*-butyl-3-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (240 mg, 0.3 mmol) and 3-[5-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione di-trifluoroacetate (200 mg, 0.3 mmol) in dichloromethane (5 mL) and isopropanol (5 mL) were added *N,N*-diisopropylethylamine (0.1 mL, 0.8 mmol) and sodium triacetoxyborohydride (115 mg, 0.5 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with water (15 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (300 mg, 85%) as a yellow solid. LC/MS (ESI) *m/z*: 1294.9 $[M+H]^+$.

Step 2: Preparation of *tert*-butyl 3-[2-[2-[3-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



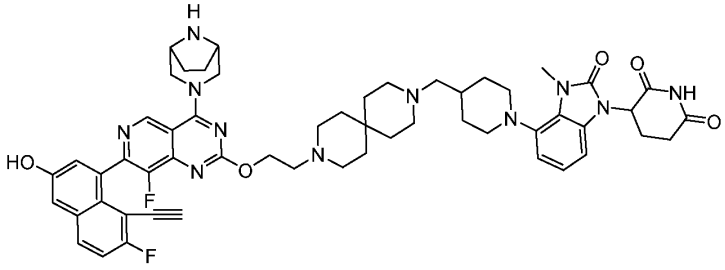
To a solution of *tert*-butyl 3-[2-[2-[3-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (375 mg, 0.3 mmol) in *N,N*-dimethylformamide (5 mL) was added cesium fluoride (1.32 g, 8.7 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with water (0.5 mL), filtered, and the filtrate solution was purified by prep-HPLC (20% to 50% acetonitrile in water (trifluoroacetic acid) over 9 min) to afford the title compound (145 mg, 44%) as an off-white solid. LC/MS (ESI) *m/z*: 1138.7 $[M+H]^+$.

Step 3: Preparation of 3-(5-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione



To a solution of *tert*-butyl 3-[2-[2-[3-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (145 mg, 0.1 mmol) in dichloromethane (3 mL) was added 4 M HCl in 1,4-dioxane (0.03 mL), and the mixture was stirred at 25 °C for 15 min. The reaction mixture was triturated with ethyl acetate/methyl tertiary butyl ether (1/10, 100 mL) and then purified by prep-HPLC (1% to 25% acetonitrile in water (formic acid) over 10 min) to afford the title compound (39.4 mg, 28%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 994.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 - 11.02 (m, 1 H), 9.09 – 8.98 (m, 1 H), 8.20 (s, 2 H), 7.97 (dd, *J* = 9.2, 6.0 Hz, 1 H), 7.50 - 7.43 (m, 1 H), 7.39 (d, *J* = 2.4 Hz, 1 H), 7.21 - 7.14 (m, 1 H), 6.91 (br d, *J* = 8.8 Hz, 1 H), 6.80 (s, 1 H), 6.64 - 6.58 (m, 1 H), 5.28 (br dd, *J* = 12.8, 5.2 Hz, 1 H), 4.50 (br d, *J* = 2.0 Hz, 1 H), 4.45 (br t, *J* = 5.2 Hz, 2 H), 4.36 - 4.30 (m, 1 H), 3.93 - 3.91 (m, 1 H), 3.67 (br s, 2 H), 3.56 (br d, *J* = 12.0 Hz, 5 H), 3.29 (s, 6 H), 2.70 (br d, *J* = 6.4 Hz, 3 H), 2.65 - 2.57 (m, 4 H), 2.33 (br s, 6 H), 2.19 (br d, *J* = 6.0 Hz, 2 H), 2.01 – 1.95 (m, 1 H), 1.79 - 1.74 (m, 2 H), 1.69 (br s, 4 H), 1.41 (br s, 8 H), 1.29 - 1.27 (m, 1 H), 1.26 - 1.19 (m, 2 H).

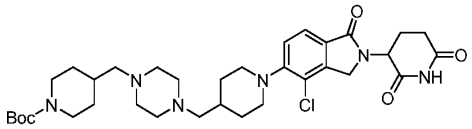
Example 78: Synthesis of 3-(4-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 83**)



The title compound was prepared in an analogous manner to 3-(5-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (white solid, formic acid salt). LC/MS (ESI) *m/z*: 994.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.09 (s, 1H), 9.05 (s, 1H), 8.21 (s, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.47 (t, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.01 - 6.93 (m, 1H), 6.92 - 6.83 (m, 2H), 5.35 (br dd, J = 5.6, 12.4 Hz, 1H), 4.54 - 4.43 (m, 3H), 4.35 (br d, J = 11.6 Hz, 1H), 3.94 (s, 1H), 3.70 - 3.57 (m, 9H), 3.10 (br d, J = 8.4 Hz, 2H), 2.93 - 2.83 (m, 1H), 2.76 - 2.61 (m, 6H), 2.46 (br s, 4H), 2.35 (br s, 4H), 2.26 - 2.19 (m, 2H), 2.03 - 1.96 (m, 1H), 1.84 - 1.76 (m, 2H), 1.71 (br s, 4H), 1.66 - 1.58 (m, 1H), 1.42 (br s, 8H), 1.35 - 1.25 (m, 2H).

Example 79: Synthesis of 3-[4-chloro-5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 219**)

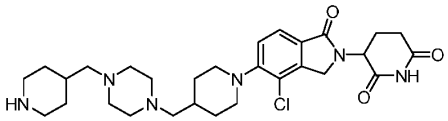
Step 1: Preparation of tert-butyl-4-[[4-[[1-[4-chloro-2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]piperidine-1-carboxylate



To a solution of 1-[4-chloro-2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperidine-4-carbaldehyde (243 mg, 0.6 mmol) and tert-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (247 mg, 0.9 mmol) in dichloromethane (5 mL), isopropanol (5 mL) and THF (5 mL) was added acetic acid (0.2 mL, 4 mmol), and the resulting mixture was stirred at 40 °C for 12 h. 2-Methylpyridine borane (333 mg, 3 mmol) was then added, and the reaction mixture was stirred at 40 °C for 1 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (0 to 5% methanol in

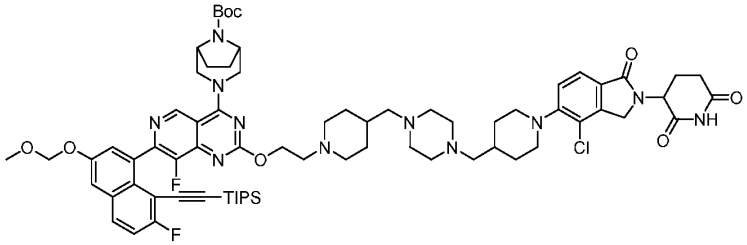
dichloromethane) to afford the title compound (191 mg, 47%) as a yellow solid. LC/MS (ESI) *m/z*: 657.3 $[M+H]^+$.

Step 2: Preparation of 3-[4-chloro-1-oxo-5-[4-[[4-(4-piperidylmethyl)piperazin-1-yl]methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione



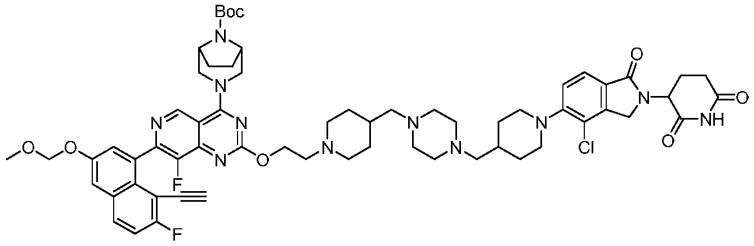
To a solution of tert-butyl-4-[[4-[[1-[4-chloro-2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]piperidine-1-carboxylate (191 mg, 0.3 mmol) in dichloromethane (3 mL) was added 4 M HCl in 1,4-dioxane (3 mL), and the mixture was stirred at 20 °C for 30 min. The mixture was triturated with petroleum ether (20 mL) to afford the title compound (190 mg, crude, 3 HCl salt) as a white solid.

Step 3: Preparation of tert-butyl-3-[2-[2-[4-[[4-[[1-[4-chloro-2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



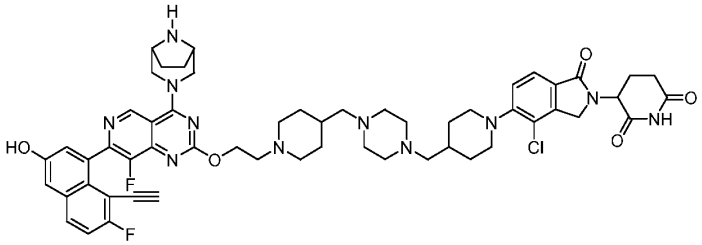
To a solution of 3-[4-chloro-1-oxo-5-[4-[[4-(4-piperidylmethyl)piperazin-1-yl]methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione (190 mg, 0.3 mmol, 3 HCl) and tert-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (457 mg, 0.6 mmol) in dichloromethane (10 mL), isopropanol (10 mL) and DMSO (4 mL) were added sodium acetate (187 mg, 2 mmol) and 2-methylpyridine borane (152 mg, 1.4 mmol), and the mixture was stirred at 15 °C for 16 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with saturated sodium bicarbonate solution to adjust the pH to 8 and extracted with ethyl acetate (3 x 50 mL). The combined organic extract was washed with water (4 x 10 mL) followed by brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (0 to 8% then up to 10% methanol in dichloromethane) to afford the title compound (275 mg, 61%) as a yellow solid. LC/MS (ESI) *m/z*: 1342.7 $[M+H]^+$.

Step 4: Preparation of tert-butyl 3-[2-[2-[4-[[4-[[1-[4-chloro-2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of tert-butyl-3-[2-[2-[4-[[4-[[1-[4-chloro-2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (275 mg, 0.2 mmol) in THF (5 mL) was added TBAF (1 M, 0.3 mL), and the reaction mixture was stirred at 20 °C for 2 h. The mixture was diluted with ethyl acetate (100 mL), then washed with water (6 x 10 mL) followed by brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford the title compound (305 mg, crude) as a yellow solid. LC/MS (ESI) *m/z*: 1186.5 $[M+H]^+$.

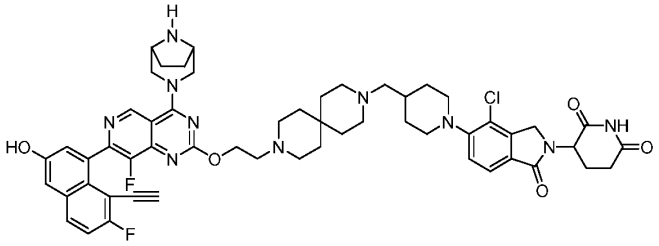
Step 5: Preparation of 3-[4-chloro-5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione



To a solution of tert-butyl 3-[2-[2-[4-[[4-[[1-[4-chloro-2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (242 mg, 0.2 mmol) in dichloromethane (3 mL) was added 4 M HCl in 1,4-dioxane (3 mL), and the mixture was stirred at 20 °C for 20 min. The mixture was suspended in petroleum ether (30 mL), filtered, and the filter cake was diluted with THF (50 mL) and triethylamine (3 mL). The resulting mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by prep-HPLC (20% to 60% acetonitrile in water (ammonium bicarbonate) over 36 min) to afford the title compound (88.9 mg, 42%) as a

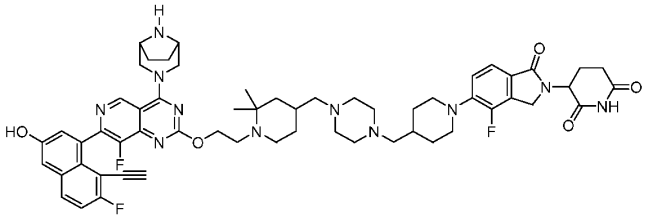
yellow solid. LC/MS (ESI) *m/z*: 1042.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.00 (s, 1H), 7.86 (dd, *J* = 9.2, 5.6, Hz 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.36 - 7.28 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 5.17 - 5.08 (m, 1H), 4.71 - 4.54 (m, 5H), 4.52 - 4.37 (m, 2H), 3.77 - 3.61 (m, 4H), 3.54 - 3.43 (m, 2H), 3.37 (s, 1H), 3.15 - 3.03 (m, 2H), 2.97 - 2.83 (m, 3H), 2.82 - 2.70 (m, 3H), 2.63 - 2.36 (m, 8H), 2.29 (d, *J* = 6.8 Hz, 2H), 2.25 - 2.11 (m, 5H), 1.97 - 1.70 (m, 9H), 1.67 - 1.53 (m, 1H), 1.51 - 1.36 (m, 2H), 1.34 - 1.19 (m, 2H).

Example 80: Synthesis of 3-(4-chloro-5-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 220**)



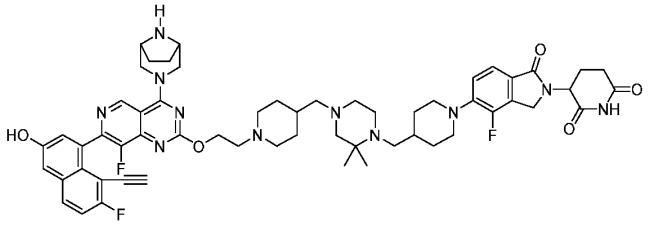
The title compound was prepared in an analogous manner to 3-[4-chloro-5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (yellow solid). LC/MS (ESI) *m/z*: 1013.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 7.86 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.76 - 7.64 (m, 1H), 7.39 - 7.24 (m, 3H), 7.21 (d, *J* = 2.4 Hz, 1H), 5.19 - 5.06 (m, 1H), 4.68 - 4.56 (m, 5H), 4.52 - 4.36 (m, 3H), 3.75 - 3.64 (m, 4H), 3.48 (br d, *J* = 2.0 Hz, 2H), 2.94 - 2.85 (m, 3H), 2.83 - 2.73 (m, 3H), 2.65 (br s, 4H), 2.59 - 2.50 (m, 4H), 2.40 (br d, *J* = 5.2 Hz, 2H), 2.21 - 2.12 (m, 1H), 1.92 - 1.77 (m, 7H), 1.59 (br s, 7H), 1.53 - 1.38 (m, 3H).

Example 81: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-2,2-dimethylpiperidin-4-yl)methyl]piperazin-1-yl}methyl)piperidin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 168**)



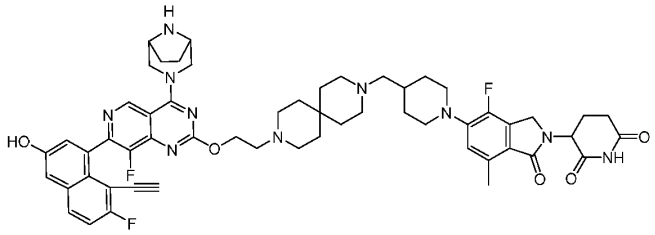
The title compound was prepared in an analogous manner to 3-[4-chloro-5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. z, 1H), 7.87 (dd, J = 8.8, 5.6 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.24 - 7.13 (m, 2H), 5.11 (dd, J = 13.2, 5.2 Hz, 1H), 4.71 - 4.42 (m, 7H), 3.79 - 3.64 (m, 4H), 3.63 - 3.55 (m, 2H), 3.45 - 3.34 (m, 2H), 2.95 - 2.73 (m, 5H), 2.61 - 2.39 (m, 9H), 2.33 - 2.25 (m, 2H), 2.20 - 2.11 (m, 3H), 1.94 - 1.70 (m, 10H), 1.65 - 1.57 (m, 1H), 1.48 - 1.32 (m, 2H), 1.29 - 1.03 (m, 8H).

Example 82: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]-2,2-dimethylpiperazin-1-yl}methyl)piperidin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 169**)



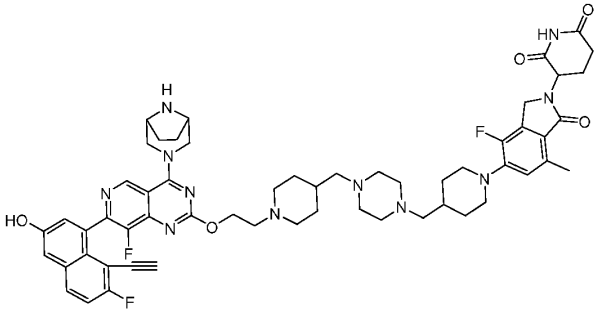
The title compound was prepared in an analogous manner to 3-[4-chloro-5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (yellow solid). LC/MS (ESI) *m/z*: 1054.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.03 (s, 1H), 7.89 -7.86 (m, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.38 - 7.31 (m, 2H), 7.25 - 7.15 (m, 2H), 5.15 - 5.10 (m, 1H), 4.72 - 4.56 (m, 5H), 4.54 - 4.43 (m, 2H), 3.78 - 3.65 (m, 4H), 3.63 - 3.57 (m, 2H), 3.38 (s, 1H), 3.18 - 3.08 (m, 2H), 2.96 - 2.75 (m, 6H), 2.69 - 2.59 (m, 2H), 2.55 - 2.42 (m, 2H), 2.33 - 2.10 (m, 8H), 1.96 - 1.78 (m, 8H), 1.65 - 1.54 (m, 2H), 1.40 - 1.21 (m, 5H), 1.06 (s, 6H).

Example 83: Synthesis of 3-(5-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}-4-fluoro-7-methyl-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 153**)



The title compound was prepared in an analogous manner to 3-[4-chloro-5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1011.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.06 (s, 1H), 8.18 (s, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 5.02 (dd, J = 5.2, 13.2 Hz, 1H), 4.58 - 4.44 (m, 3H), 4.39 (d, J = 16.8 Hz, 2H), 4.22 (d, J = 16.8 Hz, 1H), 3.94 (s, 1H), 3.81 (s, 2H), 3.72 (t, J = 14.0 Hz, 2H), 3.47 (d, J = 6.4 Hz, 2H), 2.95 - 2.84 (m, 1H), 2.79 - 2.69 (m, 4H), 2.61 - 2.54 (m, 2H), 2.53 (s, 3H), 2.49 - 2.38 (m, 8H), 2.35 - 2.19 (m, 3H), 1.99 - 1.91 (m, 1H), 1.83 - 1.60 (m, 8H), 1.44 (s, 8H), 1.30 - 1.20 (m, 2H).

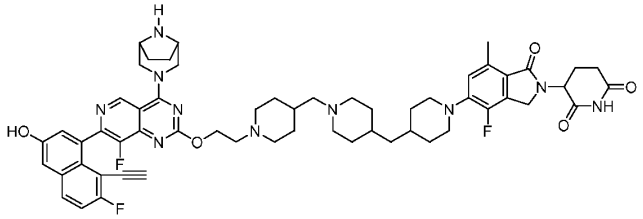
Example 84: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperazin-1-yl}methyl)piperidin-1-yl]-4-fluoro-7-methyl-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 148**)



The title compound was prepared in an analogous manner to 3-[4-chloro-5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1040.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 11.00 - 10.90 (m, 1H), 9.06 (s, 1H), 8.18 (s, 2H), 8.01 - 7.94 (m, 1H), 7.46 (t, J = 8.8 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.1 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 5.02 (dd, J = 5.2, 13.2 Hz, 1H), 4.53 (d, J = 12.8 Hz, 1H), 4.46 (s, 2H), 4.42 - 4.33 (m, 2H), 4.23 (d, J = 17.2 Hz, 1H), 3.93 (s, 1H), 3.76 (s, 2H), 3.73 - 3.64 (m, 2H), 3.47 (

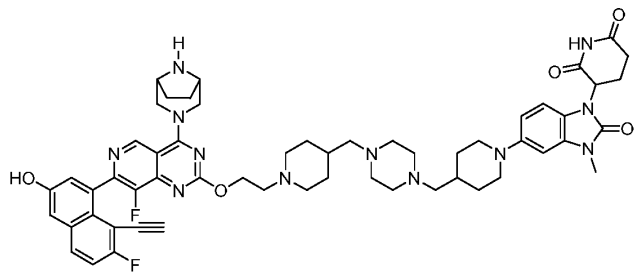
dd, J = 2.4, 9.2 Hz, 2H), 2.99 - 2.88 (m, 3H), 2.79 - 2.65 (m, 5H), 2.63 - 2.55 (m, 2H), 2.53 (s, 3H), 2.43 - 2.24 (m, 9H), 2.16 (d, J = 7.2 Hz, 2H), 2.09 (d, J = 7.2 Hz, 2H), 2.06 - 2.00 (m, 2H), 1.97 - 1.92 (m, 1H), 1.81 - 1.72 (m, 6H), 1.65 (d, J = 12.0 Hz, 3H), 1.53 - 1.41 (m, 1H), 1.30 - 1.18 (m, 2H), 1.15 - 1.01 (m, 2H).

Example 85: Synthesis of 3-{5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-4-fluoro-7-methyl-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 170**)



The title compound was prepared in an analogous manner to 3-[4-chloro-5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. LC/MS (ESI) *m/z*: 1039.5 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 7.86 (dd, J = 5.6, 9.2 Hz, 1H), 7.38 - 7.29 (m, 2H), 7.21 (d, J = 2.4 Hz, 1H), 6.87 (br d, J = 7.2 Hz, 1H), 5.06 (dd, J = 5.2, 13.2 Hz, 1H), 4.67 - 4.56 (m, 5H), 4.51 - 4.30 (m, 3H), 3.76 - 3.63 (m, 4H), 3.56 (br d, J = 9.2 Hz, 2H), 3.15 - 3.08 (m, 2H), 3.01 (br d, J = 10.0 Hz, 2H), 2.92 - 2.85 (m, 3H), 2.81 - 2.73 (m, 3H), 2.58 (s, 3H), 2.48 (br dd, J = 4.8, 13.2 Hz, 1H), 2.32 (br d, J = 6.4 Hz, 2H), 2.28 - 2.00 (m, 6H), 1.88 - 1.70 (m, 10H), 1.42 - 1.22 (m, 9H).

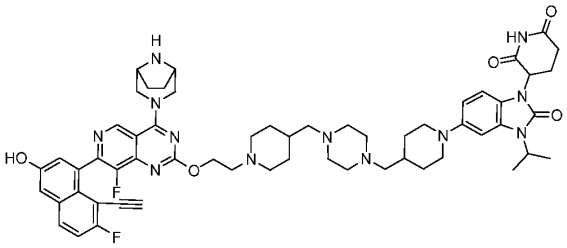
Example 86: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperazin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 221**)



The title compound was prepared in an analogous manner to 3-[4-chloro-5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-

pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. LC/MS (ESI) *m/z*: 1023.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 7.87 - 7.84 (m, 1H), 7.35 - 7.30 (m, 2H), 7.21 - 7.20 (m, 1H), 6.98 - 6.96 (m, 1H), 6.87 - 6.86 (m, 1H), 6.81 - 6.78 (m, 1H), 5.30 - 5.25 (m, 1H), 4.64 - 4.56 (m, 5H), 3.73 - 3.66 (m, 4H), 3.60 - 3.56 (m, 2H), 3.40 (s, 3H), 3.37 (s, 1H), Step 10: - 3.07 (m, 2H), 2.92 - 2.66 (m, 7H), 2.49 (s, 6H), 2.28 - 2.16 (m, 8H), 1.91 - 1.60 (m, 10H), 1.43 - 1.22 (m, 4H).

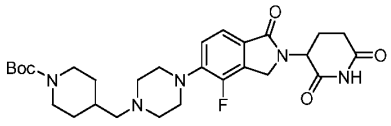
Example 87: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperazin-1-yl}methyl)piperidin-1-yl]-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 222**)



The title compound was prepared in an analogous manner to 3-[4-chloro-5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (yellow solid). LC/MS (ESI) *m/z*: 1051.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 7.86 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.40 - 7.28 (m, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.06 - 6.88 (m, 2H), 6.80 (dd, *J* = 1.6, 8.4 Hz, 1H), 5.26 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.69 - 4.51 (m, 6H), 3.77 - 3.60 (m, 4H), 3.58 - 3.50 (m, 2H), 3.37 (s, 1H), 3.15 - 3.05 (m, 3H), 2.93 - 2.67 (m, 7H), 2.57 - 2.42 (m, 6H), 2.31 - 2.09 (m, 7H), 1.96 - 1.75 (m, 8H), 1.73 - 1.53 (m, 8H), 1.43 - 1.37 (m, 2H), 1.29-1.26 (m, 2H).

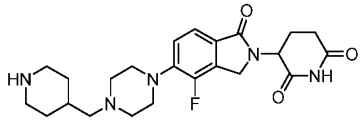
Example 88: Synthesis of 3-{5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperazin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 223**)

Step 1: Preparation of *tert*-butyl 4-[[4-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]piperidine-1-carboxylate



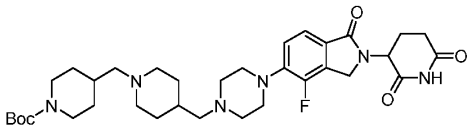
To a mixture of 3-(4,5-difluoro-1-oxo-isoindolin-2-yl)piperidine-2,6-dione (3.0 g, 11 mmol) and *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (6.07 g, 21 mmol) in DMSO (40 mL) was added DIEA (5.6 mL, 32 mmol), and the mixture was stirred at 140 °C for 15 h. The reaction mixture was cooled and poured into water (300 mL), filtered, and the filter cake was triturated with MTBE (50 mL) to afford the title compound (2.5 g, 40%) as a brown solid. LC/MS (ESI) *m/z*: 544.3 $[M+H]^+$.

Step 2: Preparation of 3-[4-fluoro-1-oxo-5-[4-(4-piperidylmethyl)piperazin-1-yl]isoindolin-2-yl]piperidine-2,6-dione



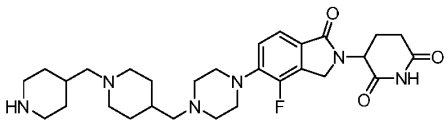
To *tert*-butyl 4-[[4-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]piperidine-1-carboxylate (0.66 g, 1 mmol) in dichloromethane (6 mL) was added 4 M HCl in 1,4-dioxane (6 mL), and the mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford the title compound (541 mg, crude, HCl salt) as an off-white solid. LC/MS (ESI) *m/z*: 444.0 $[M+H]^+$.

Step 3: Preparation of *tert*-butyl 4-[[4-[[4-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]methyl]piperidine-1-carboxylate



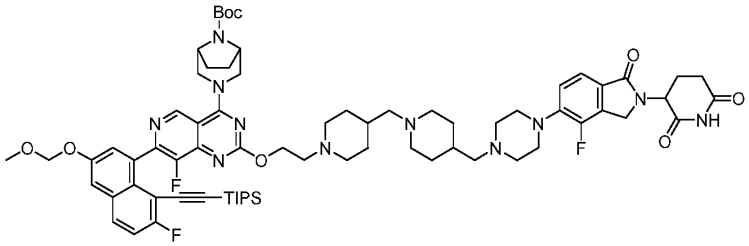
To a mixture of 3-[4-fluoro-1-oxo-5-[4-(4-piperidylmethyl)piperazin-1-yl]isoindolin-2-yl]piperidine-2,6-dione (541 mg, 1 mmol, HCl) and *tert*-butyl 4-formylpiperidine-1-carboxylate (481 mg, 2 mmol) in dichloromethane (15 mL) and isopropanol (10 mL) were added sodium acetate (462 mg, 5.6 mmol) and 2-methylpyridine borane (603 mg, 5.6 mmol), and the reaction mixture was stirred at 25 °C for 70 h. The mixture was diluted with saturated sodium bicarbonate solution (10 mL) and extracted with dichloromethane/methanol (3 x 30 mL, V:V = 10: 1). The combined organic extract was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0-8% then up to 10% 2 M NH_3/methanol in dichloromethane) to afford the title compound (440 mg, 61%) as a yellow solid. LC/MS (ESI) *m/z*: 641.7 $[M+H]^+$.

Step 4: Preparation of 3-[4-fluoro-1-oxo-5-[4-[[1-(4-piperidylmethyl)-4-piperidyl]methyl]piperazin-1-yl]isoindolin-2-yl]piperidine-2,6-dione



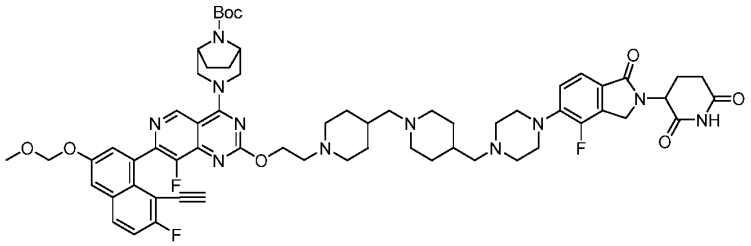
To a mixture of *tert*-butyl 4-[[4-[[4-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]methyl]piperidine-1-carboxylate (440 mg, 0.7 mmol) in dichloromethane (5 mL) was added 4 M HCl in 1,4-dioxane (5 mL), and the reaction mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated under reduced pressure to afford the title compound (396 mg, crude, HCl salt) as an off-white solid. LC/MS (ESI) *m/z*: 541.4 $[M+H]^+$.

Step 5: Preparation of *tert*-butyl 3-[2-[2-[4-[[4-[[4-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



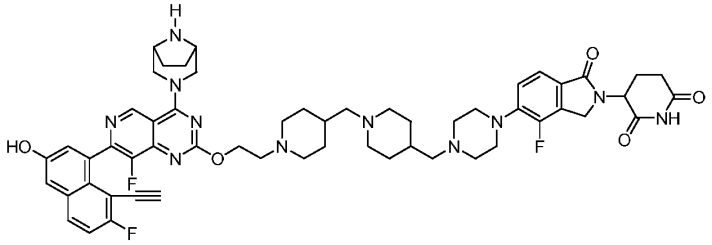
To a mixture of 3-[4-fluoro-1-oxo-5-[4-[[1-(4-piperidylmethyl)-4-piperidyl]methyl]piperazin-1-yl]isoindolin-2-yl]piperidine-2,6-dione (396 mg, 0.7 mmol, HCl) and tert-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (551 mg, 0.7 mmol) in dichloromethane (5 mL) and isopropanol (5 mL) were added sodium acetate (282 mg, 3.4 mmol) and 2-methylpyridine borane (367 mg, 3.4 mmol), and the reaction mixture was stirred at 30 °C for 15 h. The reaction was quenched with saturated sodium bicarbonate solution (10 mL) and extracted with dichloromethane/methanol (3 x 30 mL, V:V = 10: 1). The combined organic extract was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0-10% 2 M NH_3/methanol in dichloromethane) to afford the title compound (717 mg, 71%) as a yellow solid. LC/MS (ESI) *m/z*: 1327.1 $[M+H]^+$.

Step 6: Preparation of *tert*-butyl 3-[2-[2-[4-[[4-[[4-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To *tert*-butyl 3-[2-[2-[4-[[4-[[4-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (717 mg, 0.5 mmol) in THF (10 mL) was added TBAF (1.0 M, 975 µL), and the reaction mixture was stirred at 25 °C for 1 h. The mixture was diluted with ethyl acetate (50 mL) and washed with water (3 x 20 mL) followed by brine (20 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (569 mg, crude) as a yellow solid. LC/MS (ESI) *m/z*: 1170.7 $[M+H]^+$.

Step 7: Preparation of 3-{5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperazin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione

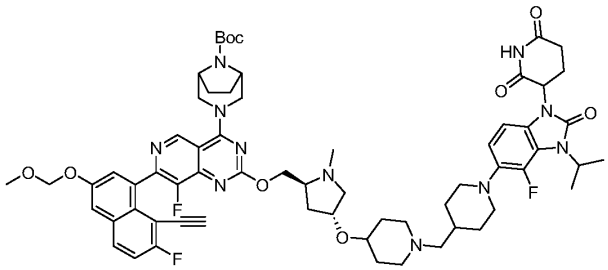


To *tert*-butyl 3-[2-[2-[4-[[4-[[4-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (569 mg, 0.5 mmol) in dichloromethane (5 mL) was added 4 M HCl in 1,4-dioxane (5 mL), and the reaction mixture was stirred at 25 °C for 5 min. The mixture was suspended in petroleum ether (30 mL) and filtered. The filter cake was dissolved in THF (30 mL) and triethylamine to adjust the pH to 8. The resulting mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (16%-56% acetonitrile in water (ammonium bicarbonate) over 36 min) to afford the title compound (162.7 mg, 33%) as an off-white solid. LC/MS (ESI) *m/z*: 1026.3 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 7.86 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.40 - 7.27 (m, 2H), 7.24 - 7.11 (m, 2H), 5.11 (dd, *J* = 5.2, 1Step 2: Hz, 1H), 4.68 - 4.41 (m, 6H), 3.78 -

3.60 (m, 4H), 3.37 (s, 1H), 3.24 (br s, 4H), Step 10: (br dd, *J* = 2.8, 4.8 Hz, 2H), 2.98 - 2.73 (m, 6H), 2.61 (br s, 4H), 2.55 - 2.43 (m, 1H), 2.32 - 2.12 (m, 7H), 2.05 - 1.96 (m, 2H), 1.93 - 1.73 (m, 8H), 1.68 - 1.56 (m, 2H), 1.28 (q, *J* = 11.2 Hz, 4H).

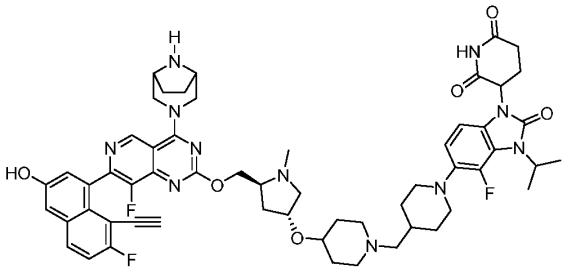
Example 89: Synthesis of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4-fluoro-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 224**)

Step 1: Preparation of tert-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,4R)-1-methyl-4-(4-piperidyloxy)pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (260 mg, 0.3 mmol) and 1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (176 mg, 0.4 mmol) in dichloromethane (4.0 mL) and isopropanol (2.0 mL) were added acetic acid (93 µL, 1.6 mmol) and 2-methylpyridine borane (174 mg, 1.6 mmol), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (0 to 7% methanol in dichloromethane) to afford the title compound (200 mg, 48%) as a yellow solid. LC/MS (ESI) m/z: 1200.8 $[M+H]^+$.

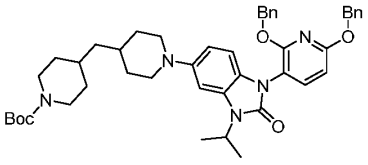
Step 2: Preparation of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4-fluoro-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione



To a solution of tert-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-4-fluoro-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.2 mmol) in dichloromethane (6.0 mL) was added 4 M HCl in 1,4-dioxane (1.7 mL), and the mixture was stirred at 25 °C for 30 min. The mixture was suspended in petroleum ether (50 mL) and filtered. The filter cake was diluted with tetrahydrofuran (40 mL) and triethylamine (5 mL), filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (22% to 62% acetonitrile in water (ammonium bicarbonate) over 36 min) to afford the title compound (38.0 mg, 21%) as a white solid. LC/MS (ESI) m/z: 1005.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 7.87 - 7.83 (m, 1H), 7.39 - 7.26 (m, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 6.91 - 6.79 (m, 2H), 5.30 - 5.26 (m, 1H), 4.67 - 4.55 (m, 4H), 4.53 - 4.39 (m, 3H), 4.26 - 4.20 (m, 1H), 3.77 - 3.62 (m, 4H), 3.50 - 3.34 (m, 3H), 3.04 - 2.99 (m, 1H), 2.93 - 2.85 (m, 1H), 2.83 - 2.64 (m, 6H), 2.52 (s, 3H), 2.40 - 2.36 (m, 1H), 2.28 (d, *J* = 6.0 Hz, 2H), 2.22 - 2.11 (m, 3H), 2.08 - 1.98 (m, 2H), 1.96 - 1.75 (m, 8H), 1.73 - 1.57 (m, 3H), 1.51 (d, *J* = 6.8 Hz, 8H).

Example 90: Synthesis of 3-{5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 80**)

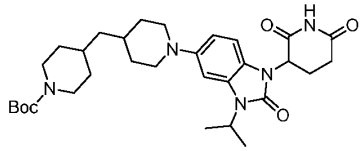
Step 1: Preparation of tert-butyl 4-[[1-[1-(2,6-dibenzyloxy-3-pyridyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperidine-1-carboxylate



To a solution of 5-bromo-1-(2,6-dibenzyloxy-3-pyridyl)-3-isopropyl-benzimidazol-2-one (711 mg, 1.3 mmol) and tert-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate (368.8 mg, 1.3 mmol) in 1,4-dioxane (10 mL) was added cesium carbonate (1.28 g, 3.9 mmol), and the resulting the mixture was degassed and purged with nitrogen for 10 min. XPhos (124.5 mg, 261

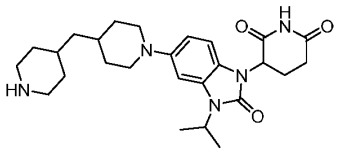
μmol) and $Pd_2(dba)_3$ (119.6 mg, 130 μmol) were then added, and the reaction mixture was stirred at 100 °C for 16 h. The crude reaction mixture was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 50% ethyl acetate in petroleum ether) to afford the title compound (800 mg, 77%) as a yellow solid. LC/MS (ESI) *m/z*: 746.7 $[M+H]^+$.

Step 2: Preparation of tert-butyl 4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperidine-1-carboxylate



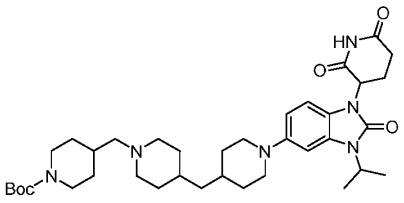
To a solution of tert-butyl 4-[[1-[1-(2,6-dibenzyloxy-3-pyridyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperidine-1-carboxylate (800 mg, 1 mmol) in THF (10 mL) was added 20% $Pd(OH)_2$ on carbon (286 mg, 0.4 mmol), and the suspension was degassed and purged with hydrogen several times. The reaction mixture was stirred under hydrogen (50 psi) at 50 °C for 16 h, then filtered and concentrated under reduced pressure to afford the title compound (578 mg, crude) as a white solid. LC/MS (ESI) *m/z*: 568.3 $[M+H]^+$.

Step 3: Preparation of 3-[3-isopropyl-2-oxo-5-[4-(4-piperidylmethyl)-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione



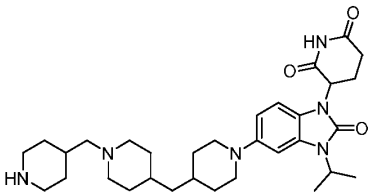
To a solution of tert-butyl 4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperidine-1-carboxylate (578 mg, 1 mmol) in dichloromethane (5 mL) was added 4 M HCl in 1,4-dioxane (5.1 mL), and the reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated and triturated with petroleum ether (3 x 10 mL) to afford the title compound (513 mg, crude, HCl salt) as a white solid. LC/MS (ESI) *m/z*: 468.3 $[M+H]^+$.

Step 4: Preparation of tert-butyl 4-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]piperidine-1-carboxylate



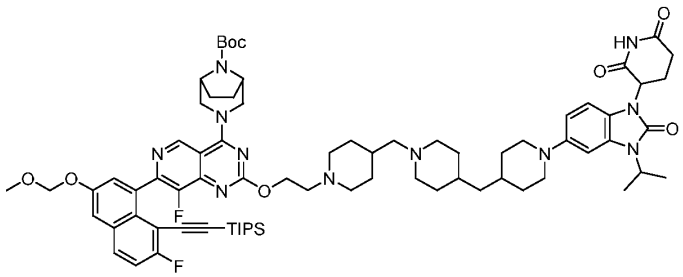
To a solution of 3-[3-isopropyl-2-oxo-5-[4-(4-piperidylmethyl)-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione (513 mg, 1 mmol, HCl) in dichloromethane (5 mL) and isopropanol (5 mL) were added sodium acetate (667.9 mg, 8 mmol), tert-butyl 4-formylpiperidine-1-carboxylate (651 mg, 3 mmol), and 2-methylpyridine borane (435 mg, 4 mmol), and the reaction mixture was stirred at 25 °C for 1 h. The mixture was diluted with triethylamine to adjust the pH to 8, then concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (0 to 7% methanol in dichloromethane) to afford the title compound (642 mg, 83%) as a light yellow solid. LC/MS (ESI) *m/z*: 665.4 $[M+H]^+$.

Step 5: Preparation of 3-[3-isopropyl-2-oxo-5-[4-[[1-(4-piperidylmethyl)-4-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione



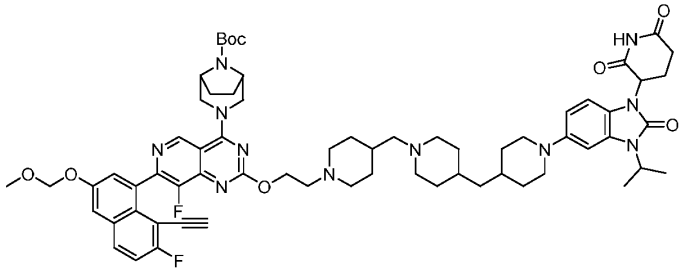
To a solution of tert-butyl 4-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]piperidine-1-carboxylate (517 mg, 0.7 mmol) in dichloromethane (4 mL) was added 4 M HCl in 1,4-dioxane (3.38 mL), and the reaction mixture was stirred at 25 °C for 30 min. The mixture concentrated *in vacuo*, and the residue was triturated with petroleum ether (3 x 10 mL) to afford the title compound (406 mg, crude, HCl salt) as a purple solid. LC/MS (ESI) *m/z*: 565.3 $[M+H]^+$

Step 6: Preparation of tert-butyl 3-[2-[2-[4-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 3-[3-isopropyl-2-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione (406 mg, 0.7 mmol, HCl) in dichloromethane (4 mL) and isopropanol (4 mL) were added sodium acetate (755.4 mg, 9 mmol), tert-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-*d*]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (492.3 mg, 0.6 mmol), and 2-methylpyridine borane (262.7 mg, 2.5 mmol), and the reaction mixture was stirred at 25 °C for 1 h. The mixture was diluted with triethylamine to adjust the pH to 8, and then the suspension was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (0 to 7% methanol in dichloromethane) to afford the title compound (612 mg, 66%) as a white solid. LC/MS (ESI) *m/z*: 676.4 $[M/2+H]^+$.

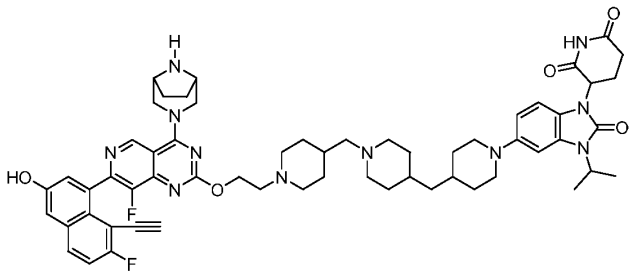
Step 7: Preparation of tert-butyl (1R,5S)-3-(2-(2-(4-((4-((1-(1-(2,6-dioxopiperidin-3-yl)-3-isopropyl-2-oxo-2,3-dihydro-1*H*-benzo[d]imidazol-5-yl)piperidin-4-yl)methyl)piperidin-1-yl)methyl)piperidin-1-yl)ethoxy)-7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of tert-butyl 3-[2-[2-[4-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (600 mg, 0.4 mmol) in DMF (10 mL) was added cesium fluoride (303.64 mg, 2 mmol), and the mixture was stirred at 25 °C for 16 h. The reaction mixture was filter, washing with ethyl acetate (30 mL), and the filtrate was diluted with water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with water (3 x 30 mL) followed brine (30 mL), dried over anhydrous sodium

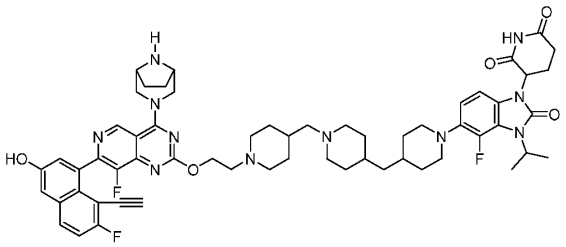
sulfate, filtered, and concentrated under reduced pressure to afford the title compound (550 mg, 92%) as a yellow solid. LC/MS (ESI) *m/z*: 598.0 [1/2 M+H]$^+$.

Step 8: Preparation of 3-{5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione



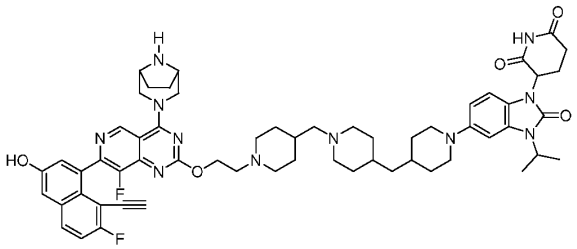
To a solution of tert-butyl 3-[2-[2-[4-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (550 mg, 0.4 mmol) in dichloromethane (5 mL) was added 4 M HCl in 1,4-dioxane (5 mL), and the mixture was stirred at 25 °C for 10 min. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (26% - 66% acetonitrile in water (ammonium bicarbonate) over 36 min) to afford the title compound (189.4 mg, 47%) as an off-white solid. LC/MS (ESI) *m/z*: 1050.6 [M+H]$^+$; ^{1}H NMR (CD_3OD, 400 MHz) δ 9.01 (s, 1H), 7.90 - 7.82 (m, 1H), 7.37 - 7.28 (m, 2H), 7.23 - 7.18 (m, 1H), 7.00 - 6.93 (m, 2H), 6.80 (dd, *J* = 2.0, 8.4 Hz, 1H), 5.26 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.70 - 4.57 (m, 6H), 3.74 - 3.64 (m, 4H), 3.52 (br d, *J* = 11.8 Hz, 2H), 3.37 (s, 1H), 3.12 - 3.06 (m, 2H), 2.96 - 2.91 (m, 2H), 2.86 (br t, *J* = 5.6 Hz, 2H), 2.83 - 2.75 (m, 2H), 2.74 - 2.67 (m, 2H), 2.66 - 2.63 (m, 1H), 2.28 - 2.14 (m, 5H), 2.04 - 1.96 (m, 2H), 1.90 - 1.77 (m, 8H), 1.71 (br d, *J* = 12.8 Hz, 2H), 1.56 - 1.50 (m, 7H), 1.42 - 1.30 (m, 4H), 1.30 - 1.19 (m, 6H).

Example 91: Synthesis of 3-{5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-4-fluoro-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 167**)



The title compound was prepared in an analogous manner to 3-{5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione. (yellow solid.) LC/MS (ESI) *m/z*: 1068.6 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 7.86 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.36 - 7.29 (m, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 6.89 - 6.80 (m, 2H), 5.28 (dd, *J* = 5.2, 12.4 Hz, 1H), 4.67 - 4.55 (m, 5H), 3.74 - 3.64 (m, 4H), 3.37 (s, 1H), 3.14 - 3.08 (m, 2H), 2.99 (br d, *J* = 11.2 Hz, 2H), 2.93 - 2.85 (m, 3H), 2.83 - 2.75 (m, 2H), 2.74 - 2.67 (m, 2H), 2.31 (br d, J = 6.4 Hz, 2H), 2.26 - 2.19 (m, 2H), 2.18 - 2.10 (m, 2H), 2.09 - 2.00 (m, 2H), 1.90 - 1.84 (m, 2H), 1.83 - 1.77 (m, 6H), 1.73 (br d, *J* = 13.2 Hz, 2H), 1.69 - 1.58 (m, 2H), 1.51 (br d, *J* = 6.8 Hz, 6H), 1.41 (br d, *J* = 11.6 Hz, 2H), 1.33 - 1.23 (m, 8H).

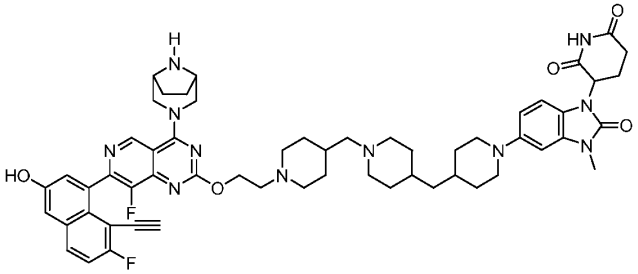
Example 92: Synthesis of 3-{4-chloro-5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 81**)



The title compound was prepared in an analogous manner to 3-{5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione. (yellow solid). LC/MS (ESI) *m/z*: 1041.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.00 (s, 1H), 7.85 (dd, J = 5.6, 9.2 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.36-7.16 (m, 4H), 5.12 (dd, J = 5.2, 13.2 Hz, 1H), 4.67-4.54 (m, 4H), 4.50-4.36 (m, 2H), 3.75-3.62 (m, 4H), 3.50-3.43 (m, 2H), 3.36 (s, 1H), 3.08 (dd, J = 1.6, 4.0 Hz, 2H), 2.98-2.82 (m, 5H), 2.81-2.70 (m, 3H), 2.57-2.43 (m, 1H), 2.28-2.10 (m,

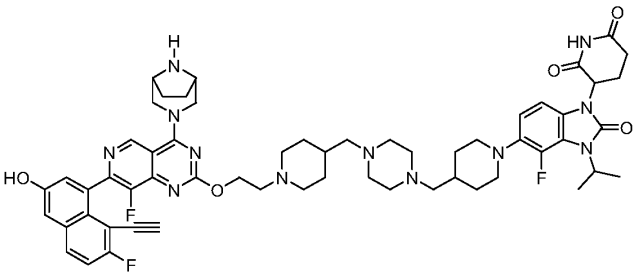
5H), 1.99 (s, 2H), 1.89-1.67 (m, 10H), 1.65-1.53 (m, 2H), 1.49-1.36 (m, 3H), 1.25 (d, J = 6.8 Hz, 6H).

Example 93: Synthesis of 3-{5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 82**)



The title compound was prepared in an analogous manner to 3-{5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (light yellow solid). LC/MS (ESI) *m/z*: 1022.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.00 (s, 1H), 7.88 - 7.84 (m, 1H), 7.35 - 7.30 (m, 2H), 7.21 - 7.20 (m, 1H), 6.99 - 6.97 (m, 1H), 6.87 - 6.86 (m, 1H), 6.81 - 6.79 (m, 1H), 5.30 - 5.25 (m, 1H), 4.66 - 4.57 (m, 5H), 3.73 - 3.66 (m, 4H), 3.59 - 3.55 (m, 2H), 3.40 (s, 3H), 3.37 (s, 1H), 3.13 - 3.09 (m, 2H), 2.95 - 2.91 (m, 3H), 2.89 - 2.85 (m, 2H), 2.82 - 2.75 (m, 2H), 2.71 - 2.65 (m, 2H), 2.25 - 2.13 (m, 5H), 2.02 - 1.96 (m, 2H), 1.89 - 1.77 (m, 8H), 1.72 - 1.69 (m, 2H), 1.40 - 1.21 (m, 10H).

Example 94: Exemplary synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperazin-1-yl}methyl)piperidin-1-yl]-4-fluoro-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 159**)

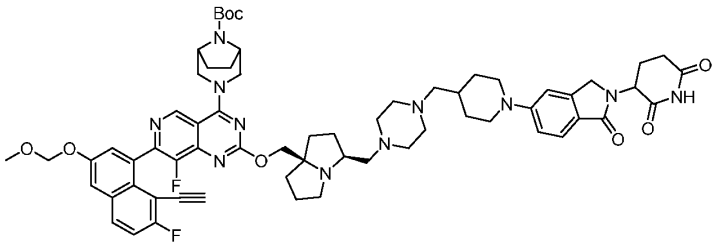


The title compound was prepared in an analogous manner to 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-

fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione. (yellow solid). LC/MS (ESI) *m/z*: 1069.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 7.86 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.40 - 7.26 (m, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 6.92 - 6.76 (m, 2H), 5.28 (dd, *J* = 12.4, 5.2 Hz, 1H), 4.69 - 4.53 (m, 5H), 3.77 - 3.64 (m, 4H), 3.37 (s, 1H), 3.15 - 3.05 (m, 2H), 2.95 - 2.65 (m, 8H), 2.60 - 2.36 (m, 8H), 2.31 - 2.09 (m, 8H), 1.95 - 1.74 (m, 9H), 1.60 - 1.40 (m, 9H), 1.35 - 1.19 (m, 2H).

Example 95: Synthesis of 3-[5-[4-[[4-[[(3S,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 84**)

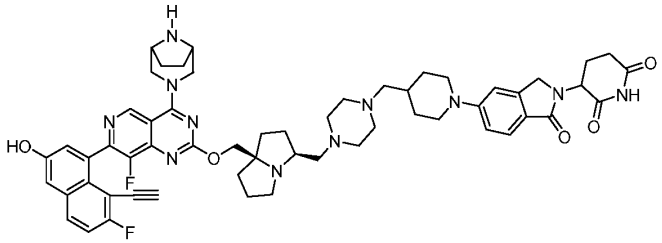
Step 1: Preparation of tert-butyl 3-[2-[[(3S,8R)-3-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a mixture of tert-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(3S,8R)-3-formyl-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (498 mg, 0.6 mmol) and 3-[1-oxo-5-[4-(piperazin-1-ylmethyl)-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione (372 mg, 0.6 mmol, HCl salt) in dichloromethane (10 mL) was added sodium triacetoxyborohydride (420 mg, 2 mmol), and the reaction mixture was stirred at 25 °C for 10 h. The reaction was quenched with saturated sodium bicarbonate solution (10 mL) and concentrated under reduced pressure. The residue was extracted with ethyl acetate (100 mL x 3), and the combined organic extract was washed with brine (100 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (0 to 4% then up to 10% methanol in dichloromethane) to afford the title compound (287 mg, 37%) as a yellow solid. LC/MS (ESI) *m/z*: 583.0 $[M/2+H]^+$.

Step 2: Preparation of 3-[5-[4-[[4-[[(3S,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-

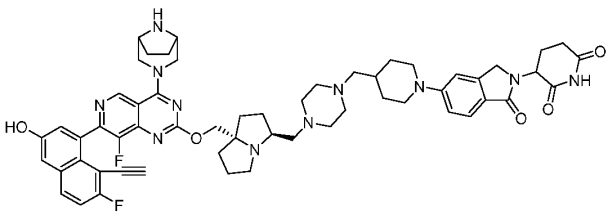
1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione



To a solution of tert-butyl 3-[2-[[(3S,8R)-3-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (287 mg, 0.2 mmol) in dichloromethane (5 mL) was added 4 M HCl in 1,4-dioxane (5.0 mL), and the mixture was stirred at 25 °C for 10 min. The reaction mixture was concentrated, and the residue was dissolved in THF (10 mL) and triethylamine to adjust the pH to 8. The resulting mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (26% to 66% acetonitrile in water (ammonium bicarbonate) over 36 min) to afford the title compound (44.1 mg, 18%) as a white solid. LC/MS (ESI) *m/z*: 1020.5 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 9.02 (d, *J* = 4.4 Hz, 1H), 7.92 - 7.80 (m, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.37 - 7.25 (m, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.09 - 7.01 (m, 2H), 5.13 - 5.08 (m, 1H), 4.69 - 4.55 (m, 4H), 4.41 - 4.25 (m, 5H), 3.92 - 3.86 (m, 2H), 3.75 - 3.64 (m, 5H), 3.37 (d, *J* = 2.0 Hz, 1H), 2.90 - 2.77 (m, 5H), 2.60 - 2.40 (m, 10H), 2.22 (d, *J* = 6.0 Hz, 4H), 1.94 - 1.71 (m, 13H), 1.31 - 1.21 (m, 2H).

Compounds 143, 145, 146 and 147, 234, and 238 were prepared using a procedure analogous to the procedure used to prepare Compound 84.

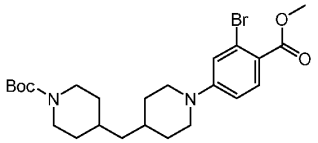
Example 96: Synthesis of 3-(5-{4-[(4-{[(3S,7aS)-7a-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-hexahydro-1H-pyrrolizin-3-yl]methyl}piperazin-1-yl)methyl]piperidin-1-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 100**)



The title compound was made in an analogous manner to 3-[5-[4-[[4-[[(3S,8R)-8-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-3-yl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (yellow solid). LC/MS (ESI) *m/z*: 1020.5 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD -d_4) δ 9.02 (s, 1H), 7.87 - 7.85 (m, 1H), 7.62 (dd, J = 2.4, 8.8 Hz, 1H), 7.40 - 7.26 (m, 2H), 7.21 (t, J = 2.0 Hz, 1H), 7.10 - 7.00 (m, 2H), 5.09 (d, J = 4.8 Hz, 1H), 4.68 - 4.54 (m, 4H), 4.48 - 4.28 (m, 5H), 3.90 (d, J = 12.4 Hz, 2H), 3.77 - 3.60 (m, 5H), 3.36 (s, 1H), 2.91 - 2.78 (m, 5H), 2.64 - 2.43 (m, 9H), 2.29 - 2.17 (m, 4H), 1.95 - 1.69 (m, 14H), 1.33 - 1.22 (m, 2H).

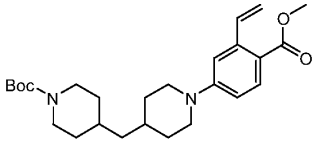
Example 97: Synthesis of 3-[5-[4-[[1-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 87**)

Step 1: Preparation of *tert*-butyl 4-[[1-(3-bromo-4-methoxycarbonyl-phenyl)-4-piperidyl]methyl] piperidine-1-carboxylate



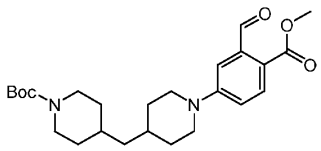
To a solution of methyl 2-bromo-4-fluoro-benzoate (5.0 g, 21 mmol) and *tert*-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate di-acetate (8.64 g, 21 mmol) in dimethyl sulfoxide (50 mL) was added *N,N*-diisopropylethylamine (11.2 mL, 64 mmol), and the mixture was stirred at 120 °C for 12 h. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over sodium sulfate anhydrous, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/0 to 7/3) to afford the title compound (7 g, 66%) as a yellow solid. LC/MS (ESI) *m/z*: 495.1 $[M+H]^+$; ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.75 - 7.69 (m, 1H), 7.15 - 7.09 (m, 1H), 6.97 - 6.90 (m, 1H), 3.96 - 3.82 (m, 4H), 3.79 - 3.72 (m, 3H), 2.86 - 2.75 (m, 2H), 2.74 - 2.56 (m, 2H), 1.75 - 1.50 (m, 6H), 1.42 - 1.36 (m, 9H), 1.05 (d, J = 4.0 Hz, 4H), 1.01 - 0.87 (m, 2H).

Step 2: Preparation of *tert*-butyl 4-[[1-(4-methoxycarbonyl-3-vinyl-phenyl)-4-piperidyl]methyl] piperidine-1-carboxylate



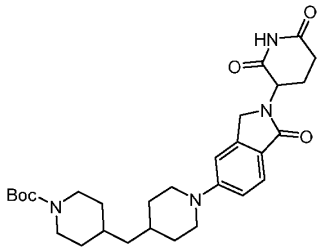
A mixture of *tert*-butyl 4-[[1-(3-bromo-4-methoxycarbonyl-phenyl)-4-piperidyl]methyl] piperidine-1-carboxylate (7.5g, 15 mmol), potassium vinyltrifuoroborate (6.08 g, 45 mmol), sodium carbonate (4.01 g, 38 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.11 g, 1.5 mmol) in 1,4-dioxane (100 mL) and water (20 mL) was degassed and purged with nitrogen several times, then stirred at 90 °C for 12 h under nitrogen atmosphere. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 1/0 to 10/1) to afford the title compound (5.4 g, 81%) as a gray solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 8.8 Hz, 1H), 7.53 - 7.42 (m, 1H), 7.03 - 6.97 (m, 1H), 6.94 - 6.84 (m, 1H), 5.75 - 5.64 (m, 1H), 5.32 - 5.23 (m, 1H), 3.91 (d, J = 12.8 Hz, 4H), 3.77 - 3.70 (m, 3H), 2.85 - 2.56 (m, 4H), 1.77 - 1.48 (m, 6H), 1.44 - 1.34 (m, 9H), 1.18 - 1.08 (m, 4H), 1.01 - 0.86 (m, 2H).

Step 3: Preparation of *tert*-butyl 4-[[1-(3-formyl-4-methoxycarbonyl-phenyl)-4-piperidyl]methyl] piperidine-1-carboxylate



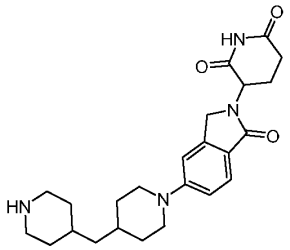
To a solution of *tert*-butyl 4-[[1-(4-methoxycarbonyl-3-vinyl-phenyl)-4-piperidyl]methyl] piperidine-1-carboxylate (5.4 g, 12 mmol) in 1,4-dioxane (75 mL) and water (25 mL) were added 2,6-dimethylpyridine (2.8 mL, 24 mmol), potassium osmate(VI) (90 mg, 0.2 mmol), and sodium periodate (4.1 mL, 73 mmol), and the mixture was stirred for 2 h at 20 °C. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extract was washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 1/0 then 85/15) to afford the title compound (1.8 g, 33%) as a yellow gum. LC/MS (ESI) *m/z*: 467.2 $[M+Na]^+$.

Step 4: Preparation of *tert*-butyl 4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperidine-1-carboxylate



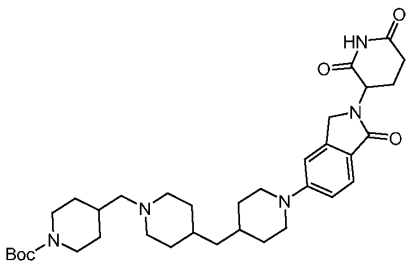
To a solution of *tert*-butyl 4-[[1-(3-formyl-4-methoxycarbonyl-phenyl)-4-piperidyl]methyl] piperidine-1-carboxylate (1.8 g, 4 mmol) and 3-aminopiperidine-2,6-dione (1 g, 6 mmol, hydrochloride) in methanol (20 mL) were added sodium acetate (498 mg, 6 mmol), sodium cyanoborohydride (509 mg, 8 mmol), and acetic acid (1.2 mL, 20 mmol), and the mixture was stirred at 40 °C for 12 h. The reaction mixture was concentrated under reduced pressure, and the residue was triturated with methyl *tert*-butyl ether to afford the title compound (1.5 g, 71%) as a gray solid. LC/MS (ESI) *m/z*: 557.3 $[M+23]^+$.

Step 5: Preparation of 3-[1-oxo-5-[4-(4-piperidylmethyl)-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione



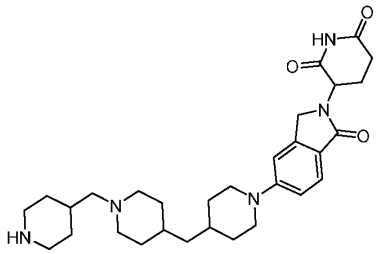
To a solution of *tert*-butyl 4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperidine-1-carboxylate (400 mg, 0.8 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1.0 mL, 13 mmol), and the reaction mixture was stirred at 20 °C for 1 h. The mixture was concentrated under reduced pressure to afford the title compound (410 mg, crude, TFA salt) as a brown gum. LC/MS (ESI) *m/z*: 425.2 $[M+H]^+$.

Step 6: Preparation of *tert*-butyl 4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]piperidine-1-carboxylate



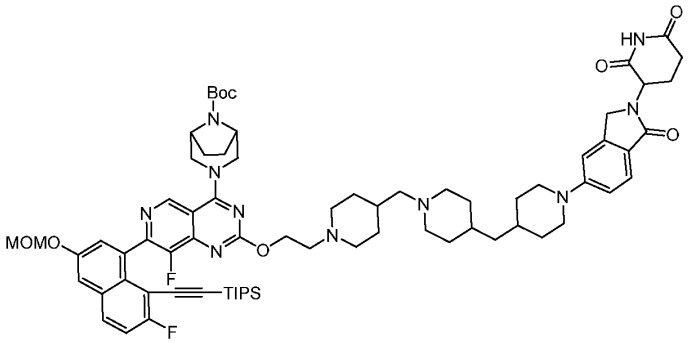
To a solution of 3-[1-oxo-5-[4-(4-piperidylmethyl)-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione (410 mg, 0.8 mmol, trifluoroacetate) and *tert*-butyl 4-formylpiperidine -1-carboxylate (246 mg, 1.1 mmol) in dichloromethane (4 mL) and isopropanol (4 mL) was added *N,N*-diisopropylethylamine (0.66 mL, 3.8 mmol), and the resulting mixture was stirred for 0.5 h. Sodium triacetoxyborohydride (323 mg, 1.5 mmol) was then added, and the reaction mixture was stirred at 25 °C for 1.5 h. The mixture was poured into water (30 mL) and extracted with dichloromethane/isopropanol (1:1, 30 mL). The combined organic extract was washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (500 mg, crude) as a yellow solid.

Step 7: Preparation of 3-[1-oxo-5-[4-[[1-(4-piperidylmethyl)-4-piperidyl]methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione



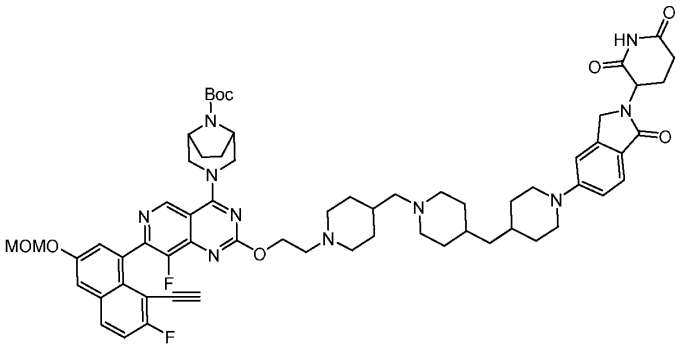
To a solution of *tert*-butyl 4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]piperidine-1-carboxylate (470 mg, 0.8 mmol) in dichloromethane (12 mL) was added trifluoroacetic acid (3.0 mL, 40 mmol), and the reaction mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated under reduced pressure to afford the title compound (480 mg, crude, TFA salt) as a light yellow gum. LC/MS (ESI) *m/z*: 522.3 $[M+H]^+$.

Step 8: Preparation of *tert*-butyl 3-[2-[2-[4-[[4-[[1-[2-(2,6-dioxo-3- piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



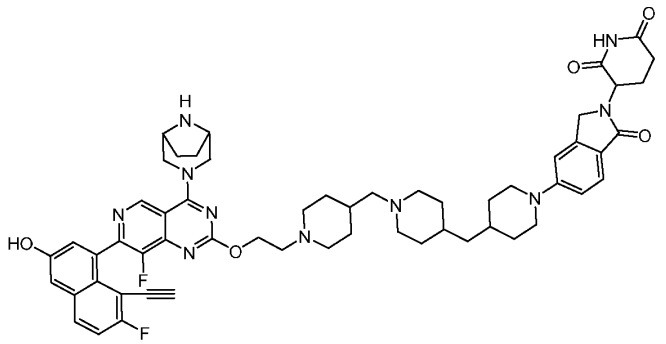
To a solution of 3-[1-oxo-5-[4-[[1-(4-piperidylmethyl)-4-piperidyl]methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione (480 mg, 0.8 mmol, trifluoroacetate) in dichloromethane (6 mL) and isopropanol (6 mL) were added *N,N*-diisopropylethylamine (0.3 mL, 1 mmol) and *tert*-butyl-3-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (666 mg, 0.8 mmol), and the resulting mixture was stirred at 25 °C for 0.5 h. Sodium triacetoxyborohydride (480 mg, 2 mmol) was then added, and the mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (22% to 52% acetonitrile in water (formic acid) over 11 min) to afford the title compound (360 mg, 36%) as a white solid. LC/MS (ESI) *m/z*: 1308.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 9.20 (s, 1H), 8.19 - 8.05 (m, 1H), 7.75 (d, *J* = 2.4 Hz, 1H), 7.57 (t, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.11 - 7.00 (m, 2H), 5.36 (s, 2H), 5.04 (dd, *J* = 5.2, 1Step 2: Hz, 1H), 4.73 (d, *J* = 12.8 Hz, 1H), 4.52 (d, *J* = 4.8 Hz, 2H), 4.38 - 4.15 (m, 5H), 3.87 (d, *J* = 12.4 Hz, 2H), 3.76 (d, *J* = 11.2 Hz, 1H), 3.43 (s, 3H), 3.40 (s, 3H), 3.24 - 3.04 (m, 3H), 2.97 - 2.70 (m, 7H), 2.67 - 2.54 (m, 2H), 2.42 - 2.23 (m, 2H), 2.03 - 1.67 (m, 12H), 1.65 - 1.53 (m, 3H), 1.46 (s, 9H), 1.39 - 1.23 (m, 4H), 1.21 - 1.06 (m, 4H), 0.81 (t, *J* = 8.0 Hz, 18H), 0.49 (quin, *J* = 7.6 Hz, 3H).

Step 8: Preparation of *tert*-butyl 3-[2-[2-[4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[2-[4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (360 mg, 0.3 mmol) in *N,N*-dimethylformamide (6 mL) was added cesium fluoride (836 mg, 5.5 mmol), and the reaction mixture was stirred at 25 °C for 2 h. The mixture was diluted with dichloromethane (150 mL) and washed with water (2 x 20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (320 mg, crude) as a brown solid. LC/MS (ESI) *m/z*: 1151.5 $[M+H]^+$.

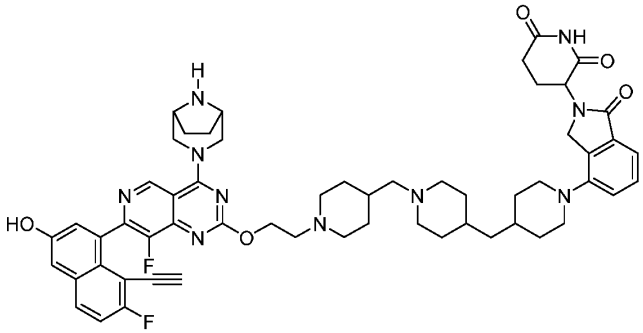
Step 9: Preparation of 3-[5-[4-[[1-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione



To a solution of *tert*-butyl 3-[2-[2-[4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (320 mg, 0.3 mmol) in dichloromethane (5 mL) was added 4 M HCl in 1,4-dioxane (5 mL), and the reaction mixture was stirred at 25 °C for 15 min. The mixture was triturated with petroleum ether (20 mL), then further purified by prep-HPLC (0% to 30% acetonitrile in water (formic acid) over 7 min) to afford the title compound (191.3

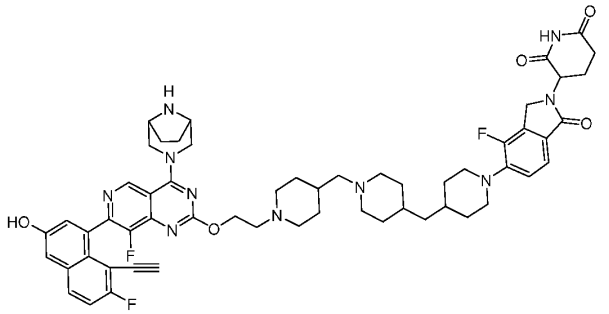
mg, 59%, tri-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 968.8 $[M+H]^+$; ^{1}HNMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 9.06 (s, 1H), 8.21 (s, 3H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.54 - 7.42 (m, 2H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.07 - 6.94 (m, 2H), 5.04 (dd, *J* = 5.2, 1Step 2: Hz, 1H), 4.61 - 4.45 (m, 3H), 4.41 - 4.26 (m, 2H), 4.22 - 4.13 (m, 1H), 3.94 (s, 1H), 3.88 - 3.75 (m, 4H), 3.70 (t, *J* = 14.0 Hz, 2H), 3.00 - 2.93 (m, 2H), 2.92 - 2.83 (m, 3H), 2.82 - 2.77 (m, 2H), 2.74 (d, *J* = 5.6 Hz, 3H), 2.59 (d, *J* = 2.4 Hz, 3H), 2.38 - 2.31 (m, 1H), 2.20 (d, *J* = 6.8 Hz, 2H), 2.10 - 1.92 (m, 5H), 1.77 (s, 3H), 1.73 - 1.58 (m, 6H), 1.57 - 1.30 (m, 3H), 1.22 - 1.01 (m, 8H).

Example 98: Synthesis of 3-{4-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 126**)



The title compound was made in an analogous manner to 3-[5-[4-[[1-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (light yellow solid). LC/MS (ESI) *m/z*: 1007.4 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD-d_4) δ 9.00 (s, 1H), 7.88 - 7.84 (m, 1H), 7.45 - 7.42 (m, 2H), 7.35 - 7.30 (m, 2H), 7.24 - 7.21 (m, 2H), 5.16 - 5.12 (m, 1H), 4.66 - 4.56 (m, 5H), 4.48 - 4.47 (m, 2H), 3.73 - 3.66 (m, 4H), 3.40 (s, 1H), 3.38 (s, 2H), 3.13 - 3.10 (m, 2H), 3.01 - 2.99 (m, 2H), 2.92 - 2.86 (m, 3H), 2.80 - 2.73 (m, 3H), 2.58 - 2.50 (m, 1H), 2.34 - 2.31 (m, 2H), 2.24 - 2.07 (m, 5H), 1.87 - 1.72 (m, 10H), 1.48 - 1.22 (m, 10H).

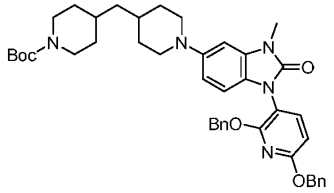
Example 99: Synthesis of 3-{5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 88**)



The title compound was made in an analogous manner to 3-[5-[4-[[1-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1025.8 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.06 (s, 1H), 8.20 (s, 3H), 8.01 - 7.92 (m, 1H), 7.51 - 7.41 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.21 - 7.10 (m, 2H), 5.07 (dd, J = 5.2, 13.2 Hz, 1H), 4.59 - 4.42 (m, 4H), 4.41 - 4.26 (m, 2H), 3.93 (s, 1H), 3.80 - 3.64 (m, 4H), 3.47 (d, J = 1.2 Hz, 2H), 2.99 - 2.82 (m, 5H), 2.80 - 2.69 (m, 4H), 2.64 - 2.53 (m, 2H), 2.45 - 2.30 (m, 2H), 2.23 - 2.14 (m, 2H), 2.08 - 1.92 (m, 5H), 1.81 - 1.69 (m, 6H), 1.64 (t, J = 11.6 Hz, 4H), 1.51 (d, J = 1.6 Hz, 2H), 1.42 - 1.32 (m, 1H), 1.31 - 1.22 (m, 2H), 1.21 - 1.03 (m, 6H).

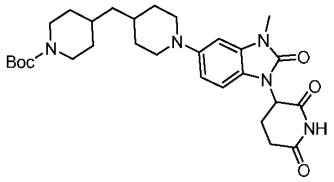
Example 100: Synthesis of 3-(5-{4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 89**)

Step 1: Preparation of *tert*-butyl 4-[[1-[1-(2,6-dibenzyloxy-3-pyridyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperidine-1-carboxylate



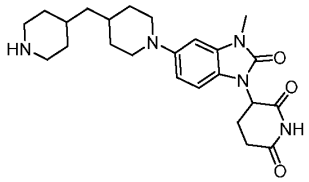
To a mixture of 5-bromo-1-(2,6-dibenzyloxy-3-pyridyl)-3-methyl-benzimidazol-2-one (1 g, 2 mmol), *tert*-butyl4-(4-piperidylmethyl)piperidine-1-carboxylate acetate (800 mg, 2 mmol), and cesium carbonate (1.89 g, 5.8 mmol) in 1,4-dioxane (30 mL) was added CPhos Pd G3 (156 mg, 0.2 mmol), and the mixture was stirred at 100 °C for 16 h under nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (acetonitrile in water (formic acid) to afford the title compound (810 mg, 58%) as a brown solid. LC/MS (ESI) *m/z*: 718.5 $[M+H]^+$.

Step 2: Preparation of *tert*-butyl 4-[[1-[1-(2,6-dioxo-3-piperidyl)-3- methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperidine-1-carboxylate



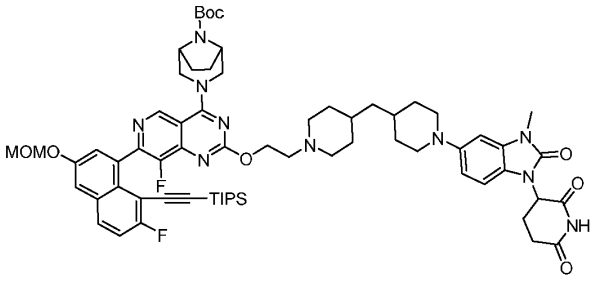
To a solution of *tert*-butyl 4-[[1-[1-(2,6-dibenzyloxy-3-pyridyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperidine-1-carboxylate (810 mg, 1 mmol) in tetrahydrofuran (20 mL) was added 10% palladium on carbon (300 mg) under nitrogen atmosphere, and the resulting mixture was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen at 50 °C for 16 h. The reaction mixture was filtered and concentrated under reduced pressure to afford the title compound (570 mg, 94%) as a brown solid. LC/MS (ESI) *m/z*: 540.5 $[M+H]^+$.

Step 3: Preparation of 3-[3-methyl-2-oxo-5-[4-(4-piperidylmethyl)-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione



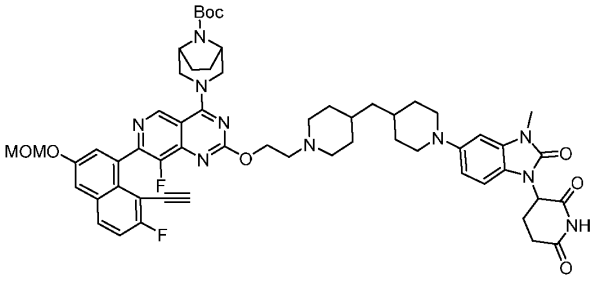
To *tert*-butyl 4-[[1-[1-(2,6-dioxo-3-piperidyl)-3- methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperidine-1-carboxylate (570 mg, 1 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1.0 mL, 13 mmol), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (1% to 20% acetonitrile in water (formic acid) over 11 min) to afford the title compound (520 mg, 93%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 440.3 $[M+H]^+$.

Step 4: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[1-(2,6-dioxo-3-piperidyl)- 3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



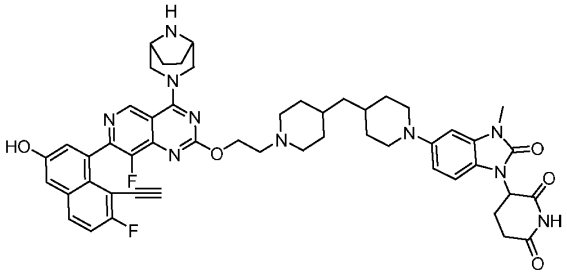
To a mixture of 3-[3-methyl-2-oxo-5-[4-(4-piperidylmethyl)-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione (300 mg, 0.6 mmol, di-formic acid salt) and tert-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (498 mg, 0.6 mmol) in isopropanol (5 mL) and dichloromethane (5 mL) were added *N,N*-diisopropylethylamine (0.3 mL, 2 mmol) and sodium triacetoxyborohydride (239 mg, 1 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with water (15 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (680 mg, crude) as a yellow solid. LC/MS (ESI) *m/z*: 1225.6 $[M+H]^+$.

Step 5: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



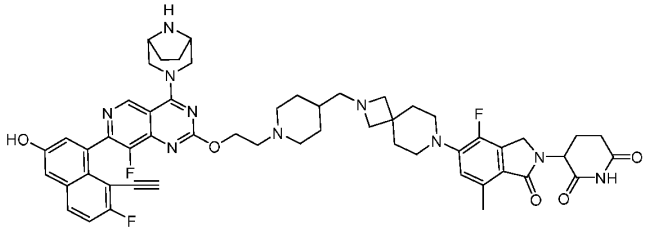
To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (680 mg, 0.6 mmol) in *N,N*-dimethylformamide (5 mL) was added cesium fluoride (2.53 g, 17 mmol), and the mixture was stirred at 25 °C for 16 h. The reaction was quenched with water (0.5 mL), and the crude solution was directly purified by prep-HPLC (25% to 55% acetonitrile in water (TFA) over 15 min) to afford the title compound (180 mg, 30%) as a yellow solid. LC/MS (ESI) *m/z*: 1069.5 $[M+H]^+$.

Step 6: Preparation of 3-(5-{4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione



To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (180 mg, 0.2 mmol) in dichloromethane (4 mL) was added 4 M HCl in 1,4-dioxane (4 mL), and the reaction was stirred at 25 °C for 15 min. The mixture was triturated with petroleum ether (20 mL), then further purified by prep-HPLC (0% to 30% acetonitrile in water (formic acid) over 7 min) to afford the title compound (33.6 mg, 19%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 925.3 $[M+H]^+$; ^{1}HNMR (400 MHz, DMSO-d_6) δ 11.06 (br d, J = 1.6 Hz, 1H), 9.05 (s, 1H), 8.20 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 6.91 (br d, J = 8.8 Hz, 1H), 6.80 (s, 1H), 6.66 - 6.55 (m, 1H), 5.28 (br dd, J = 5.2, 12.8 Hz, 1H), 4.54 - 4.43 (m, 3H), 4.36 (br d, J = 11.2 Hz, 1H), 3.94 (s, 1H), 3.73 - 3.62 (m, 4H), 3.59 - 3.42 (m, 3H), 3.29 (s, 3H), 2.97 - 2.87 (m, 3H), 2.73 - 2.61 (m, 7H), 2.07 - 1.97 (m, 3H), 1.75 - 1.67 (m, 5H), 1.62 (br d, J = 10.4 Hz, 2H), 1.51 - 1.31 (m, 3H), 1.29 - 1.20 (m, 2H), 1.19 - 1.06 (m, 4H).

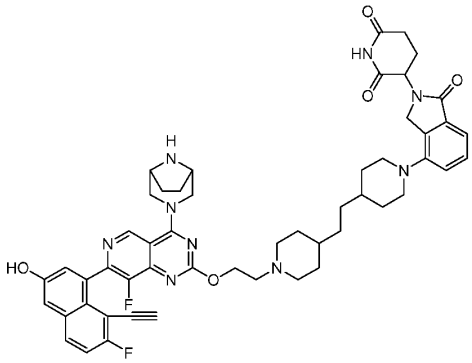
Example 101: Synthesis of 3-(5-{2-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]-2,7-diazaspiro[3.5]nonan-7-yl}-4-fluoro-7-methyl-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 154**)



The title compound was made in an analogous manner to 3-(5-{4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-

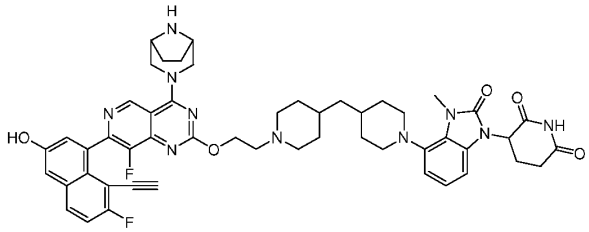
fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (orange solid, formic acid salt). LC/MS (ESI) *m/z*: 983.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 10.28 (br s, 1H), 9.13 (s, 1H), 8.14 (s, 1H), 7.99 (dd, J = 6.0, 9.2 Hz, 1H), 7.48 (t, J = 9.2 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 6.89 (br d, J = 7.2 Hz, 1H), 5.03 (br dd, J = 5.0, 13.2 Hz, 1H), 4.74 - 4.57 (m, 3H), 4.53 (br d, J = 13.6 Hz, 1H), 4.39 (br d, J = 16.8 Hz, 1H), 4.26 - 4.14 (m, 3H), 3.95 - 3.83 (m, 6H), 3.16 - 2.97 (m, 8H), 2.94 - 2.85 (m, 1H), 2.61 - 2.52 (m, 7H), 2.45 - 2.37 (m, 3H), 1.95 (br d, J = 9.6 Hz, 10H), 1.85 - 1.67 (m, 3H), 1.46 - 1.19 (m, 2H).

Example 102: Synthesis of 3-(4-{4-[2-(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)ethyl]piperidin-1-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 128**)



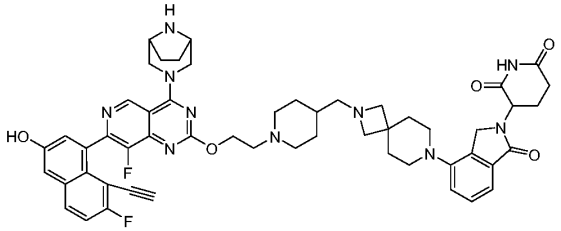
The title compound was made in an analogous manner to 3-(5-{4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 924.6 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.04 (s, 1H), 8.17 - 8.15 (m, 1H), 7.97 (dd, J1 = 6.0 Hz, J2 = 9.2 Hz, 1H), 7.51 - 7.36 (m, 3H), 7.28 (d, J = 7.2 Hz, 1H), 7.20 - 7.11 (m, 2H), 5.15 - 5.06 (m, 1H), 4.57 - 4.20 (m, 8H), 3.92 (s, 1H), 3.65-3.61 (m, 4H), 2.99 - 2.88 (m, 4H), 2.75 - 2.65 (m, 6H), 2.06 - 1.94 (m, 3H), 1.78 - 1.61 (m, 8H), 1.31 - 1.06 (m, 10H).

Example 110: Synthesis of 3-(4-{4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 129**)



The title compound was made in an analogous manner to 3-(5-{4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (yellow solid). LC/MS (ESI) *m/z*: 925.6 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 9.05 (s, 1H), 8.18 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 6.99 - 6.92 (m, 1H), 6.90 - 6.82 (m, 2H), 5.38 - 5.30 (m, 1H), 4.52 - 4.42 (m, 3H), 4.39 - 4.33 (m, 1H), 3.93 (s, 1H), 3.69 (s, 2H), 3.64 (s, 1H), 3.61 (s, 3H), 3.58 (s, 1H), 3.08 (d, J = 9.6 Hz, 2H), 2.96 (d, J = 10.4 Hz, 2H), 2.89 - 2.83 (m, 1H), 2.74 - 2.62 (m, 6H), 2.45 (s, 1H), 2.07 - 1.96 (m, 3H), 1.72 (s, 6H), 1.66 - 1.59 (m, 2H), 1.50 - 1.41 (m, 1H), 1.37 - 1.25 (m, 3H), 1.19 - 1.06 (m, 4H).

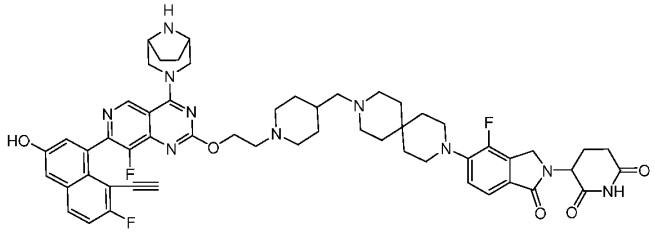
Example 103: Synthesis of 3-(4-{2-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]-2,7-diazaspiro[3.5]nonan-7-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 140**)



The title compound was made in an analogous manner to 3-(5-{4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (yellow solid). LC/MS (ESI) *m/z*: 951.6 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.03 - 10.96 (m, 1H), 9.06 (s, 1H), 8.19 (s, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.49 - 7.42 (m, 2H), 7.40 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.19 - 7.12 (m, 2H), 5.11 (dd, J = 5.2, 13.2 Hz, 1H), 4.54 (d, J = 12.4 Hz, 1H), 4.45 (d, J = 6.0 Hz, 2H), 4.41 - 4.37 (m, 2H), 4.29 - 4.26 (m, 1H), 3.94 (s, 1H), 3.82 (s, 2H), 3.71 (s, 2H), 3.35 (s, 2H), 2.95 (d, J = 6.0 Hz, 8H), 2.88 (d, J = 5.4 Hz, 1H), 2.73 - 2.70 (m, 2H), 2.61 (s, 2H),

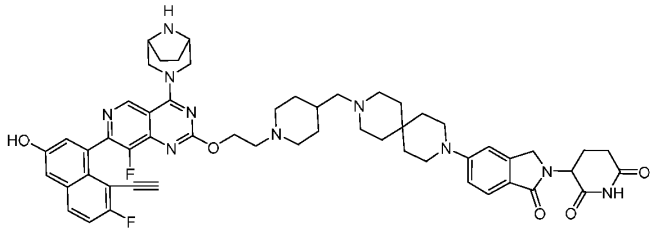
2.56 (s, 1H), 2.46 - 2.42 (m, 1H), 2.06 - 1.96 (m, 4H), 1.84 (s, 4H), 1.78 (s, 4H), 1.64 (d, J = 10.8 Hz, 2H), 1.40 (dd, J = 2.4, 7.6 Hz, 1H), 1.20 - 1.10 (m, 2H).

Example 104: Synthesis of 3-(5-{9-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]-3,9-diazaspiro[5.5]undecan-3-yl}-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 92**)



The title compound was made in an analogous manner to 3-(5-{4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (yellow solid, formic acid salt.) LC/MS (ESI) *m/z*: 997.7 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.05 (s, 1H), 8.21 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.55 - 7.42 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.21 - 7.11 (m, 2H), 5.07 (dd, J = 5.2, 13.2 Hz, 1H), 4.56 - 4.41 (m, 5H), 4.40 - 4.23 (m, 3H), 3.94 (s, 1H), 3.73 - 3.59 (m, 4H), 3.09 (b s, 4H), 2.99 - 2.86 (m, 3H), 2.71 (t, J = 4.8 Hz, 2H), 2.58 (d, J = 16.8 Hz, 1H), 2.46 - 2.31 (m, 5H), 2.19 (d, J = 6.8 Hz, 2H), 2.11 - 1.89 (m, 3H), 1.74 (s, 4H), 1.65 (d, J = 11.2 Hz, 2H), 1.60 - 1.39 (m, 9H), 1.20 - 0.99 (m, 2H).

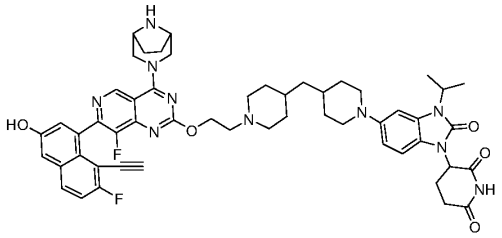
Example 105: Synthesis of 3-(5-{9-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]-3,9-diazaspiro[5.5]undecan-3-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 93**)



The title compound was made in an analogous manner to 3-(5-{4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (yellow solid, formic acid salt.) LC/MS

(ESI) *m/z*: 979.7 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 9.04 (s, 1H), 8.20 (s, 2H), 7.96 (dd, J = 6.0, 9.2 Hz, 1H), 7.58 - 7.42 (m, 2H), 7.38 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 7.07 - 6.95 (m, 2H), 5.03 (dd, J = 5.2, 13.2 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.44 (t, J = 5.6 Hz, 2H), 4.39 - 4.31 (m, 2H), 4.28 (s, 1H), 4.17 (d, J = 16.8 Hz, 2H), 3.93 (s, 1H), 3.70 (s, 2H), 3.67 - 3.60 (m, 2H), 3.28 (d, J = 0.8 Hz, 4H), 2.98 - 2.82 (m, 3H), 2.70 (t, J = 5.2 Hz, 2H), 2.62 - 2.53 (m, 1H), 2.43 - 2.26 (m, 5H), 2.21 - 2.12 (m, 2H), 2.08 - 1.88 (m, 3H), 1.73 (s, 4H), 1.68 - 1.59 (m, 2H), 1.48 (d, J = 4.4 Hz, 9H), 1.17 - 0.94 (m, 2H).

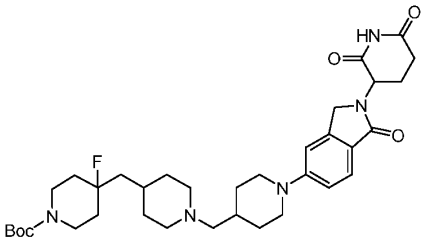
Example 106: Synthesis of 3-(5-{4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 175**)



The title compound was made in an analogous manner to 3-(5-{4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 953.6 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.08 (s, 1H), 8.15 (s, 2H), 7.98 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.47 (t, *J* = 9.2 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.94 - 6.84 (m, 2H), 6.64 - 6.57 (m, 1H), 5.26 (dd, *J* = 5.6, 13.1 Hz, 1H), 4.61 - 4.54 (m, 2H), 4.53 - 4.46 (m, 2H), 4.42 (d, *J* = 13.2 Hz, 1H), 3.94 (s, 1H), 3.90 (s, 2H), 3.75 (t, *J* = 12.4 Hz, 3H), 3.52 (d, *J* = 11.6 Hz, 4H), 3.01 (s, 3H), 2.90 - 2.83 (m, 1H), 2.78 (s, 2H), 2.68 - 2.60 (m, 2H), 2.58 (s, 1H), 2.54 (s, 1H), 2.12 (t, *J* = 10.8 Hz, 2H), 2.01 - 1.92 (m, 1H), 1.82 (s, 4H), 1.71 (d, *J* = 12.4 Hz, 2H), 1.67 - 1.61 (m, 2H), 1.44 (d, J = 6.8 Hz, 6H), 1.29 - 1.20 (m, 2H), 1.19 - 1.08 (m, 4H).

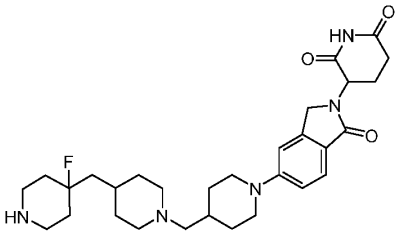
Example 107: Synthesis of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo [3.2.1]octan- 3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-fluoro-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 91**)

Step 1: Preparation of *tert*-butyl 4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-4-fluoro-piperidine-1-carboxylate



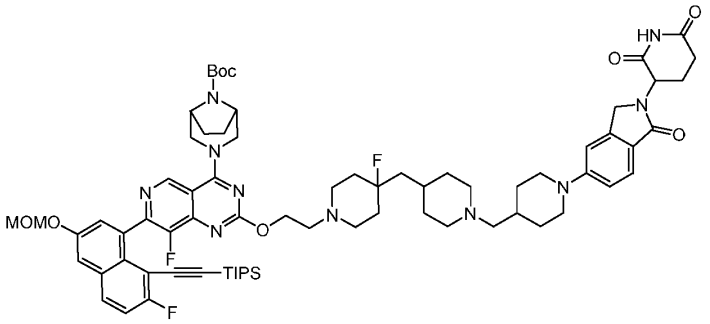
To a mixture of *tert*-butyl 4-fluoro-4-(4-piperidylmethyl)piperidine-1-carboxylate (700 mg, 2 mmol), diisopropylethylamine (0.8 mL, 5 mmol), and 1-[2-(2,6- dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperidine-4-carbaldehyde (911 mg, 2 mmol) in dimethyl sulfoxide (5 mL) and dichloromethane (5 mL) was added sodium triacetoxyborohydride (1.48 g, 7 mmol) under nitrogen atmosphere, and the mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by prep-HPLC (20% to 50% acetonitrile in water (formic acid) over 7 min) to afford the title compound (850 mg, 57%) as a white solid. LC/MS (ESI) *m/z*: 640.4 $[M+H]^+$.

Step 2: Preparation of 3-[5-[4-[[4-[(4-fluoro-4- piperidyl)methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione



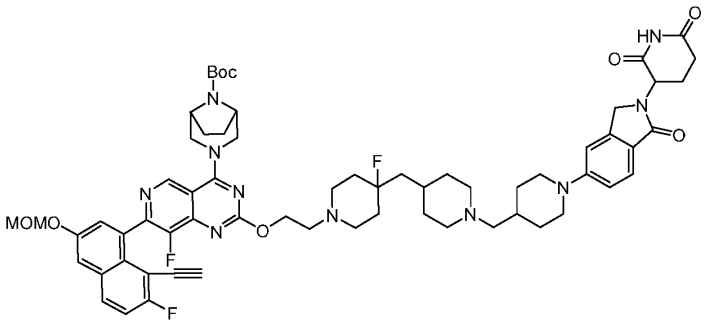
To a mixture of *tert*-butyl 4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-4-fluoro-piperidine-1-carboxylate (430 mg, 0.7 mmol) in dichloromethane (6 mL) was added trifluoroacetic acid (2.0 mL, 27 mmol) under nitrogen atmosphere, and the mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound (439 mg, crude, trifluoroacetate) as a yellow solid. LC/MS (ESI) *m/z*: 540.4 $[M+H]^+$.

Step 3: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-4-fluoro-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a mixture of tert-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (592 mg, 0.7 mmol) and 3-[5-[4-[[4-[(4-fluoro-4-piperidyl)methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (439 mg, 0.7 mmol, trifluoroacetate) in *N,N*-dimethylformamide (2 mL) were added sodium triacetoxyborohydride (427 mg, 2 mmol) and *N,N*-diisopropylethylamine (0.2 mL, 1 mmol) under nitrogen atmosphere, and the mixture was stirred at 20 °C for 16 h. The mixture was poured into ice-water (w/w = 1/1, 10 mL) and extracted with ethyl acetate (10 mL x 4). The combined organic extract was washed with brine (2 x 15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (30% to 60% acetonitrile in water (formic acid) over 9 min) to afford the title compound (530 mg, 59%) as a yellow solid. LC/MS (ESI) *m/z*: 1326.1 $[M+H]^+$.

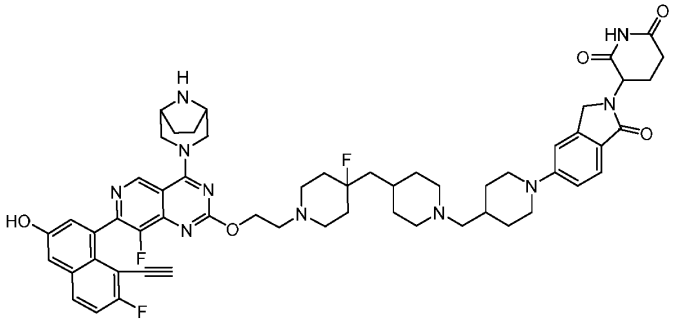
Step 4: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin -5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-4-fluoro-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl] -4-piperidyl]methyl]-4-piperidyl]methyl]-4-fluoro-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (460 mg, 0.4 mmol) in *N,N*-dimethylformamide (3 mL)

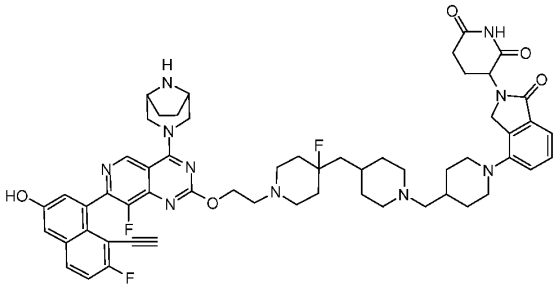
was added cesium fluoride (1.05 g, 7 mmol) under nitrogen atmosphere, and the reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure, and the residue was purified by prep-HPLC (22% to 52% acetonitrile in water (formic acid) over 7 min) to afford the title compound (280 mg, 69%) as a yellow solid. LC/MS (ESI) *m/z*: 1169.9 $[M+H]^+$.

Step 5: Preparation of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo [3.2.1]octan- 3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-fluoro-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione



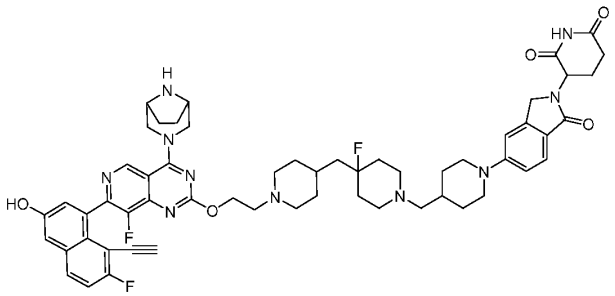
To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin -5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-4-fluoro-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (280 mg, 0.2 mmol) in dichloromethane (4 mL) was added 4 M HCl in 1,4-dioxane (4 mL), and the reaction mixture was stirred at 20 °C for 15 min. The mixture was suspended in petroleum ether (5 mL), filtered, and the filter cake was purified by prep-HPLC (0% to 30% acetonitrile in water (formic acid) over 7 min) to afford the title compound (102.6 mg, 38%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1025.5 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 9.05 (s, 1H), 8.18 (s, 2H), 7.98 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.51 - 7.43 (m, 2H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 7.05 - 6.99 (m, 2H), 5.04 (dd, *J* = 5.2, 1Step 2: Hz, 1H), 4.57 - 4.40 (m, 4H), 4.40 - 4.32 (m, 2H), 4.29 (s, 1H), 4.23 - 4.14 (m, 2H), 3.93 (d, *J* = 0.8 Hz, 1H), 3.87 (s, 1H), 3.84 (s, 1H), 3.65 (d, *J* = 14.4 Hz, 4H), 2.89 (s, 1H), 2.81 (d, *J* = 11.2 Hz, 4H), 2.72 (d, *J* = 5.6 Hz, 4H), 2.61 - 2.55 (m, 1H), 2.35 - 2.24 (m, 3H), 2.16 (d, *J* = 6.0 Hz, 2H), 1.99 - 1.88 (m, 3H), 1.74 (s, 8H), 1.66 (d, *J* = 12.0 Hz, 3H), 1.56 - 1.43 (m, 4H), 1.24 - 1.11 (m, 4H).

Example 108: Synthesis of 3-{4-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-4-fluoropiperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 124**)



The title compound was prepared in an analogous manner to 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo [3.2.1]octan- 3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-fluoro-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1025.3 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.11 (s, 1H), 8.16 (s, 1H), 7.99 (dd, J = 6.0, 9.2 Hz, 1H), 7.57 - 7.38 (m, 3H), 7.32 (d, J = 7.6 Hz, 1H), 7.24 - 7.11 (m, 2H), 5.12 (dd, J = 5.2, 13.2 Hz, 1H), 4.65 (br d, J = 12.8 Hz, 1H), 4.56 - 4.48 (m, 3H), 4.44 (br d, J = 17.6 Hz, 1H), 4.29 (br d, J = 17.2 Hz, 1H), 4.16 (br s, 2H), 3.95 (s, 1H), 3.83 (br d, J = 13.6 Hz, 2H), 3.45 - 3.33 (m, 4H), 3.23 (br d, J = 9.2 Hz, 2H), 2.97 - 2.89 (m, 1H), 2.81 (br d, J = 6.0 Hz, 4H), 2.75 (br d, J = 12.0 Hz, 3H), 2.60 (br d, J = 16.0 Hz, 2H), 2.53 (br d, J = 2.0 Hz, 1H), 2.49 - 2.34 (m, 4H), 2.05 - 1.92 (m, 5H), 1.82 (br t, J = 11.6 Hz, 6H), 1.71 (br d, J = 10.0 Hz, 2H), 1.62 - 1.48 (m, 3H), 1.45 - 1.26 (m, 4H).

Example 109: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]-4-fluoropiperidin-1-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 90**)

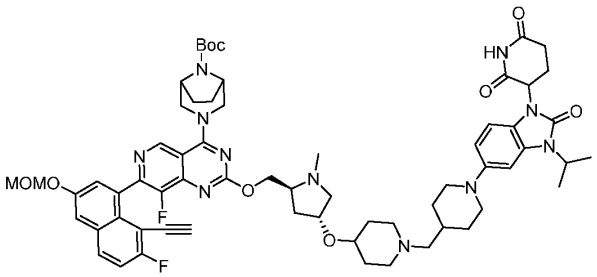


The title compound was prepared in an analogous manner to 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo [3.2.1]octan- 3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-fluoro-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1024.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 8.99 (s, 1H), 8.20 (s, 3H), 7.97 (dd, J = 6.0, 8.8 Hz, 1H), 7.53 - 7.42 (m, 2H), 7.39 (s, 1H), 7.22 - 7.08 (m, 1H), 7.07 - 6.93 (m, 2H), 5.04

(dd, J = 5.2, 13.2 Hz, 1H), 4.36 - 4.13 (m, 5H), 3.90 - 3.81 (m, 5H), 3.62 (s, 10H), 2.94 - 2.75 (m, 6H), 2.64 - 2.52 (m, 4H), 2.39 - 2.28 (m, 2H), 2.18 - 2.08 (m, 4H), 2.02 - 1.91 (m, 2H), 1.80 - 1.62 (m, 9H), 1.60 - 1.34 (m, 7H), 1.25 - 1.07 (m, 3H).

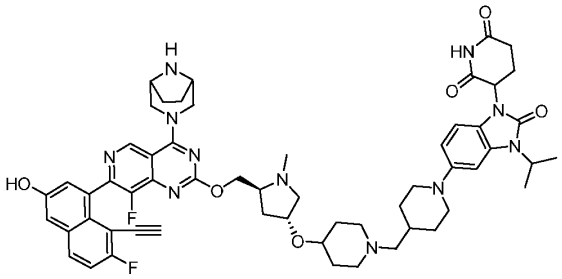
Example 110: Synthesis of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 95**)

Step 1: Preparation of *tert*-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[1-(2,6-dioxo-3- piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,4R)-1-methyl-4-(4-piperidyloxy)pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.2 mmol, formate) and 1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (113 mg, 0.3 mmol) in dichloromethane (5 mL) and isopropanol (5 mL) were added *N,N*-diisopropylethylamine (0.1 mL, 0.7 mmol) and sodium triacetoxyborohydride (100 mg, 0.5 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with water (15 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (22% to 52% acetonitrile in water (trifluoroacetic acid) over 15 min) to afford the title compound (270 mg, 97%, TFA salt) as an orange solid. LC/MS (ESI) *m/z*: 1182.9 $[M+H]^+$.

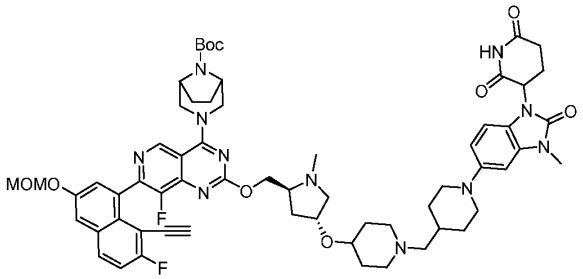
Step 2: Preparation of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione



To a solution of *tert*-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (270 mg, 0.2 mmol) in dichloromethane (4 mL) was added 4 M HCl in 1,4-dioxane (2 mL), and the mixture was stirred at 25 °C for 0.5 h. The reaction mixture was triturated with ethyl acetate/methyl tert-butyl ether (1/10, 100 mL), then further purified by prep-HPLC (1% to 30% acetonitrile in water (formic acid) over 10 min) to afford the title compound (110.7 mg, 42%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1038.7 $[M+H]^+$; ^{1}HNMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1 H), 9.06 (s, 1 H), 8.20 (s, 2 H), 7.97 (dd, *J* = 9.2, 6.0 Hz, 1 H), 7.46 (t, *J* = 9.2 Hz, 1 H), 7.39 (d, *J* = 2.4 Hz, 1 H), 7.18 (d, *J* = 2.4 Hz, 1 H), 6.94 - 6.84 (m, 2 H), 6.61 (dd, *J* = 8.8, 1.6 Hz, 1 H), 5.26 (br dd, *J* = 12.8, 5.2 Hz, 1 H), 4.64 - 4.47 (m, 3 H), 4.37 (br dd, *J* = 11.2, 4.8 Hz, 2 H), 4.24 (dt, *J* = 10.8, 5.2 Hz, 2 H), 4.16 - 4.07 (m, 2 H), 3.94 (d, *J* = 2.0 Hz, 1 H), 3.74 (br s, 3 H), 3.69 - 3.62 (m, 2 H), 3.53 (br d, *J* = 11.2 Hz, 2 H), 3.34 - 3.24 (m, 2 H), 2.93 - 2.75 (m, 2 H), 2.71 - 2.65 (m, 2 H), 2.64 - 2.56 (m, 3 H), 2.35 (s, 3 H), 2.21 - 2.14 (m, 3 H), 2.08 – 1.95 (m, 3 H), 1.92 - 1.85 (m, 2 H), 1.84 - 1.73 (m, 8 H), 1.44 (d, *J* = 6.8 Hz, 8 H), 1.29 - 1.17 (m, 2 H).

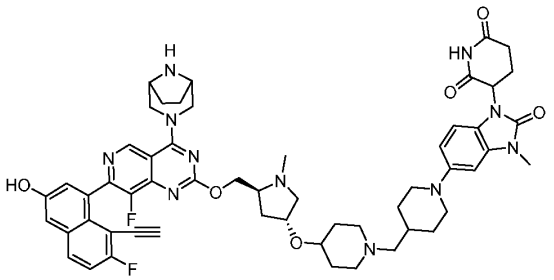
Example 111: Synthesis of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 96**)

Step 1: Preparation of *tert*-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,4R)-1-methyl-4-(4-piperidyloxy)pyrrolidin-2-yl]methoxy]pyrido[4,3-d] pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (210 mg, 0.3 mmol, formate) in dichloromethane (3 mL) and isopropanol (3 mL) at 25 °C were added *N,N*-diisopropylethylamine (0.1 mL, 0.7 mmol), 1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol- 5-yl]piperidine-4-carbaldehyde (130 mg, 0.3 mmol, trifluoroacetate), and sodium triacetoxyborohydride (105 mg, 0.5 mmol), and the reaction mixture was stirred at at 25 °C for 2 h. The mixture was diluted with water (10 mL) and extracted with dichloromethane/isopropanol (2/1, 3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (22%-52% acetonitrile in water (TFA) over 9 min) to afford the title compound (150 mg, 44%, di-TFA salt) as a brown solid. LC/MS (ESI) m/z: 1154.6 $[M+H]^+$.

Step 2: Preparation of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione

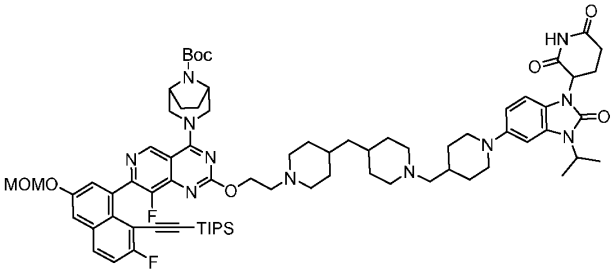


To a solution of *tert*-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150 mg, 0.1 mmol, di-trifluoroacetate) in dichloromethane (5 mL) at 25 °C was added 4 M HCl in 1,4-dioxane (3 mL), and the reaction mixture was stirred for 15 min. The mixture was suspended in methyl *tert*-butyl ether (50 mL),

filtered, and the filter cake was purified by preparative HPLC (1% - 30% acetonitrile in water (formic acid) over 10 min) to afford the title compound (78.1 mg, 63%, tri-formic acid salt) as an orange solid. LC/MS (ESI) m/z: 1010.7 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.07 (s, 1H), 8.20 (s, 3H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.47 (t, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 2.0, 8.8 Hz, 1H), 5.29 (dd, J = 5.6, 12.8 Hz, 1H), 4.58 - 4.53 (m, 1H), 4.42 - 4.37 (m, 2H), 4.28-4.24 (m, 2H), 4.16 - 4.12 (m, 2H), 3.95-3.93 (m, 1H), 3.80-3.78 (m, 2H), 3.72-3.68 (m, 2H), 3.59-3.53 (m, 2H), 3.31 - 3.24 (m, 5H), 2.90 - 2.67 (m, 5H), 2.65 - 2.56 (m, 3H), 2.36 (s, 3H), 2.23 - 2.16 (m, 3H), 2.10 - 1.96 (m, 3H), 1.94 - 1.86 (m, 2H), 1.84 - 1.73 (m, 8H), 1.66 - 1.56 (m, 1H), 1.48 - 1.37 (m, 2H), 1.29 - 1.17 (m, 2H).

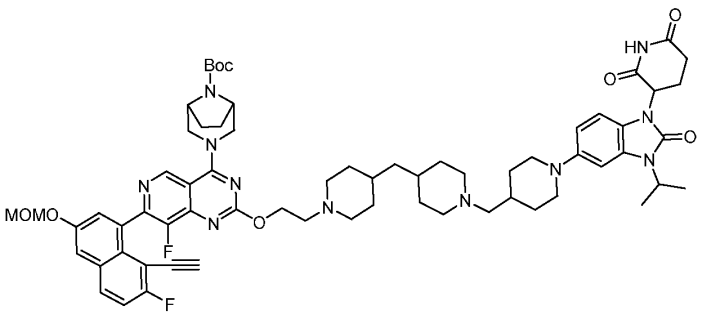
Example 112: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 98**)

Step 1: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylat



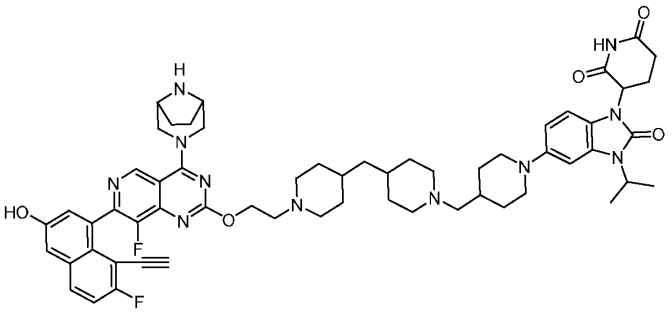
To a mixture of *tert*-butyl tert-butyl-3-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (334 mg, 0.4 mmol) and 3-[3-isopropyl-2-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione di-trifluoroacetate (300 mg, 0.4 mmol) in dichloromethane (5 mL) and isopropanol (5 mL) were added *N,N*-diisopropylethylamine (0.2 mL, 1 mmol) and sodium triacetoxyborohydride (160 mg, 0.8 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with water (15 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (480 mg, 94%) as a yellow solid. LC/MS (ESI) *m/z*: 1350.9 $[M+H]^+$.

Step 2: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (560 mg, 0.4 mmol) in *N,N*-dimethylformamide (5 mL) was added cesium fluoride (1.89 g, 12 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with water (0.5 mL), and the crude solution was directly purified by prep-HPLC (22% to 52% acetonitrile in water (trifluoroacetic acid) over 15 min) to afford the title compound (300 mg, 61%, TFA salt) as a colorless solid. LC/MS (ESI) *m/z*: 1195.8 $[M+H]^+$.

Step 3: Preparation of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione

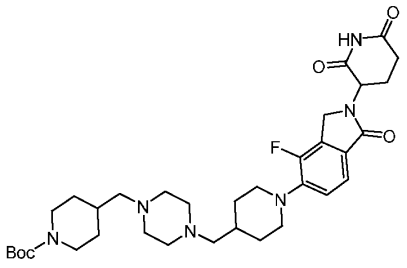


To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-isopropyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 0.3 mmol) in dichloromethane (4 mL) was

added 4 M HCl in 1,4-dioxane (2 mL), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was triturated with ethyl acetate/methyl tert-butyl ether (1/10, 100 mL), then purified by prep-HPLC (1% to 30% acetonitrile in water (formic acid) over 10 min) to afford the title compound (117.4 mg, 40%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1050.7 $[M+H]^+$; ^{1}HNMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1 H), 9.04 (s, 1 H), 8.18 (s, 2 H), 8.01 – 7.93 (m, 1 H), 7.46 (t, *J* = 9.2 Hz, 1 H), 7.39 (d, *J* = 2.4 Hz, 1 H), 7.17 (d, *J* = 2.4 Hz, 1 H), 6.95 - 6.84 (m, 2 H), 6.64 - 6.59 (m, 1 H), 5.30 - 5.22 (m, 1 H), 4.60 - 4.54 (m, 1 H), 4.52 - 4.42 (m, 3 H), 4.34 (br d, *J* = 11.2 Hz, 1 H), 3.93 (s, 1 H), 3.67 - 3.58 (m, 5 H), 3.51 (br s, 2 H), 2.97 - 2.80 (m, 6 H), 2.72 - 2.65 (m, 3 H), 2.64 - 2.55 (m, 4 H), 2.17 (br d, *J* = 6.4 Hz, 2 H), 2.03 – 1.94 (m, 3 H), 1.92 - 1.83 (m, 2 H), 1.76 (br d, *J* = 12.8 Hz, 2 H), 1.70 (br s, 3 H), 1.63 - 1.55 (m, 5 H), 1.44 (d, *J* = 6.8 Hz, 6 H), 1.32 - 1.18 (m, 4 H), 1.13 - 1.03 (m, 6 H).

Example 113: Synthesis of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 101**)

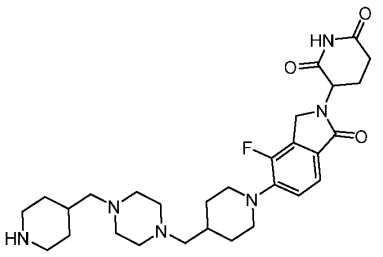
Step 1: Preparation of *tert*-butyl 4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]piperidine-1-carboxylate



To a solution of 1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]piperidine-4-carbaldehyde (500 mg, 1.3 mmol) in dichloromethane (5 mL) and dimethylsulfoxide (5 mL) were added *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (455 mg, 1.6 mmol) and sodium triacetoxyborohydride (568 mg, 2.7 mmol), and the resulting mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with water (30 mL) and extracted with dichloromethane (3 x 20 mL). The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (dichloromethane/methanol = 7/1) to afford the title compound (500 mg, 58%) as a yellow solid. LC/MS (ESI) *m/z*: 641.4 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 5.07 (dd, *J* = 5.2, 1Step 3: Hz, 1H), 4.54 - 4.40 (m, 1H), 4.30 (d, *J* = 17.2 Hz, 1H), 3.90 (d, *J* = 12.0 Hz, 2H), 3.47 (s, 2H), 3.17 (d, *J* = 5.2 Hz, 1H), 2.99 - 2.84 (m, 1H), 2.82 - 2.70 (m, 3H), 2.69 - 2.60 (m, 2H), 2.46 - 2.40 (m, 3H), 2.33 (s, 5H), 2.16

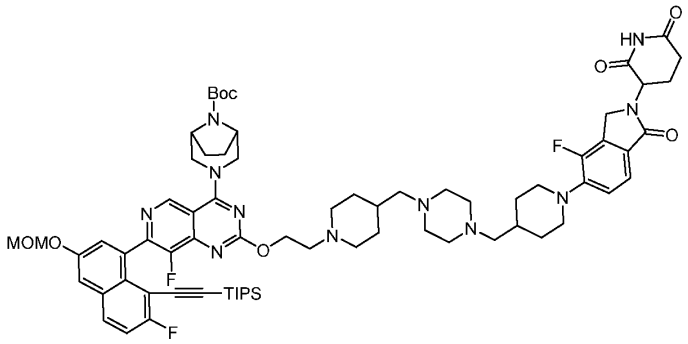
(d, *J* = 6.8 Hz, 2H), 2.09 (d, *J* = 6.0 Hz, 2H), 2.00 - 1.94 (m, 1H), 1.79 (d, *J* = 11.2 Hz, 2H), 1.64 (d, *J* = 10.8 Hz, 4H), 1.41 - 1.36 (m, 1H), 1.38 (s, 8H), 1.25 (d, *J* = 12.4 Hz, 3H), 0.91 (d, *J* = 10.4 Hz, 2H).

Step 2: Preparation of 3-[4-fluoro-1-oxo-5-[4-[[4-(4-piperidylmethyl)piperazin-1-yl]methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione



To a solution of *tert*-butyl 4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]piperidine-1-carboxylate (350 mg, 0.5 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1.0 mL, 13 mmol), and the mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated under reduced pressure to afford the title compound (357 mg, crude, TFA salt) as a yellow gum. LC/MS (ESI) *m/z*: 541.3 $[M+H]^+$.

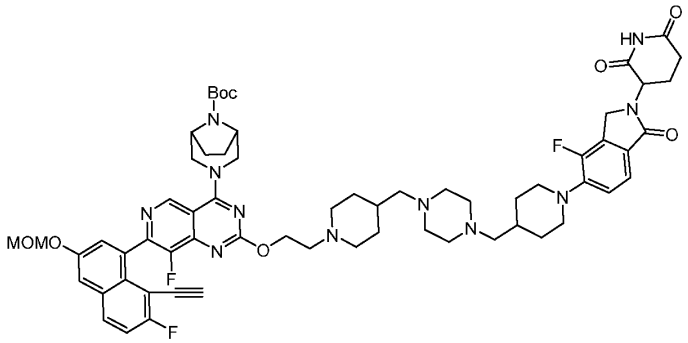
Step 3: Preparation of *tert*-butyl 3-[2-[2-[4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 3-[4-fluoro-1-oxo-5-[4-[[4-(4-piperidylmethyl)piperazin-1-yl]methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione (510 mg, 0.8 mmol, TFA) in dichloromethane (5 mL) and isopropyl alcohol (5 mL) were added diisopropylethylamine (0.41 mL, 2 mmol), *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (625 mg, 0.8 mmol), and sodium triacetoxyborohydride (330 mg, 1.6 mmol), and the reaction mixture was

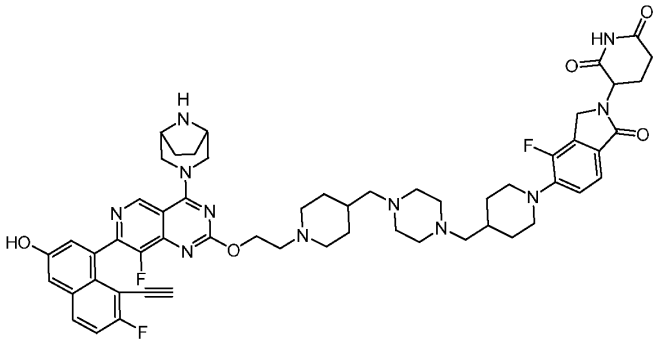
stirred at 25 °C for 12 h. The mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (dichloromethane/methanol = 8/1) to afford the title compound (550 mg, 53%) as a yellow gum. LC/MS (ESI) *m/z*: 1326.7 $[M+H]^+$.

Step 4: Preparation of *tert*-butyl 3-[2-[2-[4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[2-[4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (550 mg, 0.4 mmol) in *N,N*-dimethylformamide (6 mL) was added cesium fluoride (1.26 g, 8 mmol), and the mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with water (20 mL) and extracted with water (3 x 30 mL). The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (12% to 42% acetonitrile in water (formic acid) over 11 min) to afford the title compound (343 mg, 71%) as a yellow solid. LC/MS (ESI) *m/z*: 1170.6 $[M+H]^+$.

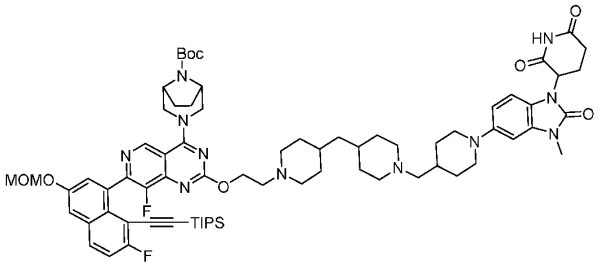
Step 5: Preparation of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione



To *tert*-butyl 3-[2-[2-[4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (548 mg, 0.5 mmol) in dichloromethane (5 mL) was added 4 M HCl in 1,4-dioxane (5 mL), and the mixture was stirred at 20 °C for 15 min. The reaction mixture suspended in petroleum ether (10 mL) and filtered. The filtered cake was purified by prep-HPLC (10% to 40% acetonitrile in water (formic acid) over 10 min) to afford the title compound (332 mg, 65%, formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1026.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 10.32 - 10.19 (m, 1H), 9.13 (s, 1H), 8.14 (s, 1H), 7.99 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.51 - 7.44 (m, 2H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.20 - 7.13 (m, 2H), 5.07 (dd, *J* = 4.8, 13.2 Hz, 1H), 4.70 - 4.58 (m, 3H), 4.55 - 4.44 (m, 2H), 4.30 (d, *J* = 17.2 Hz, 1H), 4.17 (s, 2H), 3.94 (s, 1H), 3.88 (d, *J* = 14.8 Hz, 2H), 3.52 - 3.45 (m, 4H), 3.21 - 3.13 (m, 3H), 2.96 - 2.85 (m, 2H), 2.81 - 2.75 (m, 2H), 2.61 (d, *J* = 1.6 Hz, 3H), 2.57 (s, 3H), 2.54 (s, 2H), 2.43 (d, *J* = 4.4 Hz, 1H), 2.41 - 2.36 (m, 2H), 2.32 (dd, *J* = 2.0, 6.8 Hz, 2H), 1.95 (s, 6H), 1.86 - 1.71 (m, 6H), 1.37 - 1.20 (m, 5H).

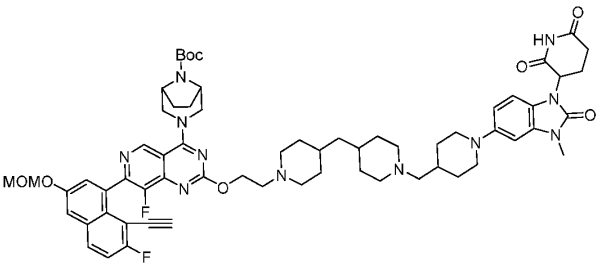
Example 114: Synthesis of -[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl] oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 102**)

Step 1: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropyl silylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo [3.2.1]octane-8-carboxylate (346 mg, 0.4 mmol) and 3-[3-methyl-2-oxo-5-[4-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione di-trifluoroacetate (300 mg, 0.4 mmol) in dichloromethane (4 mL) and isopropanol (4 mL) were added *N,N*-diisopropylethylamine (0.2 mL, 1 mmol) and sodium triacetoxyborohydride (166 mg, 0.8 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with water (15 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with ethyl acetate/methyl tert-butyl ether (1/10, 100 mL) to afford the title compound (400 mg, 77%) as a yellow solid. LC/MS (ESI) *m/z*: 662.3 $[M/2+H]^+$.

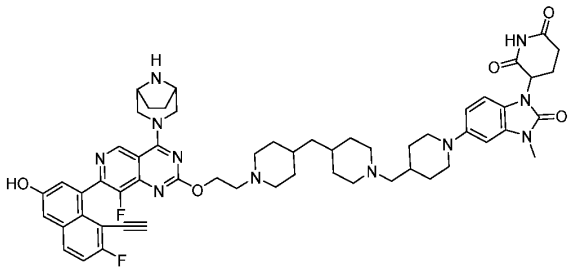
Step 2: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg, 0.3 mmol) in *N,N*-dimethylformamide (5 mL) was added cesium fluoride (1.38 g, 9 mmol), and the mixture was stirred at 25 °C for 4 h. The reaction mixture was quenched with water (0.5 mL), and the crude solution was directly purified by prep-HPLC (22% to 52% acetonitrile in water (trifluoroacetic acid) over 15 min) to

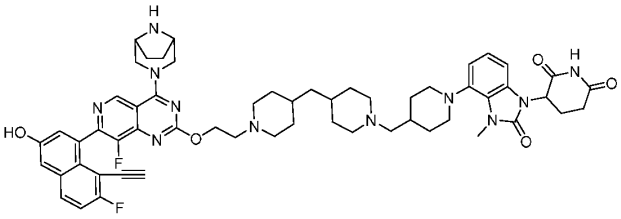
afford the title compound (190 mg, 53%, TFA salt) as an off-white solid. LC/MS (ESI) *m/z*: 584.1 $[M/2+H]^+$.

Step 3: Preparation of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl] oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



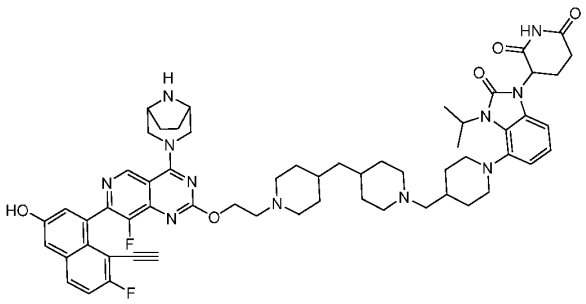
To *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (190 mg, 0.16 mmol) in dichloromethane (5 mL) was added 4 M HCl in 1,4-dioxane (2 mL), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was triturated with ethyl acetate/*tert*-butyl methyl ether (1/10, 60 mL, then purified by prep-HPLC (1% to 25% acetonitrile in water (formic acid) over 10 min) to afford the title compound (43.8 mg, 23%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1022.6 $[M+H]^+$; ^{1}HNMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1 H), 9.05 (s, 1 H), 8.18 (s, 2 H), 7.97 (dd, *J* = 9.2, 6.0 Hz, 1 H), 7.46 (t, *J* = 9.2 Hz, 1 H), 7.39 (d, *J* = 2.4 Hz, 1 H), 7.17 (d, *J* = 2.4 Hz, 1 H), 6.92 (d, *J* = 8.8 Hz, 1 H), 6.81 (d, *J* = 2.0 Hz, 1 H), 6.62 (dd, *J* = 8.8, 2.0 Hz, 1 H), 5.21 - 5.33 (m, 1 H), 4.54 - 4.48 (m, 1 H), 4.47 - 4.42 (m, 2 H), 4.36 (br d, *J* = 11.6 Hz, 1 H), 3.93 (s, 1 H), 3.69 (br s, 2 H), 3.60 (br d, *J* = 15.2 Hz, 4 H), 3.29 (s, 3 H), 2.97 - 2.91 (m, 2 H), 2.89 - 2.83 (m, 3 H), 2.71 (br s, 2 H), 2.66 - 2.55 (m, 4 H), 2.22 - 2.18 (m, 2 H), 2.04 – 1.86 (m, 6 H), 1.80 - 1.71 (m, 6 H), 1.59 (br d, *J* = 11.2 Hz, 6 H), 1.33 - 1.19 (m, 4 H), 1.13 - 1.04 (m, 6 H).

Example 115: Synthesis of 3-{4-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 133**)



The title compound was made in an analogous manner to 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl] oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1022.19 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 9.05 (s, 1H), 8.18 (s, 3H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 7.02 - 6.92 (m, 1H), 6.91 - 6.82 (m, 2H), 5.36 - 5.31 (m, 1H), 4.51 - 4.48 (m, 1H), 4.45 (t, J = 5.2 Hz, 2H), 4.36 - 4.33 (m, 1H), 3.92 (s, 1H), 3.65 (s, 2H), 3.61 (s, 3H), 3.10 (d, J = 8.4 Hz, 4H), 2.97 - 2.81 (m, 7H), 2.73 - 2.63 (m, 6H), 2.20 (dd, J = 1.2, 4.0 Hz, 2H), 2.04 - 1.96 (m, 3H), 1.93 - 1.85 (m, 2H), 1.81 - 1.76 (m, 2H), 1.71 (s, 3H), 1.60 - 1.57 (m, 5H), 1.29 (d, J = 6.4 Hz, 4H), 1.15 - 1.04 (m, 6H).

Example 116: Synthesis of 3-{4-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 94**)

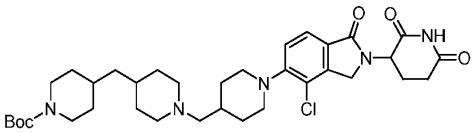


The title compound was made in an analogous manner to 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl] oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1050.8 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.06 (s, 1H), 8.16 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 7.02 - 6.91 (m, 1H), 6.90 - 6.76 (m, 2H), 5.66 - 5.54 (m, 1H), 5.28 (br dd, J = 5.2, 12.8 Hz, 1H), 4.54 (br d, J = 12.4 Hz, 1H), 4.47 (br t, J = 5.2 Hz, 2H), 4.39 (br d, J = 12.8 Hz, 1H), 3.93 (s, 1H),

3.83 (br s, 2H), 3.71 (br s, 3H), 3.08 (br d, J = 10.4 Hz, 2H), 3.00 - 2.82 (m, 6H), 2.76 - 2.70 (m, 2H), 2.69 - 2.56 (m, 4H), 2.30 (br d, J = 6.0 Hz, 2H), 2.10 - 1.92 (m, 5H), 1.85 - 1.72 (m, 6H), 1.69 - 1.55 (m, 5H), 1.45 (dd, J = 6.8, 10.8 Hz, 6H), 1.37 - 1.20 (m, 4H), 1.19 - 1.03 (m, 6H).

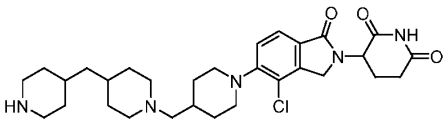
Example 117: Synthesis of 3-{4-chloro-5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-piperidine-2,6-dione (**Compound 109**)

Step 1: Preparation of *tert*-butyl 4-((1-((1-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperidin-4-yl)methyl)piperidin-4-yl)methyl)piperidine-1-carboxylate



To a solution of 1-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperidine- 4-carbaldehyde (1 g, 3 mmol) in dichloromethane (10 mL) and dimethyl sulfoxide (10 mL) was added *tert*-butyl 4-(piperidin-4-ylmethyl)piperidine-1-carboxylate acetate (878 mg, 2.6 mmol), and the resulting mixture was stirred for 30 min. Sodium triacetoxyborohydride (1.09 g, 5 mmol) was then added at 0 °C, and the reaction mixture was stirred at 25 °C for 1 h. The mixture was diluted with water (30 mL) and extracted with dichloromethane/isopropanol (5 :1, 2 x 30 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (1.61 g, 95%) as a white solid. LC/MS (ESI) *m/z*: 656.5 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.74 - 7.57 (m, 1H), 7.37 - 7.15 (m, 1H), 5.10 (br dd, *J* = 4.8, 13.2 Hz, 1H), 4.47 - 4.36 (m, 1H), 4.31 - 4.21 (m, 1H), 4.09 (q, *J* = 5.2 Hz, 1H), 3.99 - 3.82 (m, 2H), 3.59 - 3.46 (m, 2H), 3.44 - 3.37 (m, 2H), 3.17 (d, *J* = 5.2 Hz, 3H), 3.06 - 2.98 (m, 1H), 2.96 - 2.87 (m, 2H), 2.80 - 2.65 (m, 4H), 2.59 (br d, *J* = 18.8 Hz, 2H), 2.04 - 1.96 (m, 2H), 1.95 - 1.86 (m, 2H), 1.84 - 1.76 (m, 2H), 1.68 - 1.57 (m, 3H), 1.53 - 1.43 (m, 3H), 1.38 (s, 9H), 1.14 (br d, *J* = 6.0 Hz, 2H), 1.01 - 0.85 (m, 2H).

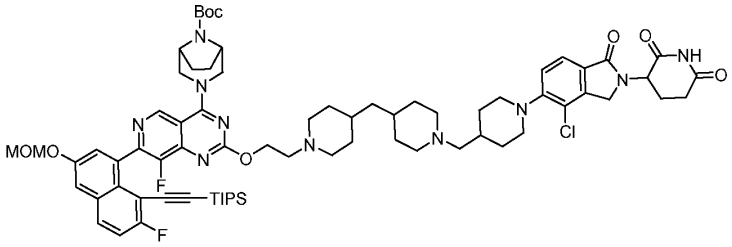
Step 2: Preparation of 3-(4-chloro-1-oxo-5-(4-((4-(piperidin-4-ylmethyl) piperidin-1-yl)methyl)piperidin-1-yl)isoindolin-2-yl)piperidine-2,6-dione



To a solution of *tert*-butyl 4-((1-((1-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperidin-4-yl)methyl)piperidin-4-yl)methyl)piperidine-1-carboxylate (1.61 g, 2 mmol) in

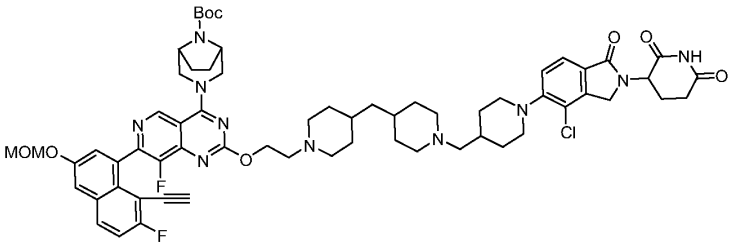
dichloromethane (16 mL) was added trifluoroacetic acid (8 mL, 0.1 mol), and the reaction mixture was stirred at at 25 °C for 1 h. The mixture was concentrated under reduced pressure to afford the title compound (1.6 g, 97%, TFA salt) as a brown oil. LC/MS (ESI) *m/z*: 556.4 $[M+H]^+$.

Step 3: Preparation of *tert*-butyl (1*R*,5*S*)-3-(2-(2-(4-((1-((1-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperidin-4-yl)methyl)piperidin-4-yl)methyl)piperidin-1-yl)ethoxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



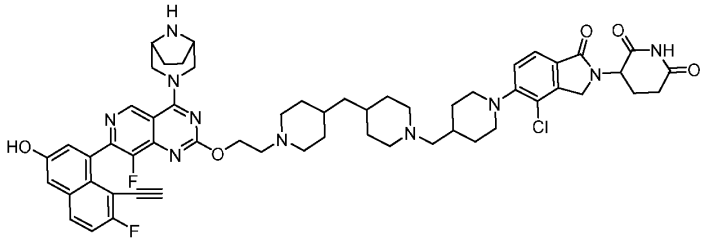
To a solution of 3-(4-chloro-1-oxo-5-(4-((4-(piperidin-4-ylmethyl) piperidin-1-yl)methyl)piperidin-1-yl)isoindolin-2-yl)piperidine-2,6-dione trifluoroacetate (1.6 g, 2 mmol) in dichloromethane (16 mL) and isopropanol (16 mL) were added *N,N*-diisopropylethylamine (0.8 mL, 5 mmol) and *tert*-butyl-3-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.11 g, 2.6 mmol), and the mixture stirred for 15 min. Sodium triacetoxyborohydride (1.01 g, 4.8 mmol) was then added at 0 °C, and the reaction mixture was stirred at 25 °C for 12 h. The mixture was diluted with water (30 mL) and extracted with dichloromethane (2 x 30 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (0 to 100% ethyl acetate/petroleum ether then 0 to 9% dichloromethane/methanol) to afford the title compound (2.2 g, 68%) as a yellow solid. LC/MS (ESI) *m/z*: 1341.7 $[M+H]^+$.

Step 4: Preparation of *tert*-butyl (1*R*,5*S*)-3-(2-(2-(4-((1-((1-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperidin-4-yl)methyl)piperidin-4-yl)methyl)piperidin-1-yl)ethoxy)-7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl (1*R*,5*S*)-3-(2-(2-(4-((1-((1-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperidin-4-yl)methyl)piperidin-4-yl)methyl)piperidin-1-yl)ethoxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.2 g, 1.6 mmol) in *N,N*-dimethylformamide (22 mL) was added cesium fluoride (7.47 g, 49 mmol), and the mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with water (30 mL) and extracted with dichloromethane/isopropanol (5:1, 2 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (30% to 60% acetonitrile in water (formic acid) over 10 min) to afford the title compound (1.8 g, 92%) as a yellow solid. LC/MS (ESI) *m/z*: 1185.6 $[M+H]^+$.

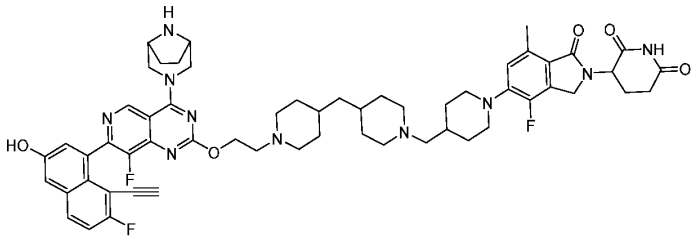
Step 5: Preparation of 3-(5-(4-((4-((1-(2-((4-(-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)ethyl)piperidin-4-yl)methyl)piperidin-1-yl)methyl)piperidin-1-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione



To *tert*-butyl (1*R*,5*S*)-3-(2-(2-(4-((1-((1-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperidin-4-yl)methyl)piperidin-4-yl)methyl)piperidin-1-yl)ethoxy)-7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.8 g, 1.5 mmol) in dichloromethane (18 mL) was added 4 M HCl in 1,4-dioxane (18 mL), and the reaction mixture was stirred at 25 °C for 15 min. The mixture was suspended in petroleum ether (50 mL) and filtered. The filter cake was dissolved in dimethyl sulfoxide and *N,N*-diisopropylethylamine to adjust the pH to 7. The mixture was purified by prep-HPLC (1% to 30% acetonitrile in water (formic acid) over 11 min) to afford the title compound (785.5 mg, 45%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1041.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.07 (s, 1H), 8.19 (s, 2H), 7.98 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.40 (d, *J* = 2.4

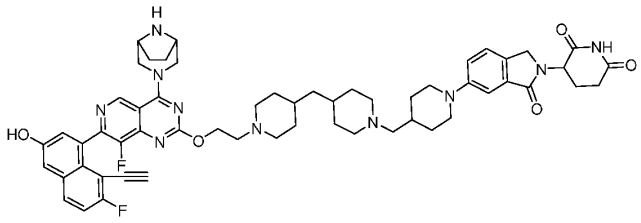
Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 5.09 (dd, *J* = 5.2, 1Step 2: Hz, 1H), 4.63 - 4.53 (m, 1H), 4.53 - 4.46 (m, 2H), 4.45 - 4.38 (m, 2H), 4.25 (br d, *J* = 17.6 Hz, 1H), 3.97 - 3.87 (m, 3H), 3.77 (br t, *J* = 11.2 Hz, 2H), 3.38 (br s, 2H), 3.04 - 2.85 (m, 5H), 2.81 - 2.68 (m, 4H), 2.59 (br d, *J* = 15.6 Hz, 1H), 2.44 (br dd, *J* = 4.4, 1Step 6: Hz, 1H), 2.36 (br d, *J* = 6.0 Hz, 2H), 2.16 - 2.04 (m, 4H), 2.02 - 1.94 (m, 1H), 1.92 - 1.68 (m, 8H), 1.62 (br d, *J* = 10.8 Hz, 4H), 1.40 - 1.25 (m, 4H), 1.24 - 1.06 (m, 6H).

Example 118: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-7-methyl-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 149**)



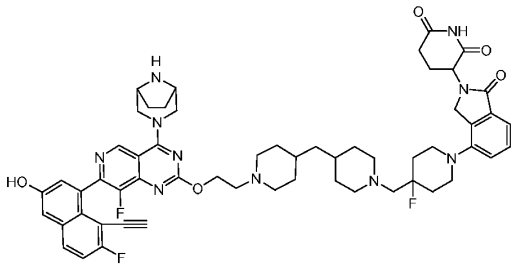
The title compound was prepared in an analogous manner to 3-(5-(4-((4-((1-(2-((4-(-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)ethyl)piperidin-4-yl)methyl)piperidin-1-yl)methyl)piperidin-1-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione. (yellow solid). LC/MS (ESI) *m/z*: 1039.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 0.97 (s, 1H), 9.05 (s, 1H), 8.21 (s, 3H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.50 - 7.34 (m, 2H), 7.18 (d, J = 2.4 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 5.02 (dd, J = 4.8, 13.2 Hz, 1H), 4.56 - 4.33 (m, 5H), 4.22 (d, J = 16.8 Hz, 1H), 3.93 (s, 1H), 3.79 - 3.60 (m, 4H), 3.47 (dd, J = 3.2, 4.4 Hz, 2H), 3.01 - 2.81 (m, 5H), 2.79 - 2.65 (m, 4H), 2.65 - 2.51 (m, 5H), 2.49 - 2.31 (m, 3H), 2.25 - 2.17 (m, 2H), 2.10 - 1.85 (m, 5H), 1.83 - 1.64 (m, 7H), 1.59 (d, J = 11.2 Hz, 4H), 1.39 - 1.19 (m, 4H), 1.16 - 1.00 (m, 6H).

Example 119: Synthesis of 3-{6-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 110**)



The title compound was prepared in an analogous manner to 3-(5-(4-((4-((1-(2-((4-(-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)ethyl)piperidin-4-yl)methyl)piperidin-1-yl)methyl)piperidin-1-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione. (yellow solid, formic acid salt.) LC/MS (ESI) *m/z*: 1007.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.08 (s, 1H), 8.21 (s, 3H), 7.99 (dd, J = 6.0, 9.2 Hz, 1H), 7.47 (t, J = 9.2 Hz, 1H), 7.44 - 7.37 (m, 2H), 7.25 (dd, J = 2.0, 8.4 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.15 (d, J = 1.6 Hz, 1H), 5.10 (dd, J = 5.2, 13.2 Hz, 1H), 4.57 (d, J = 12.4 Hz, 1H), 4.52-4.48 (m, 2H), 4.42 (d, J = 12.4 Hz, 1H), 4.37 - 4.30 (m, 1H), 4.24 - 4.17 (m, 1H), 3.95 (s, 1H), 3.90-3.88 (m, 2H), 3.81 - 3.69 (m, 4H), 3.05 - 2.87 (m, 5H), 2.82 - 2.68 (m, 4H), 2.63-2.57 (m, 2H), 2.43 - 2.29 (m, 4H), 2.13-2.07 (m, 4H), 2.01 - 1.94 (m, 1H), 1.87 - 1.71 (m, 7H), 1.63-1.57 (m, 4H), 1.41 - 1.29 (m, 2H), 1.27 - 1.04 (m, 8H).

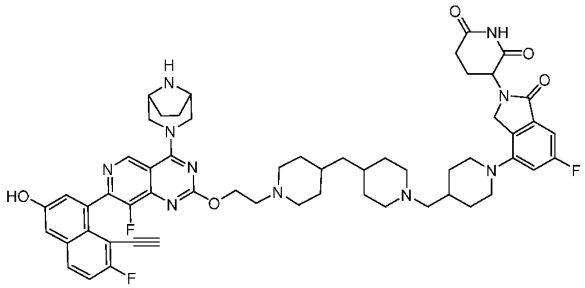
Example 120: Synthesis of 3-{4-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)-4-fluoropiperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 125**)



The title compound was prepared in an analogous manner to 3-(5-(4-((4-((1-(2-((4-(-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)ethyl)piperidin-4-yl)methyl)piperidin-1-yl)methyl)piperidin-1-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1026.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.06 (s, 1H), 8.17 (s, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.52 - 7.37 (m, 3H), 7.31 (d, J = 7.6 Hz, 1H), 7.22 - 7.13 (m, 2H), 5.12 (dd, J = 5.2, 13.2 Hz, 1H), 4.56 - 4.36 (m, 5H), 4.29 (d, J = 17.2 Hz, 1H), 3.93 (s, 1H), 3.78 (s, 3H), 3.71 (d, J = 14.8 Hz, 5H), 3.44 (dd, J = 3.2, 7.6 Hz, 3H), 3.25 - 3.20 (m, 2H), 3.02 - 2.91 (m, 5H), 2.87 (d, J = 10.4 Hz, 2H), 2.72 (t, J = 5.8 Hz, 2H), 2.59 (s, 1H), 2.05 (t, J = 10.4 Hz, 4H), 2.00 - 1.88 (m, 3H), 1.88 - 1.82 (m, 1H), 1.77 (s, 4H), 1.57 (t, J = 13.2 Hz, 3H), 1.35 - 1.22 (m, 2H), 1.15 - 1.03 (m, 5H).

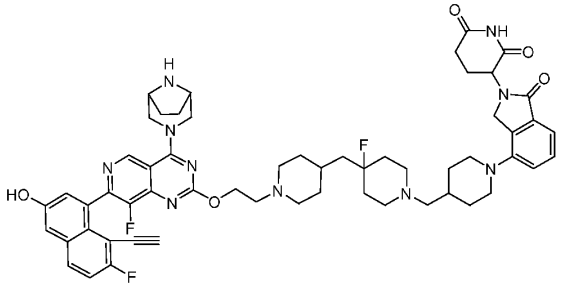
Example 121: Synthesis of 3-{4-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-

yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-6-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 130**)



The title compound was prepared in an analogous manner to 3-(5-(4-((4-((1-(2-((4-(-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)ethyl)piperidin-4-yl)methyl)piperidin-1-yl)methyl)piperidin-1-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1025.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.07 (s, 1H), 8.22 (s, 3H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.99 (dd, J = 2.0, 7.2 Hz, 1H), 6.92 (dd, J = 2.0, 12.0 Hz, 1H), 5.10 (dd, J = 5.2, 13.2 Hz, 3H), 5.00 - 4.78 (m, 3H), 4.56 (d, J = 12.8 Hz, 1H), 4.51 - 4.36 (m, 4H), 4.33 - 4.22 (m, 1H), 3.93 (s, 1H), 3.86 (s, 2H), 3.74 (t, J = 12.4 Hz, 2H), 3.54 - 3.36 (m, 2H), 3.05 - 2.94 (m, 2H), 2.89 (d, J = 11.2 Hz, 2H), 2.83 - 2.68 (m, 4H), 2.63 - 2.52 (m, 2H), 2.47 - 2.40 (m, 1H), 2.26 (d, J = 6.4 Hz, 2H), 2.15 - 1.93 (m, 5H), 1.87 - 1.68 (m, 6H), 1.60 (d, J = 11.6 Hz, 3H), 1.31 (d, J = 4.0 Hz, 2H), 1.26 - 1.18 (m, 2H), 1.18 - 1.02 (m, 5H).

Example 122: Synthesis of 3-{4-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]-4-fluoropiperidin-1-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 131**)

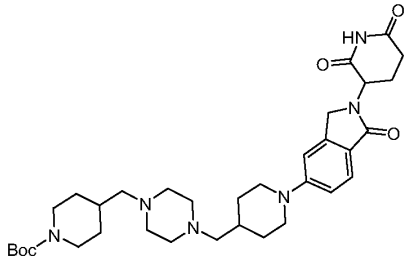


The title compound was prepared in an analogous manner to 3-(5-(4-((4-((1-(2-((4-(-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)ethyl)piperidin-4-yl)methyl)piperidin-1-yl)methyl)piperidin-1-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione. (white solid, formic acid salt). LC/MS

(ESI) *m/z*: 1025.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.79 - 9.48 (m, 2H), 9.42 - 9.26 (m, 1H), 9.16 (s, 1H), 8.00 (dd, J = 6.0, 9.2 Hz, 1H), 7.55 - 7.39 (m, 3H), 7.33 (d, J = 7.6 Hz, 1H), 7.23 - 7.14 (m, 2H), 5.13 (dd, J = 5.2, 13.2 Hz, 1H), 4.90 - 4.53 (m, 4H), 4.50 - 4.38 (m, 1H), 4.35 - 4.19 (m, 3H), 3.73 - 3.34 (m, 10H), 3.19 - 2.87 (m, 7H), 2.84 - 2.70 (m, 2H), 2.69 - 2.57 (m, 2H), 2.21 - 1.71 (m, 16H), 1.71 - 1.27 (m, 6H).

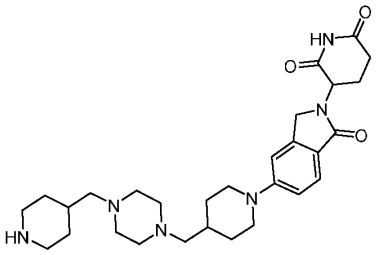
Example 123: Synthesis of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 111**)

Step 1: Preparation of *tert*-butyl 4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]piperidine-1-carboxylate



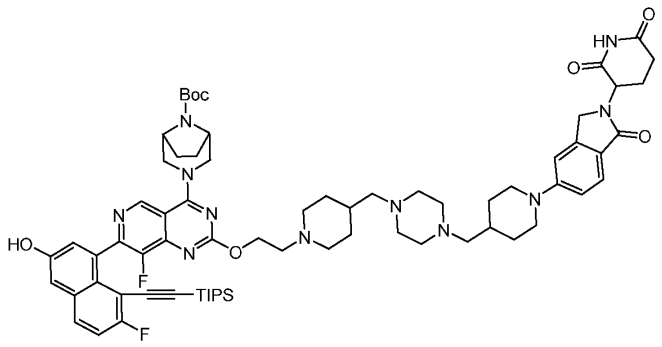
To a solution of 1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperidine-4-carbaldehyde (500 mg, 1.4 mmol) in dichloromethane (5 mL) and isopropanol (5 mL) were added *N,N*-diisopropylethylamine (0.1 mL, 0.7 mmol), *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (398 mg, 1.4 mmol), and sodium triacetoxyborohydride (894 mg, 4 mmol), and the reaction mixture was stirred at 25 °C for 12 h. The mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (dichloromethane/methanol = 8/1) to afford the title compound (242 mg, 27%) as a yellow solid. LC/MS (ESI) *m/z*: 623.5$[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 0.8 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.87 (s, 1H), 5.21 (dd, *J* = 5.2, 1Step 2: Hz, 1H), 4.46 - 4.34 (m, 1H), 4.30 - 4.21 (m, 1H), 4.18 - 4.00 (m, 2H), 3.83 (d, *J* = 12.8 Hz, 2H), 2.93 - 2.80 (m, 5H), 2.76 - 2.55 (m, 9H), 2.44 - 2.28 (m, 5H), 2.25 - 2.17 (m, 1H), 1.96 - 1.82 (m, 2H), 1.73 (d, *J* = 12.0 Hz, 3H), 1.46 (s, 9H), 1.40 - 1.22 (m, 3H), 1.18 - 1.02 (m, 2H).

Step 2: Preparation of 3-[1-oxo-5-[4-[[4-(4-piperidylmethyl)piperazin-1-yl]methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione



To a solution of *tert*-butyl 4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]piperidine-1-carboxylate (242 mg, 0.4 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (1.0 mL, 13 mmol), and the mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated to afford 3-[1-oxo-5-[4-[[4-(4-piperidylmethyl)piperazin-1-yl]methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione (247 mg, crude, TFA salt) as a yellow gum. LC/MS (ESI) *m/z*: 523.4 $[M+H]^+$.

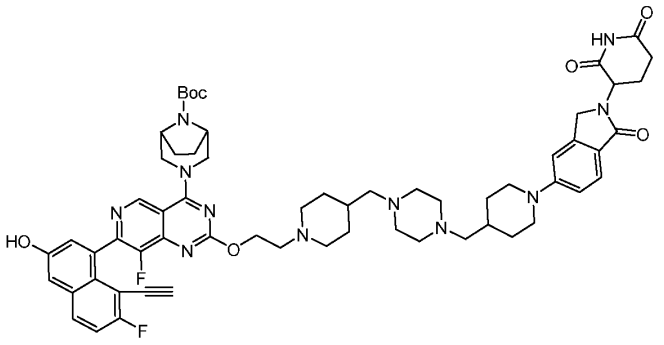
Step 3: Preparation of *tert*-butyl 3-[2-[2-[4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-hydroxy-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 3-[1-oxo-5-[4-[[4-(4-piperidylmethyl)piperazin-1-yl]methyl]-1-piperidyl]isoindolin-2-yl]piperidine-2,6-dione trifluoroacetate (247 mg, 0.4 mmol) in dichloromethane (3 mL), isopropanol (3 mL) and *N,N*-diisopropylethylamine (0.2 mL, 1 mmol) were added *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-hydroxy-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (294 mg, 0.4 mmol) and sodium triacetoxyborohydride (164 mg, 0.8 mmol), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (dichloromethane/methanol = 7/1) to afford the title compound (300 mg, 61%) as a yellow solid. LC/MS (ESI) *m/z*: 1264.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 10.26

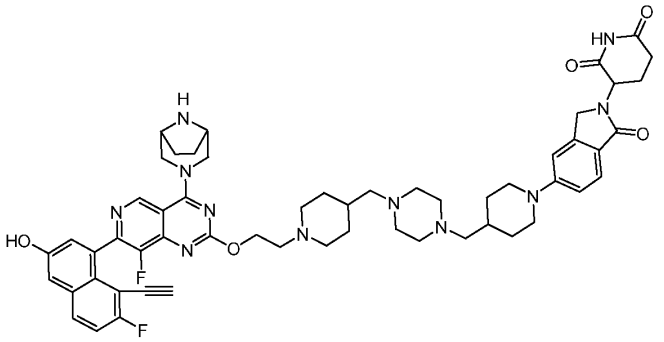
(s, 1H), 9.16 (s, 1H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.52 - 7.43 (m, 2H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.17 (d, *J* = 2.0 Hz, 1H), 7.07 - 6.98 (m, 2H), 5.03 (dd, *J* = 5.2, 1Step 2: Hz, 1H), 4.73 (d, *J* = 12.4 Hz, 1H), 4.59 - 4.40 (m, 2H), 4.35 - 4.23 (m, 4H), 3.85 (d, *J* = 12.0 Hz, 2H), 3.74 (d, *J* = 12.0 Hz, 1H), 3.64 - 3.52 (m, 1H), 3.41 - 3.34 (m, 2H), 2.95 - 2.74 (m, 5H), 2.60 (s, 2H), 2.46 - 2.30 (m, 6H), 2.28 - 2.05 (m, 5H), 2.02 - 1.92 (m, 2H), 1.89 - 1.82 (m, 2H), 1.81 - 1.62 (m, 6H), 1.46 (s, 9H), 1.33 - 1.21 (m, 6H), 1.16 (d, *J* = 8.8 Hz, 3H), 0.81 (t, *J* = 8.0 Hz, 18H), 0.57 - 0.41 (m, 3H).

Step 4: Preparation of *tert*-butyl 3-[2-[2-[4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]ethoxy]-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



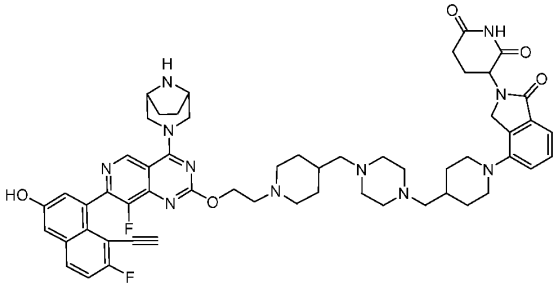
To *tert*-butyl 3-[2-[2-[4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-hydroxy-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 0.2 mmol) in *N,N*-dimethylformamide (3 mL) was added cesium fluoride (1.08 g, 7 mmol), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (dichloromethane/methanol = 7/1) to afford the title compound (274 mg, crude) as a yellow gum. LC/MS (ESI) *m/z*: 1108.6 $[M+H]^+$.

Step 5: Preparation of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione



To *tert*-butyl 3-[2-[2-[4-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]ethoxy]-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (274 mg, 0.25 mmol) in dichloromethane (6 mL) was added 4 M HCl in 1,4-dioxane (6 mL), and the reaction mixture was stirred at 25 °C for 15 min. The mixture was suspended in petroleum ether (10 mL) and filtered. The filtered cake was dissolved with dimethyl sulfoxide (3 mL) and *N,N*-diisopropylethylamine to adjust the pH to 8. The mixture was purified by prep-HPLC (1% to 30% acetonitrile in water (formic acid) over 10 min) to afford the title compound (107 mg, 43%, 3 formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1008.3 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 9.05 (s, 1H), 8.20 (s, 3H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.53 - 7.42 (m, 2H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 7.10 - 6.98 (m, 2H), 5.04 (dd, *J* = 5.2, 1Step 2: Hz, 1H), 4.57 - 4.42 (m, 3H), 4.41 - 4.26 (m, 2H), 4.20 (s, 1H), 3.93 (s, 1H), 3.85 (d, *J* = 12.4 Hz, 2H), 3.78 - 3.72 (m, 2H), 3.68 (s, 2H), 3.01 - 2.87 (m, 3H), 2.85 - 2.75 (m, 2H), 2.74 - 2.66 (m, 2H), 2.63 - 2.52 (m, 3H), 2.42 - 2.22 (m, 8H), 2.18 - 1.91 (m, 6H), 1.75 (s, 6H), 1.64 (d, *J* = 11.2 Hz, 2H), 1.47 (d, *J* = 1.2 Hz, 1H), 1.26 - 0.98 (m, 5H).

Example 124: Synthesis of 3-{4-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperazin-1-yl}methyl)piperidin-1-yl]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 136**)

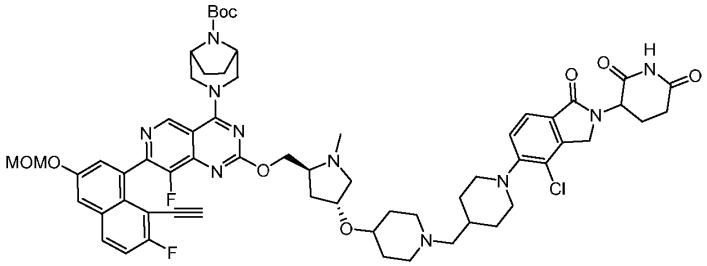


The title compound was prepared in an analogous manner to 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-

d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (orange solid, formic acid salt). LC/MS (ESI) *m/z*: 1008.8 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (br s, 1H), 9.05 (s, 1H), 8.20 (s, 3H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.57 - 7.35 (m, 3H), 7.28 (d, J = 7.6 Hz, 1H), 7.20 - 7.06 (m, 2H), 5.11 (br dd, J = 5.2, 13.2 Hz, 1H), 4.56 - 4.41 (m, 3H), 4.40 - 4.20 (m, 3H), 3.93 (s, 1H), 3.72 - 3.59 (m, 2H), 3.36 (t, J = 12.0 Hz, 2H), 3.01 - 2.83 (m, 3H), 2.77 - 2.65 (m, 4H), 2.58 (br d, J = 17.6 Hz, 4H), 2.49 - 2.43 (m, 4H), 2.41 - 2.23 (m, 6H), 2.16 (br d, J = 7.2 Hz, 2H), 2.12 - 1.93 (m, 5H), 1.83 - 1.71 (m, 5H), 1.64 (d, J = 11.2 Hz, 3H), 1.38 (s, 1H), 1.34 - 1.16 (m, 2H), 1.15 - 0.98 (m, 2H).

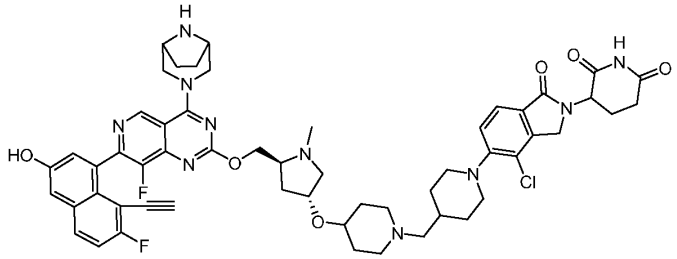
Example 125: Synthesis of 3-(5-(4-((4-(((3*R*,5*S*)-5-(((4-((1*R*,5*S*)-3,8- diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-yl)oxy)piperidin-1-yl)methyl)piperidin-1-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**Compound 113**)

Step 1: Preparation of *tert*-butyl (1*R*,5*S*)-3-(2-(((2*S*,4*R*)-4-((1-((1-(4- chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperidin-4-yl)methyl)piperidin-4-yl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



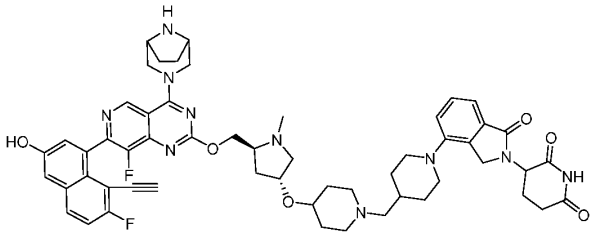
To a solution of 1-(4-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperidine-4-carbaldehyde (122 mg, 0.3 mmol) and *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8- fluoro-2-[[(2S,4R)-1-methyl-4-(4-piperidyloxy)pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (250 mg, 0.3 mmol) in dichloromethane (2 mL) and dimethyl sulfoxide (2 mL) was added *N*-methylmorpholine (63 mg, 0.6 mmol), and the resulting mixture was stirred at 25 °C for 10 min. Acetic acid (38 mg, 0.6 mmol) was added then added, and the mixture was stirred for 20 min at 25 °C. Sodium triacetoxyborohydride (132 mg, 0.6 mmol) was then added, and the reaction mixture was stirred at 25 °C for 12 h. The mixture was diluted with water (30 mL) and extracted with chloroform/isopropanol (5:1, 2 x 30 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-TLC (dichloromethane/methanol = 10:1) to afford the title compound (240 mg, 65%) as a yellow solid. LC/MS (ESI) *m/z*: 1173.6 $[M+H]^+$.

Step 2: Preparation of 3-(5-(4-((4-(((3*R*,5*S*)-5-(((4-((1*R*,5*S*)-3,8- diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-yl)oxy)piperidin-1-yl)methyl)piperidin-1-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione



To *tert*-butyl (1*R*,5*S*)-3-(2-(((2*S*,4*R*)-4-((1-((1-(4- chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperidin-4-yl)methyl)piperidin-4-yl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (240 mg, 0.2 mmol) in dichloromethane (2 mL) was added 4 M HCl in 1,4-dioxane (2 mL), and the mixture was stirred at 25 °C for 15 min. The mixture was evaporated from petroleum ether (2 x 100 mL), and the resulting residue was diluted with tetrahydrofuran (50 mL) and triethylamine to adjust the pH to 7. The resulting suspension was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (3% to 33% acetonitrile in water (formic acid) over 10 min) to afford the title compound (94.0 mg, 41%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1030.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.06 (s, 1H), 8.21 (s, 2H), 7.98 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 5.10 (dd, *J* = 4.8, 1Step 2: Hz, 1H), 4.53 (d, *J* = 12.4 Hz, 1H), 4.44 - 4.33 (m, 3H), 4.29 - 4.20 (m, 2H), 4.16 - 4.09 (m, 1H), 3.95 (d, *J* = 2.0 Hz, 1H), 3.77 - 3.61 (m, 4H), 3.37 (d, *J* = 5.6 Hz, 2H), 3.33 - 3.20 (m, 2H), 2.98 - 2.85 (m, 1H), 2.83 - 2.76 (m, 1H), 2.75 - 2.65 (m, 4H), 2.58 (d, *J* = 16.4 Hz, 1H), 2.37 - 2.32 (m, 4H), 2.23 - 2.14 (m, 3H), 2.07 - 1.96 (m, 3H), 1.93 - 1.85 (m, 2H), 1.80 (d, *J* = 10.4 Hz, 4H), 1.77 - 1.71 (m, 4H), 1.70 - 1.58 (m, 2H), 1.41 (d, *J* = 9.2 Hz, 2H), 1.33 - 1.22 (m, 2H).

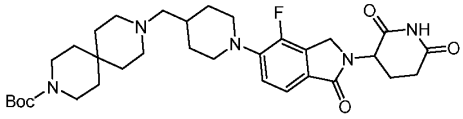
Example 126: Synthesis of 3-(4-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 115**)



The title compound was prepared in an analogous manner to 3-(5-(4-((4-(((3*R*,5*S*)-5-(((4-((1*R*,5*S*)-3,8- diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-yl)oxy)piperidin-1-yl)methyl)piperidin-1-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 995.3 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.06 (s, 1H), 8.17 (s, 2H), 7.98 (dd, J = 6.0, 9.2Hz, 1H), 7.50 - 7.37 (m, 3H), 7.32 - 7.26 (m, 1H), 7.21 - 7.11 (m, 2H), 5.11 (dd, J = 5.2, 9.2Hz, 1H), 4.61 - 4.51 (m, 1H), 4.46 - 4.36 (m, 3H), 4.33 - 4.24 (m, 2H), 4.16 - 4.10 (m, 1H), 3.95 - 3.92 (m, 1H), 3.83 (s, 2H), 3.77 - 3.69 (m, 2H), 3.40 - 3.25 (m, 4H), 2.99 - 2.86 (m, 1H), 2.85 - 2.78 (m, 1H), 2.75 - 2.66 (m, 4H), 2.62 - 2.54 (m, 2H), 2.36 (s, 3H), 2.23 - 2.16 (m, 3H), 2.11 - 1.99 (m, 3H), 1.94 - 1.73 (m, 11H), 1.69 - 1.60 (m, 1H), 1.48 - 1.36 (m, 2H), 1.34 - 1.19 (m, 2H).

Example 127: Synthesis of 3-[5-[4-[[9-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-3,9-diazaspiro[5.5]undecan-3-yl]methyl]-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 121**)

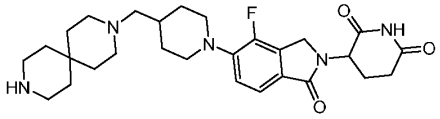
Step 1: Preparation of *tert*-butyl 9-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate



To a solution of *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (337 mg, 1.3 mmol) in dichloromethane (5 mL) and isopropanol (5 mL) were added *N*,*N*-diisopropylethylamine (0.2 mL, 1 mmol) and 1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]piperidine-4-carbaldehyde (450 mg, 1.2 mmol), and the mixture was stirred for 15 min at 25 °C. Sodium triacetoxyborohydride (766 mg, 3.6 mmol) was then added, and the mixture was stirred for 0.5 h. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was

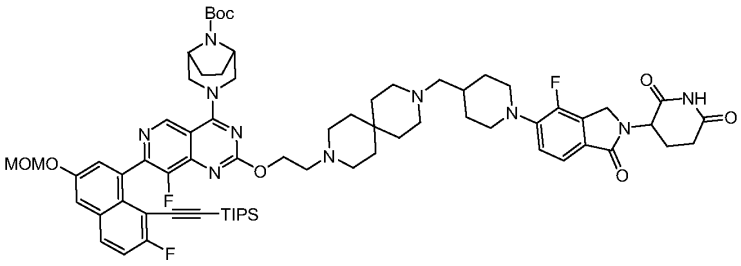
purified by preparative TLC (dichloromethane/methanol = 10:1) to afford the title compound (600 mg, 81%) as a yellow solid. LC/MS (ESI) *m/z*: 612.5 $[M+H]^+$.

Step 2: Preparation of 3-[5-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione



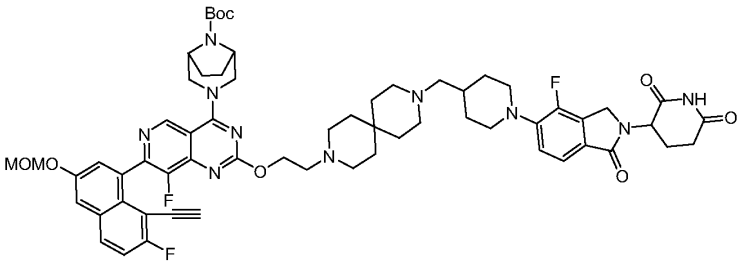
To a solution of tert-butyl 9-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate (600 mg, 1 mmol) in dichloromethane (6 mL) was added trifluoroacetic acid (6.0 mL, 81 mmol) at 20 °C, and the reaction mixture was stirred for 0.5 h at 20 °C. The mixture was concentrated *in vacuo* to afford the title compound (610 mg, 99%, TFA salt) as yellow oil. LC/MS (ESI) *m/z*: 512.4 $[M+H]^+$.

Step 3: Preparation of *tert*-butyl 3-[2-[2-[3-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



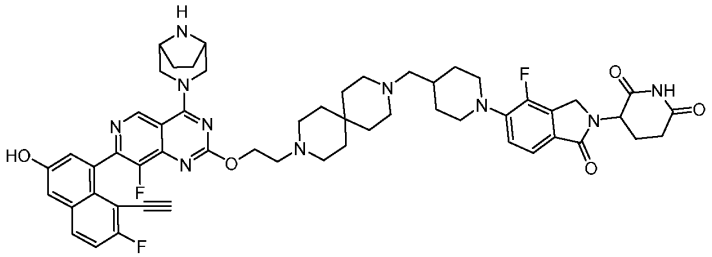
To 3-[5-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione trifluoroacetic (610 mg, 0.97 mmol) in dichloromethane (8 mL) and isopropanol (8 mL) were added *N,N*-diisopropylethylamine (0.3 mL, 2 mmol) and tert-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (860 mg, 1 mmol), and the mixture was stirred for 0.5 h at 25 °C. Sodium triacetoxyborohydride (620 mg, 2.9 mmol) was then added, and the mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (20 mL x 3). The combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (dichloromethane/methanol=10:1) to afford the title compound (1 g, 79%) as a yellow solid. LC/MS (ESI) *m/z*: 1298.8 $[M+H]^+$.

Step 4: Preparation of *tert*-butyl 3-[2-[2-[3-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To *tert*-butyl 3-[2-[2-[3-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1 g, 0.8 mmol) in *N,N*-dimethylformamide (10 mL) at 25 °C was added cesium fluoride (3.51 g, 23 mmol), and the mixture was stirred for 2 h at 25 °C. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford the title compound (700 mg, 80%) as a yellow solid. LC/MS (ESI) *m/z*: 1141.7 $[M+H]^+$.

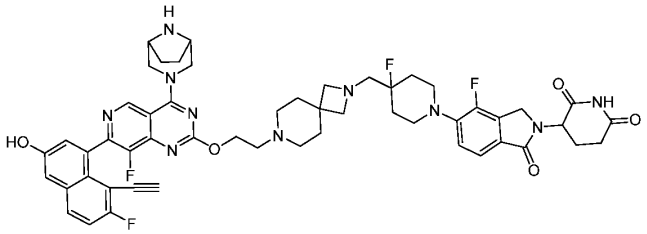
Step 5: Preparation of 3-[5-[4-[[9-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-3,9-diazaspiro[5.5]undecan-3-yl]methyl]-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione



To tert-butyl 3-[2-[2-[3-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (700 mg, 0.6 mmol) in dichloromethane (8 mL) was added 4 M HCl in 1,4-dioxane (4 mL) at 20 °C, and the mixture was stirred for 0.5 h at 20 °C. The reaction mixture was poured into methyl tert-butyl ether (10 mL) and filtered. The filter cake was purified by prep-HPLC (0%-30% acetonitrile in water (formic acid) over 11min) to afford the

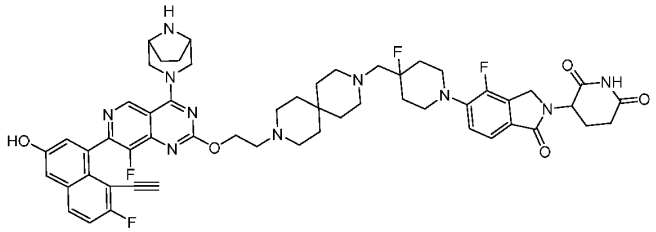
title compound (214 mg, 33%, formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 997.8 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.07 (s, 1H), 8.17 (s, 2H), 8.01 – 7.95 (m, 1H), 7.49 – 7.43 (m, 2H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.20 – 7.10 (m, 2H), 5.07 (dd, *J* = 13.6, 5.2 Hz, 1H), 4.57 – 4.52 (m, 1H), 4.50 – 4.45 (m, 3H), 4.42 – 4.36 (m, 2H), 4.35 – 4.25 (m, 2H), 3.93 (s, 1H), 3.85 – 3.81 (m, 3H), 3.77 – 3.70 (m, 4H), 3.50 – 3.43 (m, 4H), 2.97 – 2.85 (m, 2H), 2.80 – 2.72 (m, 4H), 2.62 – 2.56 (m, 1H), 2.41 – 2.37 (m, 1H), 2.35 – 2.27 (m, 3H), 2.00 – 1.93 (m, 1H), 1.85 – 1.75 (m, 6H), 1.74 – 1.65 (m, 1H), 1.50 – 1.40 (m, 8H), 1.33 – 1.22 (m, 2H).

Example 128: Synthesis of 3-(5-{4-[(7-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-2,7-diazaspiro[3.5]nonan-2-yl)methyl]-4-fluoropiperidin-1-yl}-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 119**)



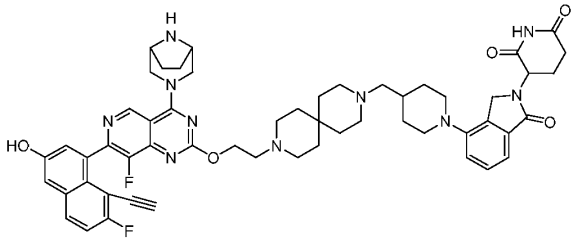
The title compound was made in an analogous manner to 3-[5-[4-[[9-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-3,9-diazaspiro[5.5]undecan-3-yl]methyl]-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (orange solid, formic acid salt). LC/MS (ESI) *m/z*: 987.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.08 (s, 1H), 8.14 (s, 2H), 7.98 (dd, J = 5.6, 9.2 Hz, 1H), 7.56 - 7.43 (m, 2H), 7.40 (d, J = 2.6 Hz, 1H), 7.27 - 7.13 (m, 2H), 5.07 (dd, J = 4.6, 13.4 Hz, 1H), 4.60 (d, J = 13.2 Hz, 1H), 4.54 - 4.40 (m, 4H), 4.31 (d, J = 16.8 Hz, 1H), 3.99 (s, 2H), 3.93 (s, 1H), 3.79 - 3.70 (m, 2H), 3.53 - 3.40 (m, 3H), 3.04 (s, 4H), 3.00 - 2.82 (m, 3H), 2.72 (d, J = 12.4 Hz, 3H), 2.65 (s, 1H), 2.62 - 2.53 (m, 3H), 2.47 - 2.34 (m, 4H), 1.98 (dd, J = 6.0, 11.2 Hz, 1H), 1.91 - 1.81 (m, 6H), 1.80 - 1.71 (m, 2H), 1.68 (s, 3H).

Example 129: Synthesis of 3-(5-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]-4-fluoropiperidin-1-yl}-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 120**)



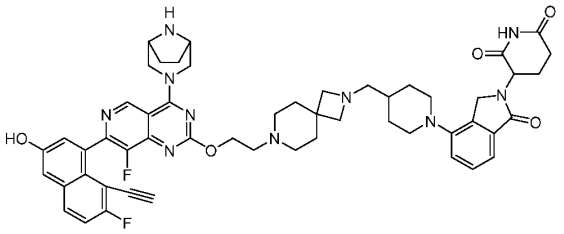
The title compound was made in an analogous manner to 3-[5-[4-[[9-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-3,9-diazaspiro[5.5]undecan-3-yl]methyl]-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (yellow solid). LC/MS (ESI) *m/z*: 1015.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.07 (s, 1H), 8.15 (s, 2H), 7.98 (dd, J = 6.0, 9.0 Hz, 1H), 7.50 - 7.44 (m, 2H), 7.40 (d, J = 2.4 Hz, 1H), 7.23 - 7.15 (m, 2H), 5.07 (dd, J = 5.2, 13.2 Hz, 1H), 4.65 - 4.36 (m, 6H), 4.31 (d, J = 16.8 Hz, 1H), 3.96 - 3.87 (m, 4H), 3.74 (t, J = 12.8 Hz, 4H), 3.02 (dd, J = 10.0, 11.2 Hz, 4H), 2.96 - 2.88 (m, 2H), 2.81 (s, 3H), 2.60 (s, 1H), 2.55 (s, 4H), 2.02 - 1.88 (m, 4H), 1.87 - 1.68 (m, 6H), 1.49 - 1.35 (m, 8H).

Example 130: Synthesis of 3-(4-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 132**)



The title compound was made in an analogous manner to 3-[5-[4-[[9-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-3,9-diazaspiro[5.5]undecan-3-yl]methyl]-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (yellow solid). LC/MS (ESI) *m/z*: 979.7 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.05 (s, 1H), 8.19 (s, 3H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.52 - 7.37 (m, 3H), 7.28 (d, J = 7.2 Hz, 1H), 7.20 - 7.12 (m, 2H), 5.11 (dd, J = 5.2, 13.2 Hz, 1H), 4.51 (d, J = 12.4 Hz, 1H), 4.47 - 4.43 (m, 2H), 4.41 - 4.34 (m, 2H), 4.27 (d, J = 17.2 Hz, 2H), 3.93 (s, 1H), 3.70 (s, 2H), 3.64 (s, 2H), 3.40 - 3.32 (m, 4H), 2.98 - 2.85 (m, 2H), 2.75 - 2.68 (m, 4H), 2.58 (d, J = 17.2 Hz, 2H), 2.46 - 2.43 (m, 2H), 2.35 (s, 4H), 2.22 (d, J = 7.2 Hz, 2H), 2.03 - 1.94 (m, 1H), 1.79 (d, J = 12.4 Hz, 2H), 1.72 (s, 4H), 1.41 (s, 8H), 1.28 - 1.19 (m, 2H).

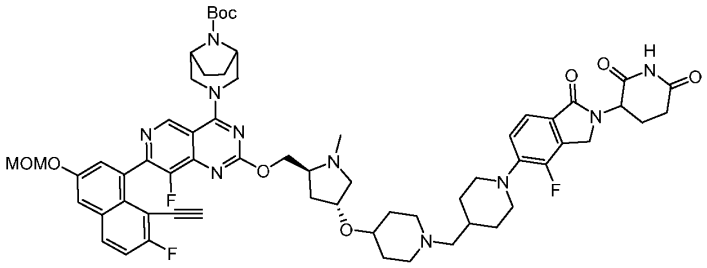
Example 131: Synthesis of 3-(4-{4-[(7-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-2,7-diazaspiro[3.5]nonan-2-yl)methyl]piperidin-1-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 135**)



The title compound was made in an analogous manner to 3-[5-[4-[[9-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-3,9-diazaspiro[5.5]undecan-3-yl]methyl]-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (white solid). LC/MS (ESI) *m/z*: 951.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.11 - 9.02 (m, 1H), 8.19 (s, 2H), 8.01 - 7.92 (m, 1H), 7.49 - 7.37 (m, 3H), 7.31 - 7.27 (m, 1H), 7.19 - 7.11 (m, 2H), 5.15 - 5.06 (m, 1H), 4.51 - 4.24 (m, 7H), 3.90 (d, J = 5.2 Hz, 1H), 3.63 (d, J = 6.0 Hz, 4H), 3.34 (s, 4H), 3.02 (s, 3H), 2.95 - 2.89 (m, 1H), 2.73 - 2.55 (m, 7H), 2.43 - 2.35 (m, 5H), 2.02 - 1.95 (m, 1H), 1.75 (d, J = 12.4 Hz, 2H), 1.71 - 1.63 (m, 7H), 1.49 - 1.41 (m, 1H), 1.30 - 1.21 (m, 2H).

Example 132: Synthesis of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 122**)

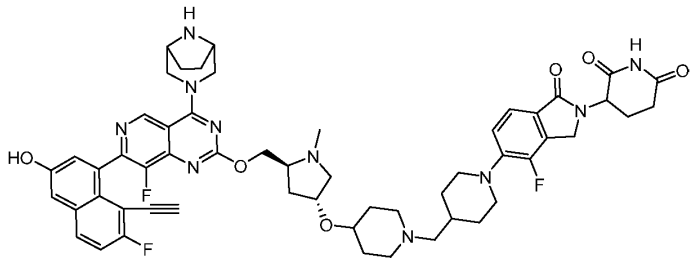
Step 1: Preparation of *tert*-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,4R)-1-methyl-4-(4-piperidyloxy)pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-

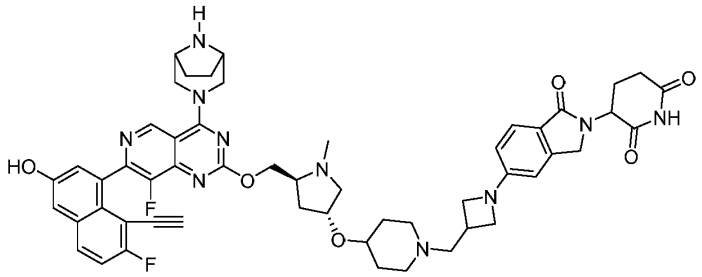
yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (260 mg, 0.3 mmol) in dichloromethane (4 mL) and isopropyl alcohol (4 mL) were added diisopropylethylamine (0.03 mL, 0.2 mmol), 1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]piperidine-4-carbaldehyde (121 mg, 0.3 mmol), and sodium triacetoxyborohydride (206 mg, 0.97 mmol), and the mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane/isopropanol (3 x 20 mL). The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (dichloromethane/methanol = 8/1) to afford the title compound (128 mg, 34%) as a yellow solid. LC/MS (ESI) *m/z*: 1157.6 $[M+H]^+$.

Step 2: Preparation of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione



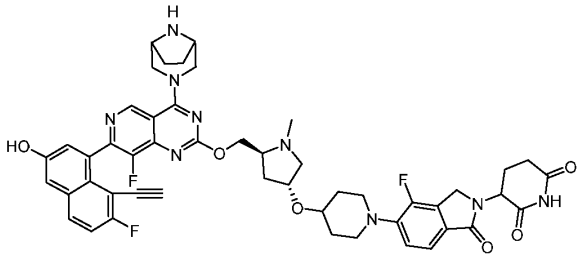
To tert-butyl 3-[2-[[(2S,4R)-4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-4-fluoro-1-oxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]oxy]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (128 mg, 0.11 mmol) in dichloromethane (3 mL) was added 4 M HCl in 1,4-dioxane (3 mL), and the mixture was stirred at 25 °C for 15 min. The reaction mixture was triturated with methyl tert-butyl ether (30 mL), then purified by prep-HPLC (1% to 30% acetonitrile in water (formic acid) over 10 min) to afford the title compound (99 mg, 85%, di-formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1013.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.05 (s, 1H), 8.18 (s, 3H), 7.97 (dd, *J* = 6.0, 9.3 Hz, 1H), 7.55 - 7.43 (m, 2H), 7.39 (d, *J* = 2.5 Hz, 1H), 7.20 - 7.10 (m, 2H), 5.07 (dd, *J* = 5.0, 1Step 3: Hz, 1H), 4.58 - 4.47 (m, 2H), 4.45 (s, 1H), 4.41 - 4.30 (m, 3H), 4.29 - 4.18 (m, 2H), 4.15 - 4.07 (m, 2H), 3.94 (d, *J* = 2.0 Hz, 1H), 3.31 - 3.23 (m, 4H), 2.98 - 2.84 (m, 2H), 2.77 (d, *J* = 1Step 8: Hz, 2H), 2.73 - 2.64 (m, 3H), 2.63 - 2.55 (m, 2H), 2.41 (dd, *J* = 4.6, 13.0 Hz, 2H), 2.36 - 2.32 (m, 3H), 2.22 - 2.12 (m, 3H), 2.07 - 1.94 (m, 3H), 1.92 - 1.84 (m, 2H), 1.83 - 1.71 (m, 7H), 1.68 - 1.56 (m, 1H), 1.49 - 1.33 (m, 2H), 1.31 - 1.17 (m, 2H).

Example 133: Synthesis of 3-(5-{3-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]azetidin-1-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 164**)



The title compound was prepared in an analogous manner to 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione. (light yellow solid). LC/MS (ESI) *m/z*: 967.6 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 7.87 - 7.84 (m, 1H), 7.59 - 7.56 (m,1H), 7.35 - 7.29 (m,2H), 7.21 - 7.20 (m,1H), 6.50 - 6.48 (m, 2H), 5.09 - 5.05 (m, 1H), 4.65 - 4.56 (m, 2H), 4.49 - 4.47 (m, 2H), 4.36 - 4.34 (m, 2H), 4.25 - 4.23 (m, 1H), 4.12 - 4.08 (m, 2H), 3.73 - 3.61 (m, 6H), 3.48 - 3.43 (m, 1H), 3.39 - 3.35 (m, 2H), 3.05 - 2.99 (m, 2H), 2.92 - 2.84 (m, 1H), 2.79 - 2.74 (m, 3H), 2.70 - 2.67 (m, 2H), 2.52 (s, 3H), 2.46 - 2.37 (m, 2H), 2.27 - 2.21 (m, 2H), 2.15 - 2.00 (m, 3H), 1.92 - 1.79 (m, 6H), 1.62 - 1.57 (m, 2H).

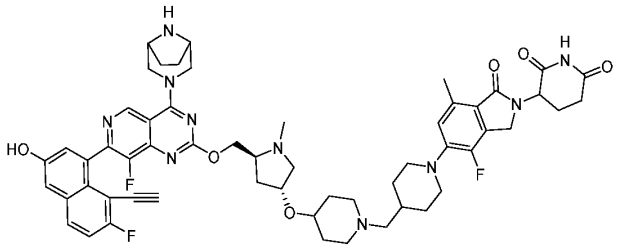
Example 134: Synthesis of 3-[5-(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl]piperidine-2,6-dione (**Compound 103**)



The title compound was prepared in an analogous manner to 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-

fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 917.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.06 (s, 1H), 8.12 (s, 1H), 8.01 – 7.93 (m, 1H), 7.50 – 7.42 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.19 - 7.12 (m, 2H), 7.24 - 7.17 (m, 1H), 7.07 - 6.97 (m, 2H), 5.05 (dd, J = 5.2, 9.2 Hz, 1H), 4.56 - 4.51 (m, 1H), 4.50 - 4.45 (m, 1H), 4.42 - 4.35 (m, 2H), 4.33 – 4.28 (m, 1H), 4.25 – 4.15 (m, 2H), 3.96 – 3.93 (m, 1H), 3.79 – 3.64 (m, 5H), 3.56 – 3.48 (m, 2H), 3.41 - 3.26 (m, 4H), 2.96 - 2.87 (m, 3H), 2.85 - 2.76 (m, 1H), 2.62 - 2.55 (m, 1H), 2.44 - 2.38 (m, 1H), 2.37 (s, 3H), 2.25 – 2.19 (m, 1H), 1.99 – 1.86 (m, 5H), 1.77 – 1.74 (m, 3H), 1.63 – 1.53 (m, 2H).

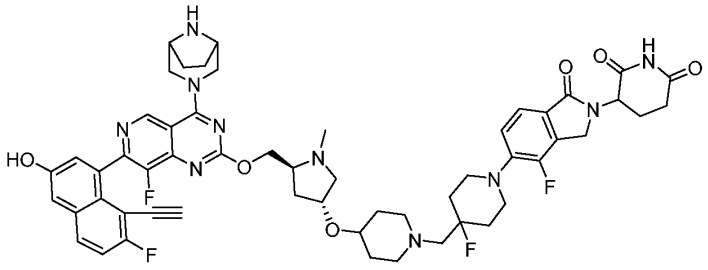
Example 135: Synthesis of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4-fluoro-7-methyl-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 151**)



The title compound was prepared in an analogous manner to 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1027.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.07 (s, 1H), 8.19 (s, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 5.02 (dd, J = 5.2, 13.2 Hz, 1H), 4.57 (br d, J = 12.8 Hz, 1H), 4.45 - 4.33 (m, 3H), 4.30 - 4.19 (m, 2H), 4.13 (quin, J = 5.6 Hz, 1H), 3.95 (d, J = 2.8 Hz, 1H), 3.89 (br s, 2H), 3.81 - 3.69 (m, 2H), 3.47 (br d, J = 8.8 Hz, 2H), 3.37 - 3.22 (m, 2H), 2.96 - 2.77 (m, 2H), 2.77 - 2.64 (m, 4H), 2.63 - 2.54 (m, 1H), 2.52 (s, 3H), 2.47 - 2.38 (m, 1H), 2.36 (s, 3H), 2.25 - 2.16 (m, 3H), 2.14 - 2.02 (m, 2H), 1.99 - 1.85 (m, 3H), 1.85 - 1.73 (m, 8H), 1.66 (br s, 2H), 1.50 - 1.36 (m, 2H), 1.30 - 1.18 (m, 2H).

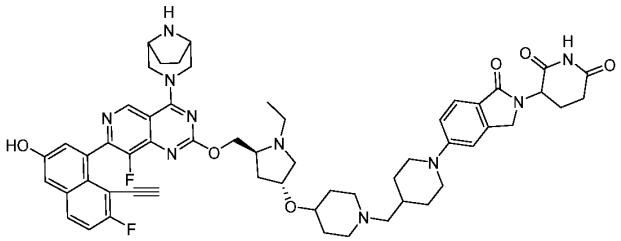
Example 136: Synthesis of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-

methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]-4-fluoropiperidin-1-yl}-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 112**)



The title compound was prepared in an analogous manner to 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1031.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.04 (s, 1H), 8.20 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.50 - 7.43 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.24 - 7.15 (m, 2H), 5.07 (dd, J = 4.8, 13.2 Hz, 1H), 4.52 - 4.45 (m, 2H), 4.41 - 4.29 (m, 3H), 4.24 - 4.20 (m, 1H), 4.14 - 4.09 (m, 1H), 3.94 (d, J = 2.0 Hz, 1H), 3.59 (s, 5H), 3.05 - 2.97 (m, 3H), 2.94 (s, 2H), 2.81 - 2.73 (m, 4H), 2.60 (d, J = 2.8 Hz, 2H), 2.37 - 2.31 (m, 5H), 2.24 - 2.13 (m, 4H), 2.02 - 1.93 (m, 3H), 1.92 - 1.85 (m, 3H), 1.78 (d, J = 8.4 Hz, 4H), 1.72 - 1.65 (m, 4H), 1.45 - 1.34 (m, 2H).

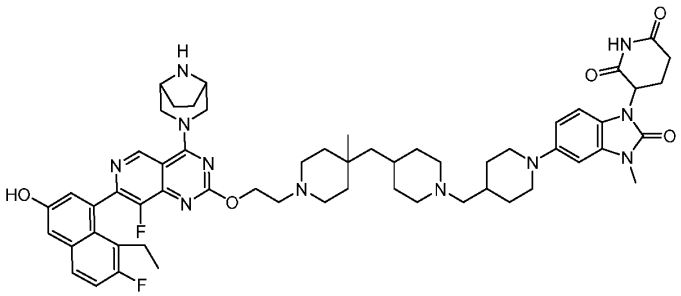
Example 137: Synthesis of 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-ethylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione (**Compound 165**)



The title compound was prepared in an analogous manner to 3-(5-{4-[(4-{[(3R,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-3-yl]oxy}piperidin-1-yl)methyl]piperidin-1-yl}-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1009.8 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6)

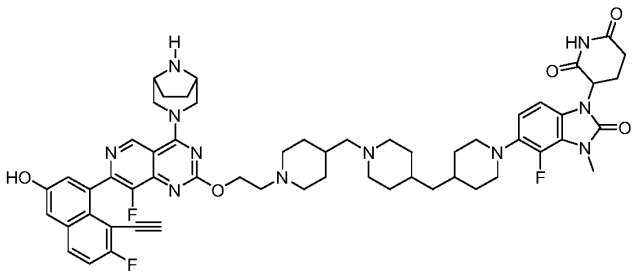
δ 10.98 - 10.91 (m, 1H), 9.06 (s, 1H), 8.16 (s, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.52 - 7.44 (m, 2H), 7.40 (d, J = 2.4 Hz, 1H), 7.18 (s, 1H), 7.06 - 7.00 (m, 2H), 5.07 - 5.00 (m, 1H), 4.54 (br d, J = 12.8 Hz, 1H), 4.42 - 4.34 (m, 2H), 4.31 (br d, J = 17.2 Hz, 1H), 4.22 - 4.12 (m, 3H), 3.94 (s, 1H), 3.86 (br d, J = 12.0 Hz, 2H), 3.79 (br s, 2H), 3.75 - 3.64 (m, 3H), 3.31 - 3.26 (m, 2H), 2.98 (br dd, J = 4.0, 10.0 Hz, 1H), 2.92 (td, J = 5.2, 8.0 Hz, 2H), 2.80 (br t, J = 11.6 Hz, 2H), 2.72 - 2.66 (m, 2H), 2.60 (br s, 1H), 2.37 (br d, J = 5.2 Hz, 1H), 2.21 - 2.12 (m, 3H), 2.03 (br dd, J = 8.4, 12.0 Hz, 2H), 1.98 - 1.93 (m, 1H), 1.90 - 1.84 (m, 2H), 1.82 - 1.70 (m, 9H), 1.45 - 1.35 (m, 2H), 1.21 - 1.12 (m, 2H), 1.03 - 0.96 (m, 3H).

Example 138: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-4-methylpiperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 179**)



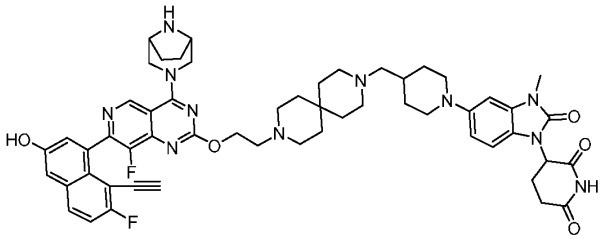
The title compound was prepared in an analogous manner to 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione. (white solid, formic acid salt.) LC/MS (ESI) *m/z*: 1040.6 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 - 10.94 (m, 1H), 9.10 (s, 1H), 8.22 (s, 2H), 7.76 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.39 - 7.27 (m, 2H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.96 - 6.87 (m, 1H), 6.84 - 6.75 (m, 1H), 6.67 - 6.55 (m, 1H), 5.27 (br dd, *J* = 5.6, 12.8 Hz, 1H), 4.54 - 4.39 (m, 4H), 3.55 (br d, *J* = 12.0 Hz, 7H), 3.31 - 3.27 (m, 3H), 2.95 - 2.83 (m, 1H), 2.79 (br d, *J* = 10.8 Hz, 2H), 2.72 (br t, *J* = 5.6 Hz, 2H), 2.69 - 2.65 (m, 1H), 2.64 - 2.54 (m, 5H), 2.52 (br d, *J* = 2.0 Hz, 2H), 2.42 - 2.31 (m, 3H), 2.21 - 2.09 (m, 3H), 2.03 - 1.88 (m, 3H), 1.76 (br d, *J* = 12.8 Hz, 2H), 1.72 - 1.65 (m, 3H), 1.59 (br d, *J* = 11.2 Hz, 3H), 1.41 - 1.16 (m, 8H), 1.13 (br d, *J* = 4.4 Hz, 2H), 0.87 (s, 3H), 0.72 (t, *J* = 7.6 Hz, 3H).

Example 139: Synthesis of 3-{5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-4-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 166**)



The title compound was prepared in an analogous manner to 3-{5-[4-({1-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-4-yl}methyl)piperidin-1-yl]-2-oxo-3-(propan-2-yl)-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione. (yellow solid, formic acid salt.) LC/MS (ESI) *m/z*: 1040.4 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H), 9.04 (s, 1H), 7.99 - 7.95 (m, 1H), 7.54 - 7.35 (m, 2H), 7.17 (d, *J* = 2.4 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.71 (t, *J* = 8.0 Hz, 1H), 5.37 - 5.24 (m, 1H), 4.54 - 4.42 (m, 3H), 4.35 (d, *J* = 12.0 Hz, 1H), 3.93 (s, 1H), 3.66 (s, 5H), 3.20 (d, *J* = 10.8 Hz, 4H), 2.97 - 2.79 (m, 6H), 2.72 - 2.57 (m, 7H), 2.26 (s, 1H), 2.13 (br d, *J* = 6.4 Hz, 2H), 2.06 - 1.96 (m, 3H), 1.88 (t, *J* = 10.8 Hz, 2H), 1.71 (s, 5H), 1.62 (t, *J* = 11.8 Hz, 4H), 1.52 - 1.39 (m, 2H), 1.36 - 1.21 (m, 3H), 1.19 - 1.02 (m, 6H).

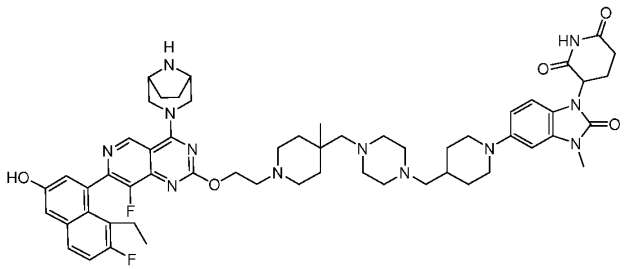
Example 140: Synthesis of 3-(5-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione (**Compound 171**)



The title compound was prepared in an analogous manner to 3-(5-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (yellow solid, formic acid salt.) LC/MS (ESI) *m/z*: 998.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.11 (s, 1H), 8.20 (s, 3H), 7.76 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.40 - 7.30 (m, 2H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.62 (dd, *J* = 2.0, 8.8 Hz, 1H), 5.28 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.54 - 4.39 (m, 5H), 3.83 - 3.62 (m, 5H), 3.56 (d, *J* = 12.0 Hz, 2H), 3.29 (s, 3H), 2.94 - 2.83 (m, 1H), 2.78 - 2.66 (m, 3H), 2.64 - 2.56 (m, 3H), 2.47 (s, 3H),

2.43 - 2.31 (m, 5H), 2.24 (d, *J* = 6.8 Hz, 2H), 2.18 - 2.09 (m, 1H), 2.02 - 1.94 (m, 1H), 1.82 - 1.58 (m, 7H), 1.42 (s, 8H), 1.30 - 1.15 (m, 3H), 0.72 (t, *J* = 7.2 Hz, 3H).

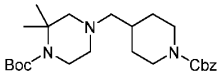
Example 141: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-4-methylpiperidin-4-yl)methyl]piperazin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 180**)



The title compound was prepared in an analogous manner to 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione. (yellow solid, formic acid salt.) LC/MS (ESI) *m/z*: 1041.3 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (br s, 1H), 9.12 (s, 1H), 8.22 (s, 2H), 7.77 (dd, J = 6.0, 9.2 Hz, 1H), 7.39 - 7.31 (m, 2H), 7.02 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 2.0, 8.8 Hz, 1H), 5.29 (dd, J = 5.2, 12.8 Hz, 1H), 4.55 - 4.39 (m, 4H), 3.77 - 3.66 (m, 3H), 3.56 (br d, J = 11.6 Hz, 2H), 3.30 (s, 3H), 3.00 - 2.67 (m, 2H), 2.55 (s, 4H), 2.47 (br d, J = 4.0 Hz, 7H), 2.41 - 2.27 (m, 8H), 2.20 - 2.03 (m, 6H), 2.01 - 1.94 (m, 1H), 1.79 - 1.68 (m, 6H), 1.63 - 1.54 (m, 1H), 1.51 - 1.42 (m, 2H), 1.22 (br d, J = 8.0 Hz, 4H), 0.85 (s, 3H), 0.73 (t, J = 7.2 Hz, 3H).

Example 142: Synthesis of 3-{5-[4-({4-[(4-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,3-dimethylpiperazin-1-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 162**)

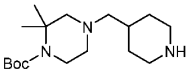
Step 1: Preparation of *tert*-butyl 4-[(1-benzyloxycarbonyl-4-piperidyl)methyl]-2,2-dimethyl-piperazine-1-carboxylate



To a solution of *tert*-butyl 2,2-dimethylpiperazine-1-carboxylate (10 g, 47 mmol) in dichloromethane (250 mL) were added benzyl 4-formylpiperidine-1-carboxylate (12.5 g, 50 mmol), acetic acid (1.3 mL, 23 mmol), and sodium triacetoxyborohydride (19.8 g, 93 mmol),

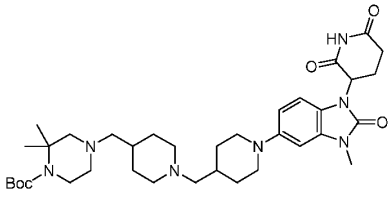
and the reaction mixture was stirred at 25 °C for 16 h. The reaction was diluted with saturated aqueous sodium bicarbonate solution (50 mL) and extracted with dichloromethane (300 mL × 3). The combined organic layers were washed with and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (acetonitrile in water (formic acid)) to afford the title compound (20 g, 96%) as a colorless oil. LC/MS (ESI) *m/z*: 446.3 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.29 (m, 5H), 5.13 (s, 2H), 4.25 - 4.14 (m, 2H), 3.49 - 3.32 (m, 2H), 2.78 (s, 2H), 2.36 (t, *J* = 5.6 Hz, 2H), 2.12 (s, 3H), 1.77 (d, *J* = 13.2 Hz, 2H), 1.70 - 1.60 (m, 2H), 1.46 (s, 9H), 1.37 (s, 6H), 1.18 - 1.02 (m, 2H).

Step 2: Preparation of *tert*-butyl 2,2-dimethyl-4-(4-piperidylmethyl)piperazine-1-carboxylate



To a solution of *tert*-butyl 4-[(1-benzyloxycarbonyl-4-piperidyl)methyl]-2,2-dimethyl-piperazine-1-carboxylate (23.4 g, 52 mmol) in tetrahydrofuran (300 mL) was added 10% palladium on carbon (4 g) under nitrogen, and the resulting mixture was degassed under vacuum and purged with hydrogen, then stirred under hydrogen (50 psi) at 40 °C for 20 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure to afford the title compound (16 g, crude) as a brown oil. LC/MS (ESI) *m/z*: 312.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.45 - 3.37 (m, 2H), 3.09 (d, *J* = 12.0 Hz, 2H), 2.60 (dt, *J* = 2.4, 12.0 Hz, 2H), 2.40 - 2.31 (m, 2H), 2.13 - 2.08 (m, 4H), 2.03 (s, 1H), 1.76 (d, *J* = 12.0 Hz, 2H), 1.58 (tdd, *J* = 3.6, 7.2, 14.8 Hz, 1H), 1.46 (s, 9H), 1.37 (s, 6H), 1.17 - 1.05 (m, 2H).

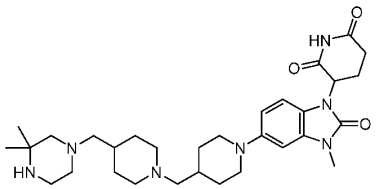
Step 3: Preparation of *tert*-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-2,2-dimethyl-piperazine-1-carboxylate



To a solution of *tert*-butyl 2,2-dimethyl-4-(4-piperidylmethyl)piperazine-1-carboxylate (360 mg, 1.2 mmol) in dichloromethane (15 mL) and dimethyl sulfoxide (5 mL) were added 1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde trifluoroacetate (500 mg, 1 mmol), *N,N*-diisopropylethylamine (0.7 mL, 4 mmol), and sodium triacetoxyborohydride (438 mg, 2 mmol), and the reaction mixture was stirred at 25 °C for 1 h. The mixture was diluted with saturated aqueous sodium bicarbonate solution (20 mL) and extracted with dichloromethane (50 mL x 2). The combined organic extracts were washed with

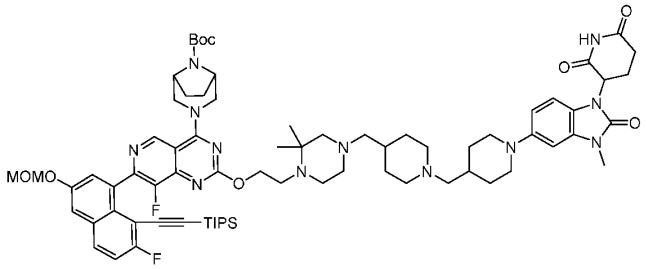
brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with methyl *tert*-butyl ether (40 mL) to afford the title compound (680 mg, crude) as an off-white solid. LC/MS (ESI) *m/z*: 666.5 $[M+H]^+$.

Step 4: Preparation of 3-[5-[4-[[4-[(3,3-dimethylpiperazin-1-yl) methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxobenzimidazol-1-yl]piperidine-2,6-dione



To a solution of *tert*-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol -5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-2,2-dimethyl-piperazine-1-carboxylate (680 mg, 1 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (5.0 mL, 67 mmol), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by prep-HPLC (acetonitrile in water (formic acid)) to afford the title compound (420 mg, 58%, 3 formic acid salt) as a colorless oil. LC/MS (ESI) *m/z*: 566.4 $[M+H]^+$.

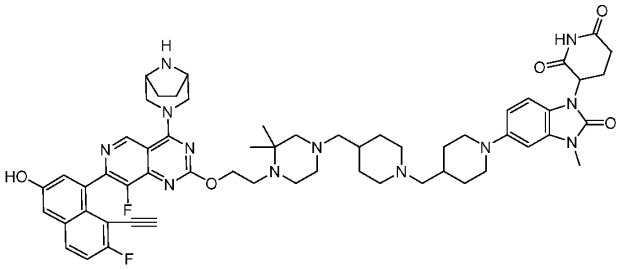
Step 5: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-\3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-2,2-dimethyl-piperazin-1-yl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a mixture of 3-[5-[4-[[4-[(3,3-dimethylpiperazin-1-yl) methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxobenzimidazol-1-yl]piperidine-2,6-dione (171 mg, 0.2 mmol, 3 formate) and *tert*-butyl-3-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (234 mg, 0.3 mmol) in dimethyl sulfoxide (3 mL) and dichloromethane (3 mL) were added *N,N*-diisopropylethylamine (171 mg, 1.3 mmol) and titanium(IV) isopropylate (0.1 mL, 0.5 mol), and the mixture was allowed to stir at 45 °C for 3 h. Sodium triacetoxyborohydride (103 mg, 0.5 mmol) was then added, and the reaction mixture

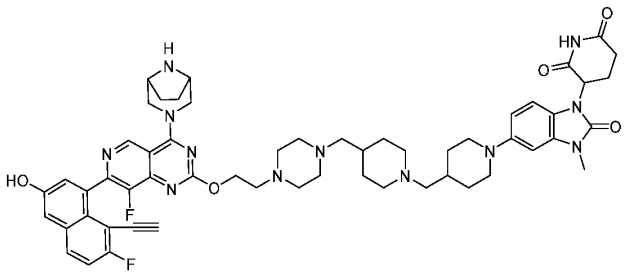
was stirred at 45 °C for 6 h. The mixture was diluted with ethyl acetate (50 mL) and washed with brine (20 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (dichloromethane/methanol = 100/1 to 10/1) to afford the title compound (200 mg, 61%) as a yellow solid. LC/MS (ESI) *m/z*: 676.7 $[M/2+H]^+$.

Step 6: Preparation of 3-{5-[4-({4-[(4-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,3-dimethylpiperazin-1-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione



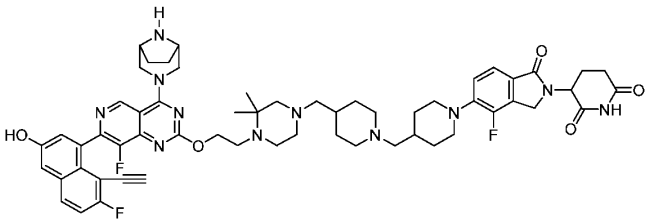
The title compound can be prepared in an analogous manner to step 17 and 18 of 3-(5-{4-[(9-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}-4-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1051.6 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.04 (s, 1H), 8.23 (s, 2H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 1.6 Hz, 1H), 6.65 - 6.57 (m, 1H), 5.28 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.52 - 4.46 (m, 1H), 4.38 - 4.29 (m, 3H), 3.91 (s, 1H), 3.65 (s, 8H), 3.56 (d, *J* = 12.4 Hz, 5H), 3.29 (s, 3H), 2.89 - 2.79 (m, 3H), 2.67 - 2.56 (m, 6H), 2.18 (d, *J* = 6.8 Hz, 2H), 2.03 - 1.94 (m, 4H), 1.89 (t, *J* = 11.2 Hz, 2H), 1.77 (d, *J* = 11.2 Hz, 2H), 1.72 - 1.57 (m, 7H), 1.44 (d, *J* = 4.0 Hz, 1H), 1.28 - 1.17 (m, 2H), 1.15 - 1.03 (m, 2H), 0.98 (s, 6H).

Example 143: Synthesis of 3-{5-[4-({4-[(4-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperazin-1-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 173**)



The title compound was prepared in an analogous manner to 3-{5-[4-({4-[(4-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,3-dimethylpiperazin-1-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1023.6 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.05 (s, 1H), 8.21 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 2.0, 8.8 Hz, 1H), 5.28 (dd, J = 5.2, 12.8 Hz, 1H), 4.52 (d, J = 12.4 Hz, 1H), 4.45 (t, J = 5.6 Hz, 2H), 4.41 - 4.34 (m, 1H), 3.92 (s, 1H), 3.77 - 3.60 (m, 4H), 3.56 (d, J = 11.6 Hz, 2H), 3.30 (s, 3H), 2.95 - 2.80 (m, 3H), 2.72 - 2.67 (m, 2H), 2.66 - 2.54 (m, 4H), 2.49-2.47 (m, 4H), 2.33 (d, J = 1.6 Hz, 4H), 2.22 (d, J = 6.8 Hz, 2H), 2.10 (d, J = 6.8 Hz, 2H), 2.00 - 1.88 (m, 3H), 1.65 (d, J = 10.4 Hz, 3H), 1.85 - 1.57 (m, 6H), 1.47 (s, 1H), 1.31 - 1.18 (m, 2H), 1.15 - 1.05 (m, 2H).

Example 144: Synthesis of 3-{5-[4-({4-[(4-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,3-dimethylpiperazin-1-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 174**)

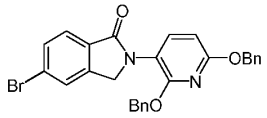


The title compound was prepared in an analogous manner to 3-{5-[4-({4-[(4-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-3,3-dimethylpiperazin-1-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione. (off-white solid). LC/MS (ESI) *m/z*: 1054.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 10.24 - 10.06 (m, 1H), 9.03 (s, 1H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.50 - 7.42 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.20 - 7.11 (m, 2H), 5.06 (dd, J = 5.2, 13.2 Hz, 1H), 4.52 - 4.42

(m, 2H), 4.37 - 4.26 (m, 4H), 3.91 (s, 1H), 3.66 - 3.55 (m, 4H), 3.52 - 3.41 (m, 3H), 2.96 - 2.71 (m, 6H), 2.61 (br s, 3H), 2.56 (br d, J = 1.6 Hz, 1H), 2.47 - 2.35 (m, 2H), 2.15 (br d, J = 4.0 Hz, 2H), 2.09 - 1.93 (m, 5H), 1.92 - 1.71 (m, 5H), 1.71 - 1.60 (m, 7H), 1.48 - 1.38 (m, 1H), 1.30 - 1.19 (m, 2H), 1.16 - 1.03 (m, 2H), 0.97 (s, 6H).

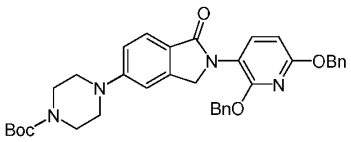
Example 145: Synthesis of [(2S,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-2-yl]methyl 4-[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazine-1-carboxylate (**Compound 114**)

Step 1: Preparation of 5-bromo-2-(2,6-dibenzyloxy-3-pyridyl)isoindolin-1-one



To a solution of 2,6-dibenzyloxypyridin-3-amine (5.0 g, 16 mmol) and methyl 4-bromo-2-(bromomethyl)benzoate (5.03 g, 16 mmol) in *N,N*-dimethylacetamide (50 mL) was added diisopropylethylamine (8.5 mL, 49 mmol), and the mixture was stirred at 120 °C for 12 h. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (60%-90% acetonitrile in water (trifluoroacetic acid) over 23min) to afford the title compound (6.02 g, 74%) as a dark brown solid. LC/MS (ESI) m/z: 501.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.72 - 7.71 (m, 1H), 7.43 - 7.28 (m, 11H), 6.55 (d, J = 8.4 Hz, 1H), 5.40 (s, 2H), 5.34 (s, 2H), 4.78 (s, 2H).

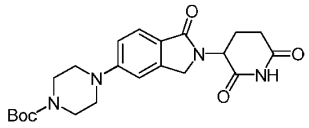
Step 2: Preparation of tert-butyl 4-[2-(2,6-dibenzyloxy-3-pyridyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate



To a solution of 5-bromo-2-(2,6-dibenzyloxy-3-pyridyl)isoindolin-1-one (900 mg, 1.8 mmol) and *tert*-butyl piperazine-1-carboxylate (334 mg, 1.8 mmol) in dioxane (10 mL) were added [2-(2-aminophenyl)phenyl]-chloro-palladium;dicyclohexyl-[3-(2,4,6-triisopropylphenyl)phenyl]phosphane (141 mg, 0.18 mmol) and cesium carbonate (1.17 g, 3.6 mmol), and the mixture was stirred at 100 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1 to 1/1) to afford the title compound (623

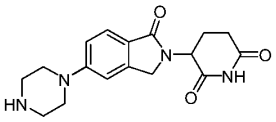
mg, 57%) as a white solid. LC/MS (ESI) m/z: 607.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.44 - 7.28 (m, 10H), 7.14 - 7.06 (m, 2H), 6.53 (d, J = 8.4 Hz, 1H), 5.40 (s, 2H), 5.35 (s, 2H), 4.68 (s, 2H), 3.50 - 3.44 (m, 4H), 3.32 - 3.28 (m, 4H), 1.43 (s, 9H).

Step 3: Preparation of tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate



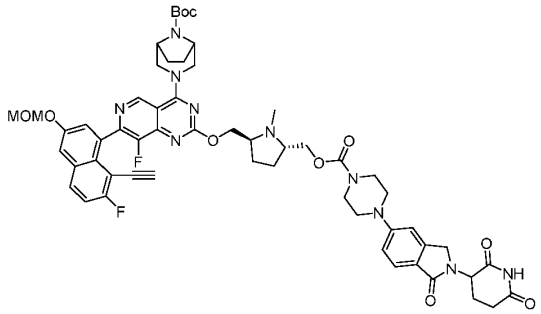
To a solution of tert-butyl 4-[2-(2,6-dibenzyloxy-3-pyridyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (673 mg, 1 mmol) in tetrahydrofuran (10 mL) was added 10% palladium on carbon (100 mg), and the resulting misture was degassed in vacuum and purged with hydrogen several times, then stirred under hydrogen (50 Psi) at 50 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to afford the title compound (480 mg, crude) as a white solid. LC/MS (ESI) m/z: 429.4 $[M+H]^+$.

Step 4: Preparation of 3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione



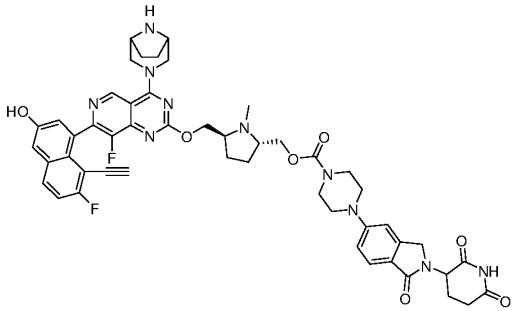
To a solution of tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (480 mg, 1.1 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.08 mL, 1 mmol), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (0%-16% acetonitrile in water (formic acid) over 10 min) to afford the title compound (366 mg, 96%, formic acid salt) as a white solid. LC/MS(ESI) m/z: 329.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 8.81 - 8.75 (m, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.24 - 7.10 (m, 2H), 5.07 (dd, J = 5.2, 13.2 Hz, 1H), 4.41 - 4.19 (m, 2H), 3.52 - 3.48 (m, 4H), 3.26 (s, 4H), 2.97 - 2.87 (m, 1H), 2.64 - 2.57 (m, 1H), 2.43 - 2.36 (m, 1H), 2.03 - 1.94 (m, 1H).

Step 5: Preparation of tert-butyl 3-[2-[[(2S,5S)-5-[[4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carbonyl]oxymethyl]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of tert-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S,5S)-1-methyl-5-[(4-nitrophenoxy)carbonyloxymethyl]pyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (490 mg, 0.5 mmol) in tetrahydrofuran (5 mL) at 0 °C were added dimethylaminopyridine (7 mg, 0.05 mmol), triethylamine (0.2 mL, 2 mmol), and 3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione formate (208 mg, 0.55 mmol), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (27%-57% acetonitrile in water (formic acid) over 10 min) to afford the title compound (220 mg, 37%) as a yellow solid. LC/MS (ESI) m/z: 1085.8 $[M+H]^+$.

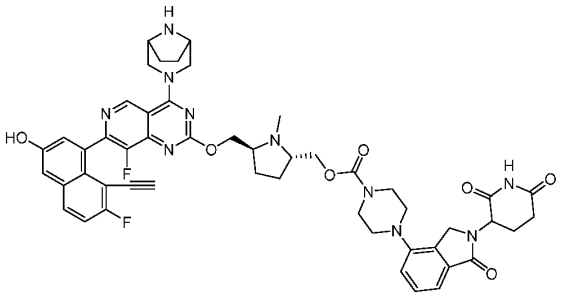
Step 6: Preparation of [(2S,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-2-yl]methyl 4-[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazine-1-carboxylate



To a solution of tert-butyl 3-[2-[[(2S,5S)-5-[[4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazine-1-carbonyl]oxymethyl]-1-methyl-pyrrolidin-2-yl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (220 mg, 0.2 mmol) in dichloromethane (1 mL) was added 4 M hydrochloric acid in dioxane (0.05 mL), and the mixture was stirred at 25 °C for 10 min. The reaction mixture was concentrated under reduced pressure, and the residue was purified by prep-HPLC (4%-34% acetonitrile in water (formic acid) over 10 min) to afford the title compound (57.0 mg, 28%, formic acid salt) as a yellow solid. LC/MS (ESI) m/z: 941.2 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 - 10.89 (m, 1H), 9.02 (t, J = 2.8 Hz, 1H), 8.16 (d, J = 3.2 Hz, 1H), 7.96 (dd, J = 6.0, 9.6 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 8.8 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.08 - 7.00 (m, 2H), 5.06 - 5.00 (m, 1H), 4.49 - 4.39 (m, 2H), 4.31 (d, J = 16.8 Hz, 2H), 4.24 - 4.16 (m, 2H), 4.04 (t, J = 5.2 Hz, 2H), 3.92 (s, 1H), 3.66 - 3.58 (m, 6H), 3.51 (d, J = 1.6 Hz, 6H), 3.19 - 3.14 (m, 4H), 2.95 - 2.83 (m, 2H), 2.60 - 2.56 (m, 2H), 2.35 (d, J = 4.0 Hz, 1H), 2.02 - 1.90 (m, 3H), 1.67 (s, 5H), 1.63 - 1.58 (m, 1H).

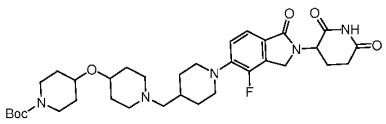
Example 146: Synthesis of [(2S,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-2-yl]methyl 4-[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]piperazine-1-carboxylate (**Compound 117**)



The title compound was made in an analogous manner to [(2S,5S)-5-{[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]methyl}-1-methylpyrrolidin-2-yl]methyl 4-[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazine-1-carboxylate. (yellow solid). LC/MS (ESI) *m/z*: 941.6 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.08 - 8.97 (m, 1H), 8.17 (s, 1H), 7.97 (dd, J = 5.6, 9.2 Hz, 1H), 7.50 - 7.40 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.20 - 7.14 (m, 2H), 5.12 (dd, J = 5.2, 13.2 Hz, 1H), 4.52 - 4.40 (m, 3H), 4.37 - 4.27 (m, 2H), 4.26 - 4.19 (m, 1H), 4.11 - 4.03 (m, 2H), 3.92 (s, 1H), 3.64 (s, 4H), 3.53 (s, 2H), 3.24 - 3.22 (m, 2H), 3.16 (d, J = 2.0 Hz, 2H), 3.06 - 3.00 (m, 4H), 2.92 - 2.87 (m, 1H), 2.64 - 2.54 (m, 2H), 2.51 - 2.51 (m, 3H), 2.45 - 2.40 (m, 1H), 2.04 - 1.95 (m, 3H), 1.70 (s, 6H).

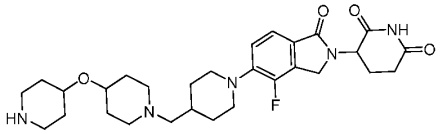
Example 147: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)oxy]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 106**)

Step 1: Preparation of *tert*-butyl 4-((1-((1-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin- 5-yl)piperidin-4-yl)methyl)piperidin-4-yl)oxy)piperidine-1-carboxylate



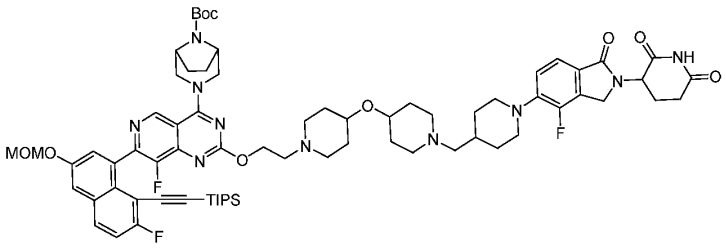
To a solution of 1-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)piperidine- 4-carbaldehyde (400 mg, 1.1 mmol) and *tert*-butyl 4-(piperidin-4-yloxy) piperidine-1-carboxylate (305 mg, 1.1 mmol) in dichloromethane (4 mL) and dimethyl sulfoxide (4 mL) was added acetic acid (0.12 mL), and the mixture was stirred at 25 °C for 10 min. Sodium triacetoxyborohydride (454 mg, 2.1 mmol) was then added, and the mixture was stirred at 25 °C for 30 min. The reaction mixture was diluted with water (30 mL) and extracted with chloroform/isopropanol (5:1, 30 mL x 2). The combined organic extracts were washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (0-100% ethyl acetate/petroleum ether, then 0-15% dichloromethane/methanol) to afford the title compound (610 mg, 89%) as a white solid. LC/MS (ESI) *m/z*: 642.2 $[M+H]^+$.

Step 2: Preparation of 3-(4-fluoro-1-oxo-5-(4-((4-(piperidin-4-yloxy)piperidin-1-yl)methyl) piperidin-1-yl)isoindolin-2-yl)piperidine-2,6-dione



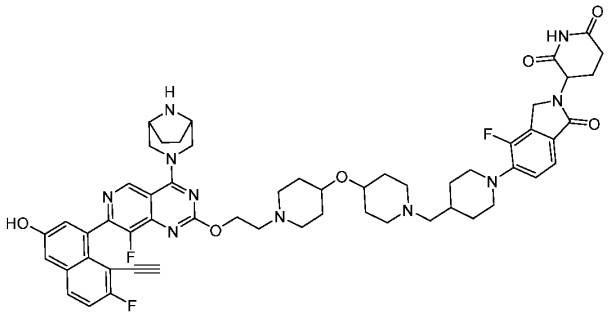
To a solution of *tert*-butyl 4-((1-((1-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)piperidin-4-yl)methyl)piperidin-4-yl)oxy)piperidine-1-carboxylate (350 mg, 0.55 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (3.5 mL), and the mixture was stirred at 25 °C for 30 min. The reaction mixture was concentrated under reduced pressure to afford the title compound (350 mg, crude, TFA salt) as a brown oil.

Step 3: Preparation of *tert*-butyl (1*R*,5*S*)-3-(2-(2-(4-((1-((1-(2-(2,6- dioxopiperidin-3-yl)-4-fluoro-1-oxoisoindolin-5-yl)piperidin-4-yl)methyl)piperidin-4-yl)oxy)piperidin-1-yl)ethoxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 3-(4-fluoro-1-oxo-5-(4-((4-(piperidin-4-yloxy)piperidin-1-yl)methyl) piperidin-1-yl)isoindolin-2-yl)piperidine-2,6-dione trifluoroacetate (350 mg, 0.5 mmol) in dichloromethane (4 mL) and isopropanol (4 mL) was added *N,N*-diisopropylethylamine (0.28 mL, 1.6 mmol), and the mixture was stirred at 25 °C for 10 minutes. *tert*-Butyl-3-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (728 mg, 0.9 mmol) and acetic acid (0.06 mL, 1 mmol) were then added, and the resulting mixture was stirred for 20 minutes. Sodium triacetoxyborohydride (226 mg, 1 mmol) was then added, and the reaction mixture was stirred at 25 °C for 1 h. The mixture was diluted with water (30 mL) and extracted with chloroform/isopropanol (5: 1, 30 mL x 2). The combined organic layers were washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (0-100% ethyl acetate/petroleum ether, then 0-15% dichloromethane/methanol) to afford the title compound (430 mg, 61%) as a brown oil. LC/MS (ESI) *m/z*: 1328.6 $[M+H]^+$.

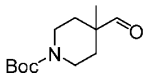
Step 4: Preparation of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)oxy]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione



The title compound can be prepared in an analogous manner to step 4 and 5 of 3-(5-(4-((4-((1-(2-((4-(-3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)ethyl)piperidin-4-yl)methyl)piperidin-1-yl)methyl)piperidin-1-yl)-4-chloro-1-oxoisoindolin-2-yl)piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1028.3 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.05 (s, 1H), 8.21 (s, 2H), 7.98 (dd, *J* = 5.8, 9.2 Hz, 1H), 7.51 - 7.42 (m, 2H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.20 - 7.10 (m, 2H), 5.07 (dd, *J* = 5.2, 13.2 Hz, 1H), 4.55 - 4.43 (m, 4H), 4.39 - 4.27 (m, 3H), 3.94 (s, 1H), 3.76 - 3.71 (m, 2H), 3.69 - 3.62 (m, 2H), 3.52 - 3.44 (m, 2H), 3.39 (s, 2H), 3.16 (s, 2H), 2.97 - 2.85 (m, 1H), 2.83 - 2.64 (m, 8H), 2.62 - 2.54 (m, 1H), 2.44 - 2.31 (m, 1H), 2.17 (d, *J* = 6.4 Hz, 3H), 2.08 - 1.94 (m, 3H), 1.75 (s, 9H), 1.69 - 1.59 (m, 1H), 1.47 - 1.32 (m, 4H), 1.31 - 1.17 (m, 2H).

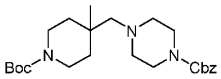
Example 148: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-4-methylpiperidin-4-yl)methyl]piperazin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 160**)

Step 1: Preparation of tert-butyl 4-formyl-4-methyl-piperidine-1-carboxylate



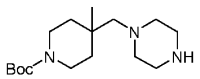
To a solution of *tert*-butyl 4-(hydroxymethyl)-4-methylpiperidine-1-carboxylate (5.0 g, 22 mmol) in dichloromethane (80 mL) were added Dess-Martin reagent (13.8 g, 33 mmol) and sodium bicarbonate (3.7 g, 44 mmol), and the mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with water/sodium bicarbonate/sodium sulfite (1:1:1, 180 mL), then extracted with dichloromethane (100 mL). The organic extract was washed with sodium bicarbonate (100 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 6/1 to 3/1) to afford the title compound (4 g, 80%) as a yellow oil.

Step 2: Preparation of benzyl 4-[(1-*tert*-butoxycarbonyl-4-methyl-4-piperidyl)methyl]piperazine-1-carboxylate



To a solution of *tert*-butyl 4-formyl-4-methyl-piperidine-1-carboxylate (3.1 g, 14 mmol) and benzyl piperazine-1-carboxylate (2.2 mL, 11 mmol) in dichloromethane (35 mL) were added chloro(triisopropoxy)titanium (5.7 mL, 17 mmol) and sodium triacetoxyborohydride (7.2 g, 34 mmol), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1 to 4/1) to afford the title compound (3.4 g, 69%) as a yellow oil. LC/MS (ESI) *m/z*: 432.2 $[M+H]^+$.

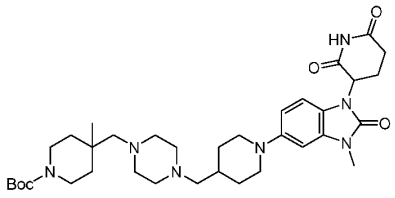
Step 3: Preparation of *tert*-butyl 4-methyl-4-(piperazin-1-ylmethyl)piperidine-1-carboxylate



To a solution of benzyl 4-[(1-*tert*-butoxycarbonyl-4-methyl-4-piperidyl)methyl]piperazine-1-carboxylate (3.4 g, 8 mmol) in tetrahydrofuran (30 mL) were added 10% palladium on carbon (500 mg) and 20% palladium hydroxide on carbon (500 mg), and the suspension was degassed under vacuum and purged with hydrogen, then stirred at 50 °C for 16 h under hydrogen (50

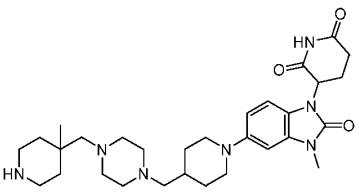
psi). The reaction mixture was filtered and concentrated under reduced pressure to afford the title compound (2.3 g, crude) as a yellow oil. LC/MS (ESI) *m/z*: 298.3 $[M+H]^+$.

Step 4: Preparation of *tert*-butyl 4-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-4-methyl-piperidine-1-carboxylate



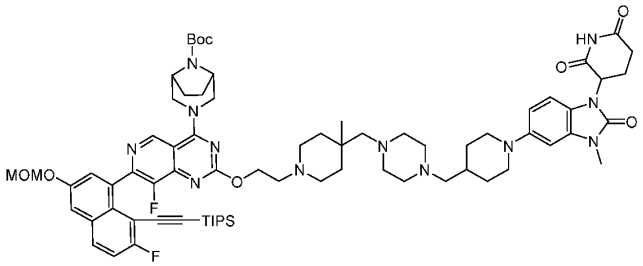
To a solution of *tert*-butyl 4-methyl-4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (2.2 g, 7.4 mmol) and 1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (2.7 g, 7.4 mmol) in dichloromethane (15 mL) and isopropanol (15 mL) were added sodium triacetoxyborohydride (4.7 g, 22 mmol) and acetic acid (0.4 mL, 7 mmol), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1 to 5/1) to afford the title compound (4.0 g, 82%) as a yellow solid. LC/MS (ESI) *m/z*: 652.4 $[M+H]^+$.

Step 5: Preparation of 3-[3-methyl-5-[4-[[4-[(4-methyl-4-piperidyl)methyl]piperazin-1-yl]methyl]-1-piperidyl]-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



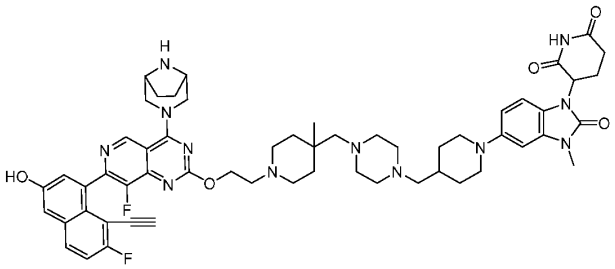
To a solution of *tert*-butyl 4-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-4-methyl-piperidine-1-carboxylate (4 g, 6 mmol) in dichloromethane (30 mL) was added trifluoroacetic acid (10.0 mL, 135 mmol), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by prep-HPLC (1%-30% acetonitrile in water (formic acid) over 9 min) to afford the title compound (2 g, 54%, formic acid salt) as a yellow solid.

Step 6: Preparation of *tert*-butyl 3-[2-[2-[4-[[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-4-methyl-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1] octane-8-carboxylate



To a solution of 3-[3-methyl-5-[4-[[4-[(4-methyl-4-piperidyl)methyl]piperazin-1-yl]methyl]-1-piperidyl]-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione formate (300 mg, 0.5 mmol) in dichloromethane (4 mL) and isopropanol (4 mL) were added *N,N*-diisopropylethylamine (0.1 mL, 0.6 mmol), acetic acid (45 mg, 0.75 mmol), *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (483 mg, 0.6 mmol), and sodium triacetoxyborohydride (319 mg, 1.5 mmol), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (dichloromethane/methanol = 6/1) to afford the title compound (570 mg, 84%) as a yellow solid. LC/MS (ESI) *m/z*: 1337.6 $[M+H]^+$.

Step 7: Preparation of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-4-methylpiperidin-4-yl)methyl]piperazin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione

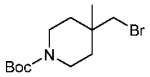


The title compound can be prepared in an analogous manner to step 4 and 5 of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-fluoro-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1037.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (br s, 1H), 9.06 (s, 1H), 8.21 (s, 2H), 8.05 - 7.92 (m, 1H), 7.47 (t, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.83 - 6.77 (m, 1H), 6.62 (dd, J = 2.0, 8.8 Hz, 1H), 5.29 (dd, J = 5.6, 12.8 Hz, 1H), 4.53 (br d, J = 12.4 Hz, 1H), 4.47 (br t, J = 5.2 Hz, 2H), 4.38 (br d, J = 12.4 Hz, 1H), 3.94 (s, 2H), 3.74 (br d, J = 10.0 Hz, 4H), 3.67 (br d, J = 14.4 Hz, 3H), 3.56

(br d, J = 11.6 Hz, 2H), 3.30 (s, 4H), 2.95 - 2.84 (m, 1H), 2.76 (br s, 2H), 2.63 - 2.62 (m, 1H), 2.69 - 2.57 (m, 6H), 2.47 (br s, 3H), 2.40 - 2.31 (m, 6H), 2.14 (br d, J = 6.8 Hz, 2H), 2.09 (s, 2H), 2.03 - 1.95 (m, 1H), 1.76 (br s, 6H), 1.65 - 1.55 (m, 1H), 1.47 - 1.47 (m, 1H), 1.47 (br d, J = 9.2 Hz, 2H), 1.22 (br d, J = 11.2 Hz, 4H), 0.85 (s, 3H).

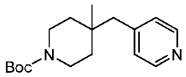
Example 149: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-4-methylpiperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione (**Compound 161**)

Step 1: Preparation of *tert*-butyl 4-(bromomethyl)-4-methyl-piperidine-1-carboxylate



To a solution of *tert*-butyl 4-(hydroxymethyl)-4-methyl-piperidine-1-carboxylate (17 g, 74 mmol) in tetrahydrofuran (300 mL) was added triphenyl phosphine (23.33 g, 89 mmol), and the mixture was stirred at 20 °C for 0.5 h. Carbon tetrabromide (27.04 g, 82 mmol) in tetrahydrofuran (100 mL) was then added dropwise at 0 °C, and the reaction mixture was stirred at 50 °C for 12 h under nitrogen. The reaction mixture was diluted with water (200 mL), then extracted with ethyl acetate (200 mL x 3). The combined organic extract was washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/0 to 10/1) to afford the title compound (20 g, 92%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (br d, *J* = 13.6 Hz, 2H), 3.36 - 3.30 (m, 2H), 3.16 (ddd, *J* = 4.0, 9.6, 13.6 Hz, 2H), 1.56 - 1.46 (m, 2H), 1.46 (s, 9H), 1.43 - 1.37 (m, 2H), 1.07 (s, 3H).

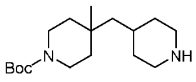
Step 2: Preparation of *tert*-butyl 4-methyl-4-(4-pyridylmethyl)piperidine-1-carboxylate



4-Bromopyridine (4.92 g, 31 mmol), *tert*-butyl 4-(bromomethyl)-4-methyl-piperidine-1-carboxylate (7.0 g, 24 mmol), bis[3,5-difluoro-2-[5-(trifluoro methyl)-2-pyridyl]phenyl]4-tertbutyl-2-(4-tert-butyl-2-pyridyl)pyridine iridium hexafluorophosphate (269 mg, 0.24 mmol), 4-*tert*-butyl-2-(4-tert-butyl-2-pyridyl)pyridine nickel(II) dichloride (48 mg, 0.12 mmol), bis(trimethylsilyl)silyl-trimethyl-silane (7.4 mL, 24 mmol), and sodium carbonate (5.08 g, 48 mmol) in 1,2-dimethoxyethane (50 mL) were combined in a sealed tube under nitrogen. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away) with cooling fan to keep the reaction temperature at 25 °C for 4 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine

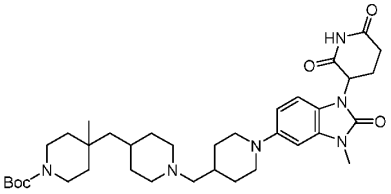
(20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/1 to 3/1) to afford the title compound (2.9 g, 42%) as a yellow oil.

Step 3: Preparation of *tert*-butyl 4-methyl-4-(4-piperidylmethyl)piperidine-1-carboxylate



To a solution of *tert*-butyl 4-methyl-4-(4-pyridylmethyl)piperidine-1-carboxylate (2.6 g, 9 mmol) and acetic acid (1.1 mL, 19 mmol) in ethanol (30 mL) was added platinum(iv) oxide (407 mg, 1.8 mmol) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen, then stirred under hydrogen (2 mpa) at 50 °C for 48 h. The mixture was filtered through celite, and the filtrate was concentrated *in vacuo* to afford the title compound (3 g, 80%, acetic acid salt) as a yellow oil. LC/MS (ESI) *m/z*: 297.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 - 6.22 (m, 3H), 3.49 - 3.39 (m, 2H), 3.18 - 3.08 (m, 2H), 3.03 (br d, J = 12.4 Hz, 2H), 2.72 - 2.61 (m, 2H), 1.70 - 1.61 (m, 2H), 1.59 - 1.48 (m, 1H), 1.38 (s, 9H), 1.33 - 1.20 (m, 6H), 1.15 (d, J = 4.8 Hz, 2H).

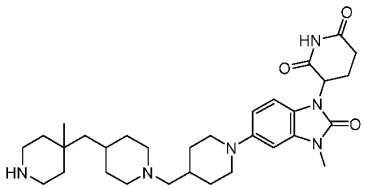
Step 4: Preparation of *tert*-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-4-methyl-piperidine-1-carboxylate



To a solution of *tert*-butyl 4-methyl-4-(4-piperidylmethyl)piperidine-1-carboxylate diacetate (1.29 g, 3 mmol) in dichloromethane (10 mL) and dimethyl sulfoxide (10 mL) was added *N*,*N*-diisopropylethylamine (1.1 mL, 6 mmol), and the mixture was stirred at 25 °C for 10 min. 1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde trifluoroacetate (1 g, 2 mmol) was then added, and the resulting mixture was stirred for 20 minutes. Sodium triacetoxyborohydride (1.31 g, 6 mmol) was then added, and the reaction mixture was stirred at 25 °C for 0.5 h. The mixture was diluted with water (20 mL) and extracted with dichloromethane (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 100/1 to 10/1) to afford the title compound (1 g, 74%) as a yellow solid. LC/MS (ESI) *m/z*: 651.5 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 - 7.93 (m, 1H), 6.74 - 6.52 (m, 3H), 5.20 (dd, J = 5.2, 12.8 Hz, 1H), 3.66 - 3.51 (m, 4H), 3.49 (s, 1H), 3.40 (s, 3H), 3.39 - 3.28 (m, 2H), 3.15 (ddd, J = 3.6, 9.6, 13.2

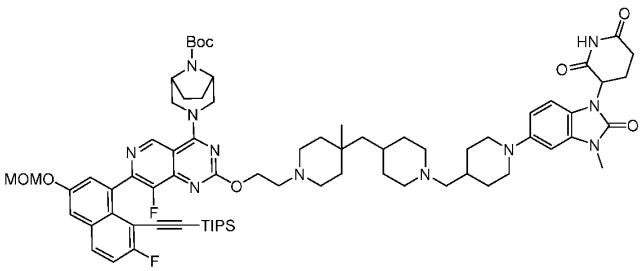
Hz, 2H), 3.08 - 3.08 (m, 1H), 2.99 - 2.79 (m, 2H), 2.74 - 2.65 (m, 4H), 2.55 - 2.38 (m, 2H), 2.29 - 2.14 (m, 1H), 1.93 (br d, *J* = 13.2 Hz, 2H), 1.88 - 1.62 (m, 5H), 1.51 (br dd, *J* = 2.8, 12.8 Hz, 2H), 1.46 (s, 9H), 1.39 - 1.25 (m, 7H).

Step 5: Preparation of 3-[3-methyl-5-[4-[[4-[(4-methyl-4-piperidyl)methyl]-1-piperidyl]methyl]-1-piperidyl]-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



To a solution of *tert*-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-4-methyl-piperidine-1-carboxylate (1 g, 1 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL), and the mixture was stirred for 0.5 h at 25 °C. The reaction mixture was concentrated *in vacuo* to afford the title compound (1 g, 97%, TFA salt) as a yellow solid. LC/MS (ESI) *m/z*: 551.3 $[M+H]^+$.

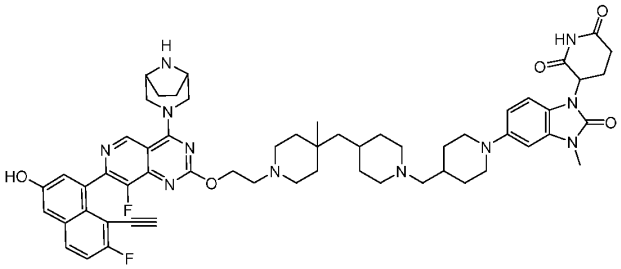
Step 6: Preparation of *tert*-butyl 3-[2-[2-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-4-methyl-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of 3-[3-methyl-5-[4-[[4-[(4-methyl-4-piperidyl)methyl]-1-piperidyl]methyl]-1-piperidyl]-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione trifluoroacetate (350 mg, 0.5 mmol) in dichloromethane (5 mL) and isopropanol (5 mL) was added *N,N*-diisopropylethylamine (0.3 mL, 1 mmol), and the mixture was stirred at 25 °C for 10 min. *Tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (422 mg, 0.5 mmol) was then added, and the resulting mixture was stirred for 20 minutes at 25 °C. Sodium triacetoxyborohydride (335 mg, 1.6 mmol) was then added, and the reaction mixture was stirred at 25 °C for 0.5 h. The mixture was diluted with water (20 mL) and extracted with dichloromethane (20 mL x 3). The combined organic phase was washed with brine (20 mL),

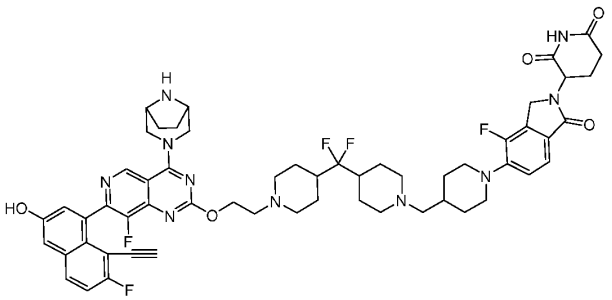
dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (dichloromethane/methanol = 10/1) to afford the title compound (300 mg, 43%) as a yellow solid. LC/MS (ESI) *m/z*: 1337.0 $[M+H]^+$.

Step 7: Preparation of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}-4-methylpiperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}piperidine-2,6-dione



The title compound was prepared in an analogous manner to step 4 and 5 of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-fluoro-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 1036.5 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (br s, 1H), 9.05 (s, 1H), 8.21 (s, 2H), 7.97 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.61 (dd, *J* = 2.0, 8.8 Hz, 1H), 5.27 (dd, *J* = 5.6, 12.8 Hz, 1H), 4.51 (br d, *J* = 13.2 Hz, 1H), 4.46 (br t, *J* = 5.6 Hz, 2H), 4.35 (br d, *J* = 10.8 Hz, 1H), 3.92 (s, 1H), 3.55 - 3.51 (m, 5H), 3.29 (s, 3H), 2.93 - 2.84 (m, 1H), 2.79 (br d, *J* = 11.6 Hz, 2H), 2.73 (br t, *J* = 5.2 Hz, 2H), 2.70 - 2.66 (m, 1H), 2.65 - 2.60 (m, 2H), 2.58 (br d, *J* = 9.2 Hz, 3H), 2.52 (br s, 2H), 2.42 - 2.31 (m, 3H), 2.18 (br d, *J* = 6.8 Hz, 2H), 2.02 - 1.88 (m, 3H), 1.80 - 1.69 (m, 6H), 1.60 (br d, *J* = 12.4 Hz, 3H), 1.43 - 1.28 (m, 5H), 1.27 - 1.17 (m, 4H), 1.14 (br d, *J* = 4.4 Hz, 2H).

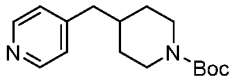
Example 150: Synthesis of 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)difluoromethyl]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Compound 79**)



The title compound was prepared in an analogous manner to 3-{5-[4-({4-[(1-{2-[(4-{3,8-diazabicyclo[3.2.1]octan-3-yl}-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy]ethyl}piperidin-4-yl)methyl]piperidin-1-yl}methyl)piperidin-1-yl]-4-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) m/z: 1061.6 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.06 (s, 1H), 8.21 (s, 2H), 7.98 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.52 - 7.43 (m, 2H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.20 - 7.13 (m, 2H), 5.07 (dd, *J* = 5.2, 13.2 Hz, 1H), 4.56 - 4.44 (m, 4H), 4.38 - 4.29 (m, 2H), 3.93 (s, 1H), 3.72 - 3.62 (m, 4H), 3.54 - 3.40 (m, 3H), 3.02 (d, *J* = 10.4 Hz, 2H), 2.95 - 2.85 (m, 3H), 2.82 - 2.67 (m, 4H), 2.64 - 2.56 (m, 1H), 2.46 - 2.37 (m, 1H), 2.17 (d, *J* = 6.8 Hz, 2H), 2.07 - 1.94 (m, 3H), 1.92 - 1.59 (m, 16H), 1.43-1.37 (m, 4H), 1.32 - 1.22 (m, 2H).

Example 151: Synthesis of 3-[5-[4-[[4-[[1-[3-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]propyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 230**)

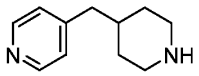
Step 1: Preparation of *tert*-butyl 4-(4-pyridylmethyl)piperidine-1-carboxylate



To a solution of *tert*-butyl 4-methylenepiperidine-1-carboxylate (25 g, 126.73 mmol, 1.0 eq) in THF (40 mL) was added 9-BBN (0.5 M, 304.15 mL, 1.2 eq) dropwise under N_2 atmosphere at 25 °C, and the reaction was stirred at 85 °C for 2 hours. The reaction was cooled to 25 °C and diluted with H_2O (45 mL). 4-Bromopyridine (28 g, 177.42 mmol, 1.4 eq), K_2CO_3 (52 g, 380.18 mmol, 3.0 eq), and $Pd(dppf)Cl_2.CH_2Cl_2$ (10 g, 12.67 mmol, 0.1 eq) were then added, and the reaction mixture was stirred at 75 °C for 16 hours under N_2 atmosphere. The reaction was quenched by addition of water (30 mL), and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (70 mL × 3), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The resulting residue was purified by flash chromatography on SiO_2 (gradient 0~50%

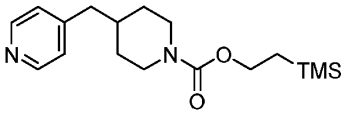
ethyl acetate in petroleum ether) to afford the title compound (32.5 g, 87% yield) as a yellow solid. LC/MS (ESI) *m/z*: 277.1 $[M+H]^+$.

Step 2: Preparation of 4-(4-piperidylmethyl)pyridine



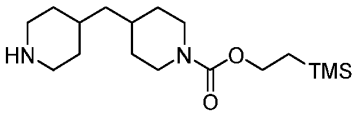
To a solution of *tert*-butyl 4-(4-pyridylmethyl)piperidine-1-carboxylate (32.5 g, 94% purity 110.54 mmol, 1.0 eq) in CH_2Cl_2 (300 mL) was added HCl in dioxane (4 M, 300 mL), and the reaction mixture was stirred at 25 °C for 0.5 hour. The mixture was diluted with petroleum ether (200 mL), filtered, and the filtrate concentrated in vacuum to afford the title compound (23 g, crude, HCl salt) as a yellow oil. LC/MS (ESI) *m/z*: 177.1 $[M+H]^+$.

Step 3: Preparation of 2-trimethylsilylethyl 4-(4-pyridylmethyl) piperidine-1-carboxylate



To a solution of 4-(4-piperidylmethyl)pyridine (20.7 g, 97.31 mmol, 1.0 eq, HCl) in CH_2Cl_2 (400 mL) were added (2, 5-dioxopyrrolidin-1-yl) 2-trimethylsilylethyl carbonate (30.28 g, 116.77 mmol) and Et_3N (10 mL, 71.85 mmol), and the reaction mixture was stirred at 25 °C for 16 hours. The mixture was diluted with water (150 mL), the organic layer separated, and the aqueous layer was further extracted with CH_2Cl_2 (100 mL × 3). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue, which was purified by flash chromatography on SiO_2 (gradient 0~26% CH_3OH in CH_2Cl_2) to afford the title compound (38 g, 99% yield) as a yellow solid. LC/MS (ESI) *m/z*: 321.2 $[M+H]^+$.

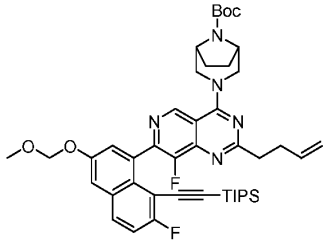
Step 4: Preparation of 2-trimethylsilylethyl 4-(4-piperidylmethyl)piperidine-1-carboxylate



To a solution of 2-trimethylsilylethyl 4-(4-pyridylmethyl) piperidine-1-carboxylate (10 g, 31.20 mmol, 1.0 eq) in EtOH (150 mL) were added HOAc (5.36 mL, 93.60 mmol, 3.0 eq) and PtO_2 (1.49 g, 6.55 mmol, 0.21 eq), and the resulting mixture was degassed and purged with Argon (3x), then with H_2 (3x). The reaction mixture was then stirred at 75 °C for 48 hours under H_2 (50 psi) atmosphere. The mixture was filtered, and the filtrate was concentrated. The resulting residue was diluted with CH_3CN (100 mL) and water (50 mL), and the pH adjusted (pH ~ 7-8) by addition of saturated $NaHCO_3$. The mixture was lyophilized, and the resulting residue was dissolved with CH_2Cl_2 (200 mL) and filtered. The filtrate was dried over anhydrous Na_2SO_4,

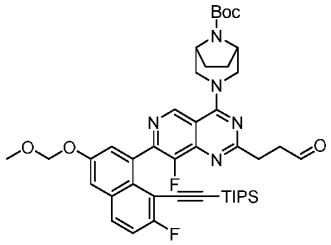
filtered, and concentrated under reduced pressure to give the title compound (12.1 g, crude) as a brown solid. LC/MS (ESI) *m/z*: 327.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 - 4.01 (m, 4H), 3.26 (d, *J* = 10.4 Hz, 1H), 2.84 - 2.61 (m, 4H), 2.60 - 2.40 (m, 1H), 1.95 (s, 1H), 1.74 (d, *J* = 13.2 Hz, 1H), 1.62 (d, *J* = 12.0 Hz, 3H), 1.54 - 1.47 (m, 1H), 1.43 - 1.35 (m, 1H), 1.35 - 1.12 (m, 3H), 1.1 - 1.04 (m, 2H), 1.04 - 0.93 (m, 3H), 0.03 (s, 9H).

Step 5: Preparation of *tert*-butyl 3-[2-but-3-enyl-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



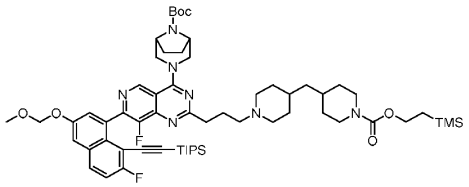
To a solution of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-methylsulfonyl-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.0 g, 1.22 mmol, 1.0 eq) in THF (20 mL) at 0 °C under N_2 was added bromo(but-3-enyl)magnesium (0.5 M, 7.30 mL, 3.0 eq), and the reaction mixture was stirred at 0 °C under N_2 for 5 minutes. The reaction was quenched with saturated NH_4Cl solution (50 mL), and the resulting mixture was extracted with ethyl acetate (40 mL × 3). The combined organic extract was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on SiO_2 (gradient 0~30% THF in petroleum ether) followed by prep-HPLC (column: Xtimate C18 150*40mm*10um;mobile phase: [64-98% CH_3CN in water (TFA)]). The pure fractions were treated with saturated $NaHCO_3$ solution to adjust the pH (pH ~ 7-8), and the resulting mixture was lyophilized). CH_2Cl_2 (60 mL) was then added, the mixture was filtered, and the filter cake was washed with CH_2Cl_2 (40 mL). The filtrate was concentrated in vacuum to give the title compound (550 mg, 57% yield) as a light yellow solid. LC/MS (ESI) *m/z*: 798.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.79 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.34 - 7.28 (m, 2H), 5.99 (dd, *J* = 6.4, 10.4, 17.2 Hz, 1H), 5.33 - 5.27 (m, 2H), 5.14 (dd, *J* = 1.2, 17.2 Hz, 1H), 5.03 (d, *J* = 10.0 Hz, 1H), 4.97 - 4.83 (m, 1H), 4.51 - 4.31 (m, 2H), 4.23 (d, *J* = 12.4 Hz, 1H), 3.93 - 3.74 (m, 1H), 3.51 (s, 3H), 3.49 - 3.38 (m, 1H), 3.12 - 2.96 (m, 2H), 2.66 (q, *J* = 7.2 Hz, 2H), 1.99 (s, 2H), 1.58 (s, 2H), 1.54 (s, 9H), 0.85 (t, *J* = 7.6 Hz, 18H), 0.50 (m, 3H).

Step 6: Preparation of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(3-oxopropyl)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[2-but-3-enyl-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (550 mg, 0.69 mmol, 1.0 eq) in dioxane (15 mL) were added 2,6-lutidine (0.32 mL, 2.76 mmol, 4.0 eq) and $NaIO_4$ (589 mg, 2.76 mmol, 4.0 eq) in water (5 mL) followed by $K_2OsO_4 \cdot 2H_2O$ (25 mg, 0.069 mmol, 0.1 eq), and the reaction mixture was stirred at 20 °C for 2 hours. The mixture was filtered, diluted with saturated aqueous Na_2SO_3 (30 mL), and then extracted with EtOAc (30 mL × 2). The combined organic extract was washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (550 mg 100% yield) as a yellow solid. LC/MS (ESI) *m/z*: 800.4 $[M+H]^+$.

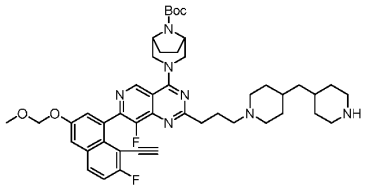
Step 7: Preparation *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-[3-[4-[[1-(2-trimethylsilylethoxycarbonyl)-4-piperidyl]methyl]-1-piperidyl]propyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(3-oxopropyl)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (550 mg, 0.69 mmol, 1.0 eq) and 2-trimethylsilylethyl 4-(4-piperidylmethyl)piperidine-1-carboxylate (673 mg, 2.06 mmol, 3.0 eq) in CH_2Cl_2 (5 mL) and *i*-PrOH (5 mL) was added HOAc (0.16 mL, 2.75 mmol, 4.0 eq) followed by $NaBH(OAc)_3$ (583 mg, 2.75 mmol, 4.0 eq), and the reaction mixture was stirred at 20 °C for 16 hours. The reaction was quenched with saturated $NaHCO_3$ solution (50 mL), and the resulting mixture was extracted with CH_2Cl_2 (40 mL × 3). The combined organic extract was washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced

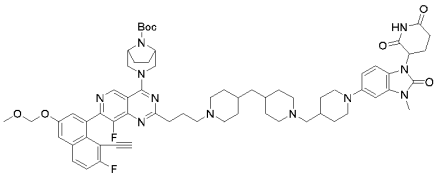
pressure. The crude product was purified by flash chromatography on SiO_2 (gradient 0~4% CH_3OH in CH_2Cl_2) to afford the title compound (670 mg, 88% yield) as a yellow solid. LC/MS (ESI) *m/z*: 1110.7 $[M+H]^+$.

Step 8: Preparation of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[3-[4-(4-piperidylmethyl)-1-piperidyl]propyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-[3-[4-[[1-(2-trimethylsilylethoxycarbonyl)-4-piperidyl]methyl]-1-piperidyl]propyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (620 mg, 0.56 mmol, 1.0 eq) in DMF (10 mL) was added CsF (848 mg, 5.58 mmol, 10.0 eq), and the reaction mixture was stirred at 60 °C for 6 hours. The mixture was filtered, and the filter cake was washed with ethyl acetate (50 mL). The resulting mixture was diluted with water (50 mL) and extracted with ethyl acetate (40 mL × 3). The combined extract was washed with water (30 mL × 3) and brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (450 mg, 100% yield) as a yellow solid. LC/MS (ESI) *m/z*: 810.5 $[M+H]^+$.

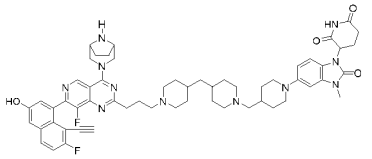
Step 9: Preparation of *tert*-butyl 3-[2-[3-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]propyl]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a solution of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[3-[4-(4-piperidylmethyl)-1-piperidyl]propyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (470 mg, 0.580 mmol, 1.0 eq) and 1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (300 mg, 0.812 mmol, 1.4 eq) in CH_2Cl_2 (3.0 mL) and i-PrOH (3.0 mL) were added HOAc (135 μL, 2.32 mmol, 4.0 eq) and $NaBH(OAc)_3$ (368 mg, 1.74 mmol, 3.0 eq), and the reaction mixture was stirred at 20 °C for

1 hour. The mixture was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography on SiO_2 (gradient: 0~10% CH_3OH in CH_2Cl_2) to afford the title compound (304 mg, 33% yield) as a yellow solid. LC/MS (ESI) *m/z*: 1164.7 $[M+H]^+$

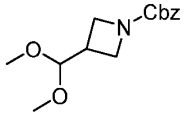
Step 10: Preparation of 3-[5-[4-[[4-[[1-[3-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]propyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



To a solution of *tert*-butyl 3-[2-[3-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]propyl]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (304 mg, 0.191 mmol, 1.0 eq) in CH_2Cl_2 (3.0 mL) was added HCl in dioxane (4 M, 1.9 mL, 30 eq), and the reaction mixture was stirred at 20 °C for 0.25 hour. The mixture was diluted with petroleum ether (40 mL) and filtered, and the filter cake was dissolved in THF (30 mL), then treated with Et_3N to adjust the pH (pH~9). The resulting mixture was filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by pre-HPLC (FA condition: column: Xtimate C18 150*40mm*10um; mobile phase: [0-24% CH_3CN in water (FA)]), then lyophilized to afford the title compound (105.3 mg, 36% yield, 2HCOOH) as a yellow solid. LC/MS (ESI) *m/z*: 1020.5 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 9.16 (s, 1H), 8.46 (s, 2H), 7.90 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.43 - 7.30 (m, 2H), 7.24 (d, *J* = 2.4 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.90 - 6.75 (m, 2H), 5.29 (dd, *J* = 5.4, 12.4 Hz, 1H), 4.80 (br d, *J* = 12.8 Hz, 3H), 4.00 (br s, 2H), 3.91 - 3.80 (m, 2H), 3.66 - 3.48 (m, 6H), 3.40 (s, 3H), 3.36 (s, 1H), 3.21 (br s, 2H), 3.07 (br t, *J* = 6.8 Hz, 2H), 3.00 - 2.72 (m, 11H), 2.39 - 2.24 (m, 2H), 2.19 - 2.11 (m, 1H), 2.03 - 1.86 (m, 10H), 1.73 - 1.60 (m, 2H), 1.56 - 1.40 (m, 6H), 1.29 - 1.16 (m, 2H).

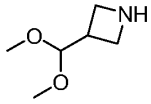
Example 152: Synthesis of 3-[5-[3-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]azetidin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 235**)

Step 1: Preparation of benzyl 3-(dimethoxymethyl)azetidine-1-carboxylate



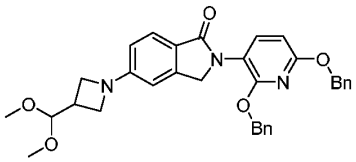
To a solution of benzyl 3-formylazetidine-1-carboxylate (8.9 g, 40.69 mmol, 1.0 *eq*) in MeOH (180 mL) were added $TsOH \cdot H_2O$ (387 mg, 2.03 mmol, 0.05 *eq*) and trimethoxymethane (22.3 mL, 203.43 mmol, 5.0 *eq*), and the reaction mixture was stirred at 25 °C for 10 hours. The mixture was concentrated, and the residue was diluted with water (50 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic extract was washed with brine (100 mL × 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on SiO_2 (gradient: 0~30% ethyl acetate in petroleum ether) to afford the title compound (7.3 g, 68% yield) as a colorless oil. LC/MS (ESI) *m/z*: 266.2 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.31 (m, 5H), 5.10 (s, 2H), 4.53 (d, *J* = 6.8 Hz, 1H), 4.09 - 4.00 (m, 2H), 3.87 (dd, *J* = 5.6, 8.8 Hz, 2H), 3.35 (s, 6H), 2.91 - 2.78 (m, 1H).

Step 2: Preparation of 3-(dimethoxymethyl)azetidine



To a solution of benzyl 3-(dimethoxymethyl)azetidine-1-carboxylate (7.3 g, 27.52 mmol, 1.0 *eq*) in 2,2,2- trifluoroethanol (150 mL) was added Pd/C (730 mg, 0.686 mmol, 10% purity), and the reaction mixture was stirred at 45 °C for 16 hours under H_2 (15 psi). The mixture was filtered through celite pad under vacuum and rinsed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure to afford the title compound (3.8 g) as a yellow oil. ^1H NMR (400MHz, $CDCl_3$) δ 4.60 (d, *J* = 6.4 Hz, 1H), 3.84 - 3.78 (m, 2H), 3.74 - 3.67 (m, 2H), 3.36 (s, 6H), 3.09 - 2.98 (m, 1H).

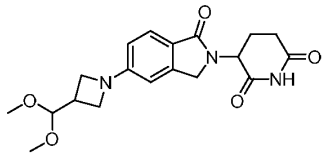
Step 3: Preparation of 2-(2-benzyloxy-6-hydroxy-3-pyridyl)-5-[3-(dimethoxymethyl)azetidin-1-yl]isoindolin-1-one



To a solution of 5-bromo-2-(2,6-dibenzyloxy-3-pyridyl)isoindolin-1-one (3.4 g, 6.78 mmol, 1.0 eq) in dioxane (40 mL) were added 3-(dimethoxymethyl)azetidine (1.23 g, 8.82 mmol, 1.3 eq), Cs_2CO_3 (6.63 g, 20.34 mmol, 3.0 eq), and BrettPhos Pd G_3 (615 mg, 0.68 mmol, 0.1 eq), and the reaction mixture was stirred at 100 °C for 16 hours under N_2. The mixture was diluted with water (30 mL) and extracted with dichloromethane (50 mL × 3). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on SiO_2 (gradient:

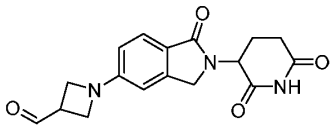
0~3% methanol in dichloromethane) to afford the title compound (1.0 g, 32% yield) as a brown solid. LC/MS (ESI) *m/z*: 552.2 $[M+H]^+$.

Step 4: Preparation of 3-[5-[3-(dimethoxymethyl)azetidin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione



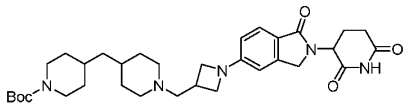
To a solution of 2-(2-benzyloxy-6-hydroxy-3-pyridyl)-5-[3-(dimethoxymethyl)azetidin-1-yl]isoindolin-1-one (1.0 g, 2.17 mmol, 1.0 eq) in THF (30 mL) was added $Pd(OH)_2/C$ (609 mg, 0.87 mmol, 20% purity, 0.4 eq), and the suspension was degassed and purged with H_2 (3x). The reaction mixture was stirred under H_2 (50 Psi) at 50 °C for 16 hours. The mixture was filtered and concentrated under reduced pressure to afford the title compound (691 mg, crude) as an off-white solid. LC/MS (ESI) *m/z*: 374.1 $[M+H]^+$.

Step 5: Preparation of 1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]azetidine-3-carbaldehyde



To a solution of 3-[5-[3-(dimethoxymethyl)azetidin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (335 mg, 0.90 mmol, 1.0 *eq*) in dichloromethane (2 mL) was added TFA (1 mL), and the reaction mixture was stirred at 40 °C for 2 hours. The mixture was concentrated under reduced pressure to afford the title compound (354 mg, crude, TFA salt) as a brown oil. LC.MS (ESI) *m/z*: 346.1 $[M+H_3O]^+$.

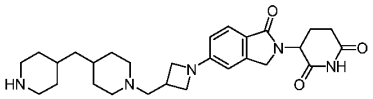
Step 6: Preparation of tert-butyl 4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]azetidin-3-yl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate



To a solution of 1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]azetidine-3-carbaldehyde (390 mg, 0.88 mmol, 1.0 eq, TFA salt) in CH_2Cl_2 (5 mL) and *i*-PrOH (5 mL) were added NaOAc (725 mg, 8.84 mmol, 10.0 eq), tert-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate (324 mg, 1.15 mmol, 1.3 eq) and 2-picoline borane complex (473 mg, 4.42 mmol, 5.0 eq), and the reaction mixture was stirred at 20 °C for 16 hours. The mixture was filtered,

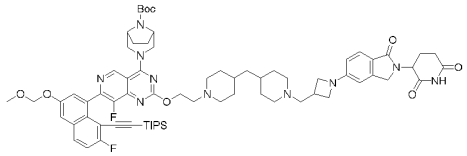
and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on SiO_2 (gradient 0~9% methanol in dichloromethane) to afford the title compound (310 mg, 59% yield) as a light yellow solid. LC/MS (ESI) *m/z*: 594.6 $[M+H]^+$.

Step 7: Preparation of 3-[1-oxo-5-[3-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]azetidin-1-yl]isoindolin-2-yl]piperidine-2,6-dione



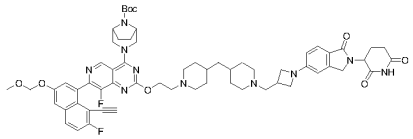
To a solution of tert-butyl 4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]azetidin-3-yl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate (300 mg, 0.51 mmol, 1.0 *eq*) in dichloromethane (2 mL) was added TFA (1 mL), and the reaction mixture was stirred at 20°C for 30 minutes. The mixture was concentrated under reduced pressure to afford the title compound (302 mg, crude, TFA salt) as a light yellow oil. LC/MS (ESI) *m/z*: 494.3 $[M+H]^+$.

Step 8: Preparation of tert-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]azetidin-3-yl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



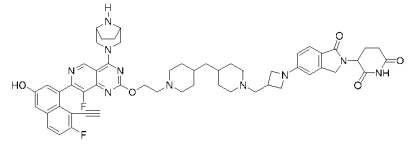
To a solution of 3-[1-oxo-5-[3-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]azetidin-1-yl]isoindolin-2-yl]piperidine-2,6-dione (302 mg, 0.49 mmol, 1.2 eq, TFA salt) in CH_2Cl_2 (4 mL) and *i*-PrOH (4 mL) were added NaOAc (506 mg, 6.17 mmol, 15.0 eq), tert-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (330 mg, 0.41 mmol, 1.0 eq), and 2-picoline borane complex (220 mg, 2.06 mmol, 5.0 eq), and the reaction mixture was stirred at 20 °C for 16 hours. The mixture was treated with triethylamine to pH ~ 6, then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified flash chromatography on SiO_2 (gradient: 0~15% methanol in dichloromethane) to afford the title compound (475 mg, 90% yield) as a light yellow oil. LC/MS (ESI) *m/z*: 1280.0 $[M+H]^+$.

Step 9: Preparation of tert-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]azetidin-3-yl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



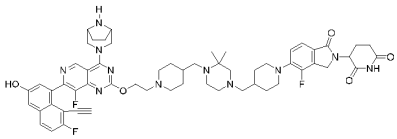
To a solution of tert-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]azetidin-3-yl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (475 mg, 0.37 mmol, 1.0 *eq*) in DMF (5 mL) was added CsF (282 mg, 1.86 mmol, 5.0 *eq*), and the reaction mixture was stirred at 20 °C for 16 hours. The mixture was diluted with ethyl acetate (30 mL) and filtered. The filtrate was washed with water (8 mL × 5), and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (243 mg, crude) as a light yellow oil. LC/MS (ESI) *m/z*: 1123.8 $[M+H]^+$.

Step 10: Preparation of 3-[5-[3-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-1-piperidyl]methyl]azetidin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione



To a solution of tert-butyl 3-[2-[2-[4-[[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]azetidin-3-yl]methyl]-4-piperidyl]methyl]-1-piperidyl]ethoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (243 mg, 0.22 mmol, 1.0 *eq*) in CH_2Cl_2 (3 mL) was added TFA (1 mL), and the reaction mixture was stirred at 20 °C for 1 hour. The mixture concentrated, and the residue was taken up in THF (20 mL) and adjusted to pH ~ 8 by adding solid $NaHCO_3$. The resulting mixture was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC {column: Xtimate C18 150*40mm*10um; mobile phase: [20-60% CH_3CN in water (NH_4HCO_3)]}. Pure fractions were combined and dried by lyophilization to afford the title compound (40.1 mg, 19% yield) as a light yellow solid. LC/MS (ESI) *m/z*: 979.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 7.88 - 7.84 (m, 1H), 7.59 - 7.56 (m, 1H), 7.35 - 7.30 (m,2H), 7.21 - 7.20 (m,1H), 6.51 - 6.49 (m, 2H), 5.11 - 5.06 (m, 1H), 4.64 - 4.57 (m, 4H), 4.37 - 4.35 (m, 2H), 4.14 - 4.10 (m, 2H), 3.74 - 3.61 (m, 6H), 3.38 (s, 1H), 3.13 - 3.02 (m, 3H), 2.93 - 2.85 (m, 5H), 2.79 - 2.66 (m, 3H), 2.47 - 2.40 (m, 1H), 2.21 - 2.03 (m, 5H), 1.89 - 1.79 (m, 4H), 1.72 - 1.70 (m, 4H), 1.47 - 1.39 (m, 2H), 1.29 - 1.17 (m, 6H).

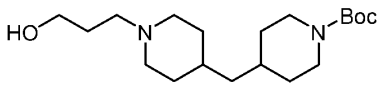
Example 153: Synthesis of 3-[5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]-3,3-dimethyl-piperazin-1-yl]methyl]-1-piperidyl]-4-fluoro-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (**Compound 239**)



The title compound was made in an analogous manner to 3-[4-chloro-5-[4-[[4-[[1-[2-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxyethyl]-4-piperidyl]methyl]piperazin-1-yl]methyl]-1-piperidyl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione. (white solid). LC/MS (ESI) *m/z*: 1054.5 $[M+1]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 9.02 (s, 1H), 7.87 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.40 - 7.30 (m, 2H), 7.23 - 7.15 (m, 2H), 5.12 (dd, *J* = 5.2, 13.2 Hz, 1H), 4.70 - 4.56 (m, 5H), 4.53 - 4.40 (m, 2H), 3.77 - 3.64 (m, 4H), 3.63 - 3.53 (m, 2H), 3.39 (s, 1H), 3.17 - 3.09 (m, 2H), 2.95 - 2.85 (m, 3H), 2.82 (m, 3H), 2.62 - 2.55 (m, 2H), 2.53 - 2.43 (m, 2H), 2.27 - 2.09 (m, 8H), 1.96 - 1.78 (m, 8H), 1.74 - 1.63 (m, 1H), 1.50 - 1.35 (m, 3H), 1.31 - 1.16 (m, 3H), 1.04 (s, 6H).

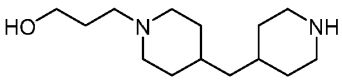
Example 154: Synthesis of 3-[5-[4-[[4-[[1-[3-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxypropyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 226**)

Step 1: Preparation of *tert*-butyl 4-[[1-(3-hydroxypropyl)-4-piperidyl]methyl]piperidine-1-carboxylate



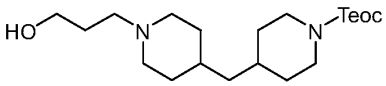
To a mixture of *tert*-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate (3 g, 7.45 mmol, 1 eq, 2 acetic acid) and 3-bromopropan-1-ol (1.04 g, 7.45 mmol, 673 µL, 1 eq) in dimethylsulfoxide (30 mL) was added *N, N*-diisopropylethylamine (2.89 g, 22.36 mmol, 3.89 mL, 3 eq) and potassium iodide (619 mg, 3.73 mmol, 0.5 eq), and the reaction mixture was stirred at 100 °C for 12 h. mixture was concentrated, and the resulting residue was purified by prep-HPLC {column: Waters Xbridge 150*25mm* 5um; mobile phase: [10-40% CH_3CN in water (FA)]} to afford the title compound (1.1 g, 43% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 4.10 – 4.00 (m, 2H), 3.79 (t, *J* = 5.2 Hz, 2H), 3.13 – 3.07 (m, 2H), 2.67 – 2.60 (m, 4H), 2.04 – 1.95 (m, 2H), 1.77 – 1.73 (m, 2H), 1.72 – 1.65 (m, 2H),1.63 – 1.55 (m, 2H), 1.45 (s, 9H), 1.40 – 1.35 (m, 1H), 1.32 – 1.22 (m, 3H), 1.15 (t, *J* = 6.8 Hz, 2H), 1.10 – 1.00 (m, 2H).

Step 2: Preparation of 3-[4-(4-piperidylmethyl)-1-piperidyl]propan-1-ol



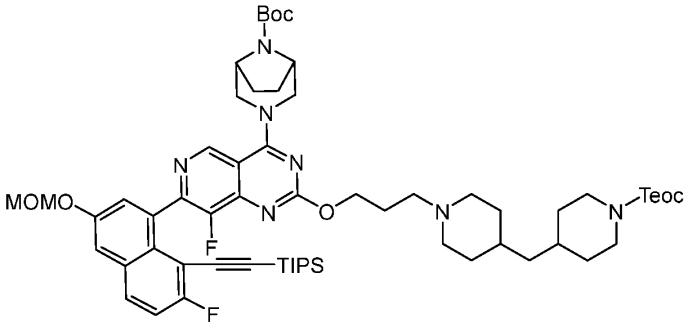
To a solution of *tert*-butyl 4-[[1-(3-hydroxypropyl)-4-piperidyl]methyl]piperidine-1-carboxylate (1.1 g, 3.23 mmol, 1 eq) in dichloromethane (15 mL) was added TFA (23.03 g, 201.93 mmol, 15 mL, 62.51 eq), and the reaction mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated to afford the title compound (777 mg, crude, trifluoroacetic acid salt) as a yellow oil. LC/MS (ESI) *m/z*: 241.0 $[M+H]^+$.

Step 3: Preparation of 2-trimethylsilylethyl 4-[[1-(3-hydroxypropyl)-4-piperidyl]methyl]piperidine-1-carboxylate



To 3-[4-(4-piperidylmethyl)-1-piperidyl]propan-1-ol (777 mg, 2.19 mmol, 1 eq, TFA salt) in dichloromethane (12 mL) and water (6 mL) were added sodium bicarbonate (1.10 g, 13.15 mmol, 512 µL, 6 eq) and (2,5-dioxopyrrolidin-1-yl) 2-trimethylsilylethyl carbonate (682 mg, 2.63 mmol, 1.2 eq), and the reaction mixture was stirred at 25 °C for 12 h. The mixture was diluted with water (20 mL) and extracted with dichloromethane (20 mL x 3). The combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (Dichloromethane: Methanol = from 100/1 to 10/1) to afford the title compound (700 mg, 83% yield) as a yellow oil. LC/MS (ESI) *m/z*: 385.2 $[M+H]^+$.

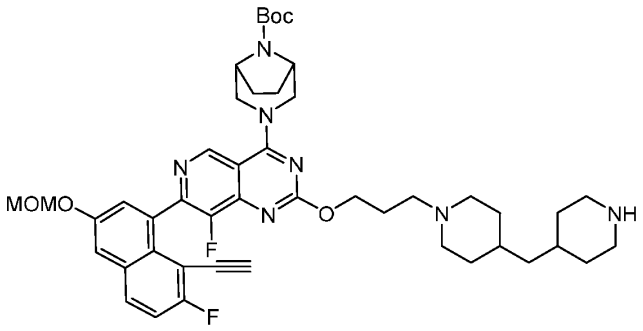
Step 4: Preparation of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-[3-[4-[[1-(2-trimethylsilylethoxycarbonyl)-4-piperidyl]methyl]-1-piperidyl]propoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To 2-trimethylsilylethyl 4-[[1-(3-hydroxypropyl)-4-piperidyl]methyl]piperidine-1-carboxylate (600 mg, 1.56 mmol, 1 eq) in tetrahydrofuran (20 mL) was added lithium tert-

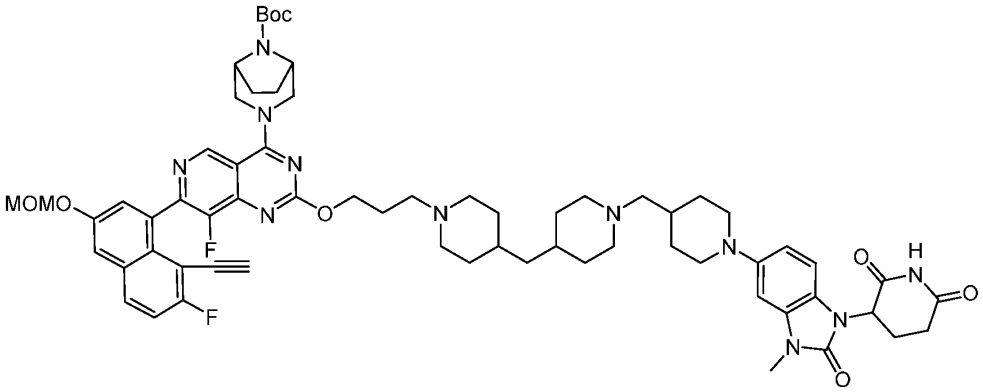
butoxide (1 M, 2.4 mL, 1.54 eq), and the mixture was stirred at 0 °C for 0.5 h. *tert*-Butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-methylsulfonyl-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.54 g, 1.87 mmol, 1.2 eq) was then added, and the reaction mixture was stirred for 1 h at 25 °C. The reaction was quenched with ammonium chloride solution (20 mL), and the resulting mixture was extracted with ethyl acetate (20 mL x 3). The combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*40mm* 15um;mobile phase: [70-100% CH_3CN in water (TFA)]) to afford the title compound (450 mg, 26% yield) as a yellow solid. LC/MS (ESI) *m/z*: 1126.7 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.77 – 7.51 (m, 1H), 7.33 (m, 1H), 7.34 – 7.26 (m, 2H), 5.32 – 5.28 (m, 2H), 4.72 (d, J = 7.2 Hz, 1H), 4.63 – 4.48 (m, 2H), 4.47 – 4.26 (m, 3H), 4.24 – 4.15 (m, 5H), 3.80 – 3.70 (m, 1H), 3.50 (s, 3H), 3.12 – 2.90 (m, 2H), 2.70 – 2.60 (m, 2H), 2.55 – 2.50 (m, 1H), 2.16 – 2.10 (m, 1H), 2.05 – 1.95 (m, 4H), 1.65 – 1.52 (m, 6H), 1.50 (s, 9H), 1.40 – 1.30 (m, 6H), 1.20 – 1.10 (m, 2H), 1.05 – 0.95 (m, 3H), 0.86 (t, J = 7.2 Hz, 18H), 0.56 – 0.53 (m, 3H), 0.07 (s, 9H).

Step 5: Preparation of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[3-[4-(4-piperidylmethyl)-1-piperidyl]propoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



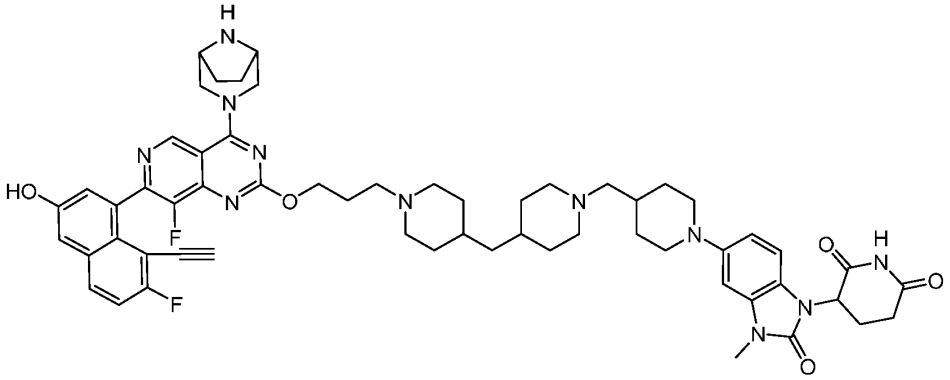
To a solution of *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-[3-[4-[[1-(2-trimethylsilylethoxycarbonyl)-4-piperidyl]methyl]-1-piperidyl]propoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (540 mg, 0.48 mmol, 1 eq) in dimethylsulfoxide (6 mL) was added cesium fluoride (728 mg, 4.79 mmol, 10 eq) at 25 °C, and the reaction mixture was stirred for 2 h at 50 °C. mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the title compound (390 mg, 98% yield) as a yellow solid. LC/MS (ESI) *m/z*: 826.4 $[M+H]^+$.

Step 6: Preparation of *tert*-butyl 3-[2-[3-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]propoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



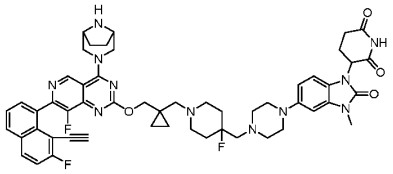
To a solution of *tert*-butyl 3-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[3-[4-(4-piperidylmethyl)-1-piperidyl]propoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (340 mg, 0.41 mmol, 1 eq) in dichloromethane (4 mL) and dimethylsulfoxide (4 mL) were added *N,N*-diisopropylethylamine (106 mg, 0.82 mmol, 143 µL, 2 eq) and 1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]piperidine-4-carbaldehyde (190 mg, 0.41 mmol, 1 eq), and the resulting mixture was stirred at 25 °C for 30 minutes. Sodium triacetoxyborohydride (262 mg, 1.23 mmol, 3 eq) was then added, and the reaction mixture was stirred at 25 °C for 0.5 h. The mixture was poured onto water (20 mL) and extracted with dichloromethane (20 mL × 2). The combined organic extracts were washed with brine (20 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (Dichloromethane: Methanol = 10: 1, Rf =0.24) to afford the title compound (290 mg, 60% yield) as a yellow solid. LC/MS (ESI) *m/z*: 1180.8 $[M+H]^+$.

Step 7: Preparation of 3-[5-[4-[[4-[[1-[3-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxypropyl]-4-piperidyl]methyl]-1-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



To a solution of *tert*-butyl 3-[2-[3-[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-4-piperidyl]methyl]-1-piperidyl]propoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (320 mg, 0.27 mmol, 1 eq) in dichloromethane (4 mL) was added hydrochloric acid solution in dioxane (2 M, 4 mL, 29.51 eq), and the reaction mixture was stirred for 0.5 h at 25 °C. The mixture was concentrated, and the resulting residue was purified by prep-HPLC {column: YMC-Actus Triart C18 150*30mm*7um; mobile phase: [5-35% CH_3CN in water(FA)]} to afford the title compound (194.1 mg, 62% yield, formic acid salt) as a yellow solid. LC/MS (ESI) *m/z*: 1036.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.05 (s, 1H), 8.22 (s, 2H),7.97 (dd, *J*=9.2, 6.0 Hz, 1H), 7.45 (t, *J*=9.2 Hz, 1H), 7.39 (d, *J*=2.0 Hz, 1H), 7.18 (d, *J*=2.0 Hz, 1H), 6.92 (d, *J*=8.8 Hz, 1H), 6.80 (d, *J*=2.0 Hz, 1H), 6.64 – 6.58 (m, 1H), 5.32 – 5.24 (m, 1H), 4.54 – 4.48 (m, 1H), 4.40 – 4.35 (m, 3H), 3.93 (s, 1H), 3.73 – 3.72 (m, 2H), 3.67 – 3.63 (m, 2H), 3.59 – 3.53 (m, 3H), 3.29 (s, 3H), 3.00 – 2.93 (m, 2H), 2.90 – 2.83 (m, 3H), 2.73 – 2.66 (m, 1H), 2.65 – 2.57 (m, 3H), 2.54 (s, 3H), 2.24 (d, *J*=6.8 Hz, 2H), 2.09 – 1.98 (m, 3H), 1.97 – 1.88 (m, 4H), 1.80 – 1.70 (m, 6H), 1.65 – 1.54 (m, 5H), 1.38 – 1.20 (m, 4H), 1.17 – 1.05 (m, 6H).

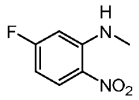
Example 155: Synthesis of 3-[5-[4-[[1-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-4-fluoro-4-piperidyl]methyl]piperazin-1-yl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 228**)



The title compound was made in an analogous manner to 3-[5-[4-[[3-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl] piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) m/z: 968.4 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 8.15 - 7.90 (m, 2H), 7.75 - 7.48 (m, 2H), 7.35 (dt, *J* = 2.0, 8.8 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.70 (s, 1H), 6.62 (d, *J* = 8.8 Hz, 1H), 5.22 (dd, *J* = 5.2, 12.4 Hz, 1H), 4.67 (d, *J* = 13.6 Hz, 2H), 4.44 (q, *J* = 11.6 Hz, 2H), 4.01 (s, 2H), 3.84 (t, *J* = 14.0 Hz, 2H), 3.59 - 3.43 (m, 3H), 3.27 - 3.23 (m, 2H), 3.16 - 2.89 (m, 9H), 2.87 - 2.78 (m, 1H), 2.75 - 2.58 (m, 6H), 2.57 - 2.42 (m, 2H), 2.09 (d, *J* = 11.2 Hz, 4H), 2.03 - 1.88 (m, 5H), 0.86 (s, 2H), 0.74 (s, 2H).

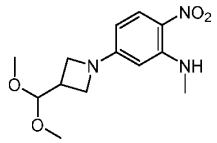
Example 156: Synthesis of 3-[5-[3-[[4-[[1-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-4-piperidyl]methyl]-1-piperidyl]methyl]azetidin-1-yl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 229**)

Step 1: Preparation of 5-fluoro-N-methyl-2-nitro-aniline



To a mixture of 2,4-difluoro-1-nitro-benzene (20 g, 125.71 mmol, 13.8 mL, 1 *eq*) and methylamine (16.98 g, 251.43 mmol, 2 *eq*, hydrochloride) in acetonitrile (200 mL) was added *N*,*N*-diisopropylethylamine (64.99 g, 502.86 mmol, 87.6 mL, 4 *eq*) in one portion at 25 °C under nitrogen. The reaction mixture was stirred at 25 °C for 16 hours. The mixture was cooled to 25 °C and concentrated under reduced pressure at 45 °C. The resulting residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=10/1, 3/1) to afford the title compound (23 g, crude) as a yellow solid.

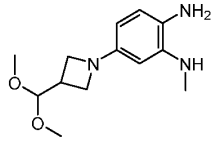
Step 2: Preparation of 5-[3-(dimethoxymethyl)azetidin-1-yl]-N-methyl-2-nitro-aniline



To a mixture of 3-(dimethoxymethyl)azetidine (17.73 g, 135.18 mmol, 1 *eq*) and 5-fluoro-N-methyl-2-nitro-aniline (23 g, 135.18 mmol, 1 *eq*) in dimethyl sulfoxide (200 mL) was added *N*,*N*-diisopropylethylamine (52.41 g, 405.55 mmol, 70.6 mL, 3 *eq*) in one portion at 20 °C under nitrogen. The reaction mixture was stirred at 120 °C for 16 hours. The mixture was poured into ice-water (w/w = 1/1) (500 mL) and stirred for 5 minutes. The aqueous phase was

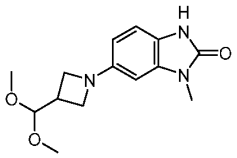
extracted with ethyl acetate (300 mL × 3). The combined organic extract was washed with brine (300 mL × 2), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=50/1, 8/1) to afford the title compound (23 g, 60% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (br d, J = 2.4 Hz, 1H), 8.08 (d, J = 9.6 Hz, 1H), 5.76 (dd, J = 2.4, 9.2 Hz, 1H), 5.33 (d, J = 2.4 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.17 - 4.03 (m, 2H), 3.94 - 3.87 (m, 2H), 3.42 (s, 6H), 3.15 - 3.04 (m, 1H), 2.96 (d, J = 5.2 Hz, 3H).

Step 3: Preparation of 5-(3-(dimethoxymethyl)azetidin-1-yl)-N1-methylbenzene-1,2-diamine



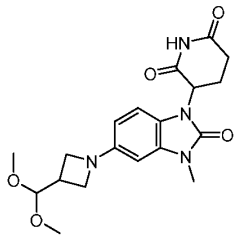
To a solution of 5-[3-(dimethoxymethyl)azetidin-1-yl]-N-methyl-2-nitro-aniline (23 g, 81.76 mmol, 1 *eq*) in tetrahydrofuran (200 mL) was added Platinum on charcoal (5 g, , 5% purity) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (50 psi) at 30 °C for 16 hours. The reaction mixture was filtered, and the filtrate was used into next step directly. LC/MS (ESI) *m/z*: 252.2 $[M+H]^+$.

Step 4: Preparation of 5-[3-(dimethoxymethyl)azetidin-1-yl]-3-methyl-1H-benzimidazol-2-one



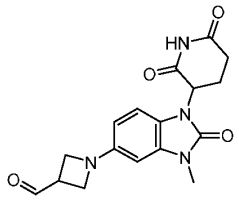
To a mixture of 5-(3-(dimethoxymethyl)azetidin-1-yl)-N1-methylbenzene-1,2-diamine (21 g, 83.56 mmol, 1 *eq*) in tetrahydrofuran (300 mL) was added N'-cyclohexyl-N-[2-(4-methylmorpholin-4-ium-4-yl)ethyl]methanediimine;4-methylbenzenesulfonate (20.32 g, 125.34 mmol, 1.5 *eq*) in one portion at 25 °C under nitrogen. The reaction mixture was stirred at 25 °C for 16 hours. The mixture was poured into ice-water (w/w = 1/1) (500 mL) and stirred for 5 minutes. The aqueous phase was extracted with ethyl acetate (200 mL × 4), and the combined organic extract was washed with brine (200 mL × 3), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=10/1, 3/1) to afford the title compound (15 g, 64% yield) as a yellow solid.LC/MS (ESI) *m/z*: 278.1$[M+H]^+$. ^{1}H NMR (400 MHz DMSO-d_6) δ 10.41 (s, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.21 (d, *J* = 2.0 Hz, 1H), 6.06 (dd, *J* = 2.0, 8.4 Hz, 1H), 4.60 (d, *J* = 7.2 Hz, 1H), 3.81 (t, *J* = 7.6 Hz, 2H), 3.55 (t, *J* = 6.8 Hz, 2H), 3.28 (s, 6H), 3.22 (s, 3H), 3.01 - 2.90 (m, 1H).

Step 5: Preparation of 3-(5-(3-(dimethoxymethyl)azetidin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione



To a mixture of 5-[3-(dimethoxymethyl)azetidin-1-yl]-3-methyl-1H-benzimidazol-2-one (15 g, 54.09 mmol, 1 *eq*) in tetrahydrofuran (300 mL) was added sodium hydride (8.65 g, 216.36 mmol, 60% in mineral oil, 4 *eq*) in portions at 0 °C under nitrogen, and the resulting mixture was stirred at 0 °C for 30 minutes. A solution of 3-bromopiperidine-2,6-dione (31.16 g, 162.27 mmol, 3 *eq*) in tetrahydrofuran (100 mL) was then added under nitrogen, and the reaction mixture was stirred at 60 °C for 4 hours. The reaction was cooled to 0 °C and quenched by addition of ammonium chloride aqueous solution (500 mL).The aqueous phase was extracted with ethyl acetate (500 mL × 2), and the combined organic extract was washed with brine (500 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna c18 250mm × 100mm × 10um;mobile phase: [5-30% CH_3CN in water(TFA)]) to afford the title compound (13.2 g, 62% yield) as a yellow solid.LC/MS (ESI) *m/z*: 389.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 - 8.06 (m, 1H), 6.57 (d, J = 8.4 Hz, 1H), 6.15 - 5.96 (m, 2H), 5.30 - 5.18 (m, 1H), 5.10 (dd, J = 5.2, 12.8 Hz, 1H), 4.56 (d, J = 7.2 Hz, 1H), 3.92 - 3.81 (m, 2H), 3.70 - 3.59 (m, 2H), 3.38 - 3.26 (m, 9H), 3.02 - 2.90 (m, 1H), 2.89 - 2.80 (m, 1H), 2.79 - 2.68 (m, 1H), 2.67 - 2.54 (m, 1H), 2.13 (dd, J = 2.8, 12.8 Hz, 1H).

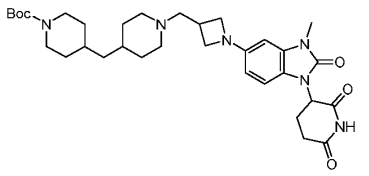
Step 6: Preparation of 1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]azetidine-3-carbaldehyde



A mixture of 3-(5-(3-(dimethoxymethyl)azetidin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (500 mg, 1.29 mmol, 1 *eq*) and trifluoroacetic acid (1.54 g, 13.46 mmol, 1 mL, 10.46 *eq*) in dichloromethane (1 mL) was stirred at 40 °C for 1 h. The mixture was concentrated under reduced pressure at 40 °C. The crude product was

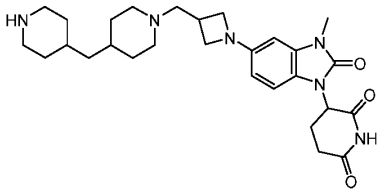
triturated with t-butyl methyl ether (50 mL) at 25 °C for 30 minutes to afford the title compound (710 mg, crude, trifluoroacetate) as a white solid. LC/MS (ESI) *m/z*: 361.0 $[M+H_3O]^+$.

Step 7: Preparation of *tert*-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]azetidin-3-yl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate



To a mixture of *tert*-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate (600 mg, 1.75 mmol, 1 *eq*, acetate) and 1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]azetidine-3-carbaldehyde (800 mg, 1.75 mmol, 1 *eq*, trifluoroacetate) in isopropanol (5 mL) and dichloromethane (15 mL) was added *N*,*N*-diisopropylethylamine (680 mg, 5.26 mmol, 0.9 mL, 3 *eq*) and sodium triacetoxyborohydride (743 mg, 3.51 mmol, 2 *eq*) in one portion at 20 °C under nitrogen. The reaction mixture was stirred at 20 °C for 16 hours. The mixture was concentrated under reduced pressure at 45 °C. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 40 mm × 15um; mobile phase: [15-45% CH_3CN in water (FA)]) to afford the title compound (930 mg, 87% yield) as a white solid. LC/MS (ESI) *m/z*: 609.5 $[M+H]^+$.

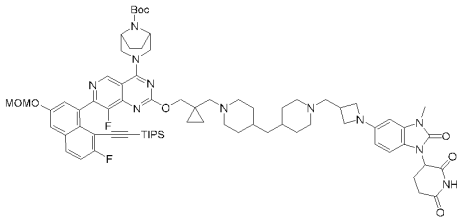
Step 8: Preparation of 3-[3-methyl-2-oxo-5-[3-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]azetidin-1-yl]benzimidazol-1-yl]piperidine-2,6-dione



To a mixture of *tert*-butyl 4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]azetidin-3-yl]methyl]-4-piperidyl]methyl]piperidine-1-carboxylate (930 mg, 1.53 mmol, 1 *eq*) in dichloromethane (4 mL) was added trifluoroacetic acid (3.07 g, 26.92 mmol, 2 mL, 17.62 *eq*) in one portion at 25 °C. The reaction mixture was stirred at 25 °C for 1 hours. The mixture was concentrated under reduced pressure at 45 °C to afford the title compound (950 mg, crude, trifluoroacetate) as a yellow oil. LC/MS (ESI) *m/z*: 509.4 $[M+H]^+$.

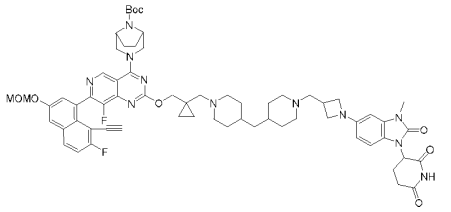
Step 9: Preparation of *tert*-butyl 3-[2-[[1-[[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]azetidin-3-yl]methyl]-4-piperidyl]methyl]-1-piperidyl]methyl]cyclopropyl]methoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-

triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



A mixture of 3-[3-methyl-2-oxo-5-[3-[[4-(4-piperidylmethyl)-1-piperidyl]methyl]azetidin-1-yl]benzimidazol-1-yl]piperidine-2,6-dione (950 mg, 1.53 mmol, 1 *eq*, trifluoroacetate), *N*,*N*-diisopropylethylamine (394 mg, 3.05 mmol, 0.5 mL, 2 *eq*), titanium tetraisopropanolate (650 mg, 2.29 mmol, 0.7 mL, 1.5 *eq*), and *tert*-butyl 3-[8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]-2-[(1-formylcyclopropyl)methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.28 g, 1.53 mmol, 1 *eq*) in dichloromethane (20 mL) and dimethyl sulfoxide (8 mL) was stirred at 45 °C for 10 h, then cooled to 25 °C. Sodium triacetoxyborohydride (647 mg, 3.05 mmol, 2 *eq*) was then added, and the reaction mixture was stirred at 25°C for 2 hours. The mixture was poured into ice-water (w/w = 1/1) (30 mL) and filtered. The filtrate was extracted with dichloromethane (20 mL × 3), and the combined organic extract was washed with brine (15 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC (TFA condition;column: Phenomenex luna C18 150 × 40mm × 15um; mobile phase: [42-72% CH_3CN in water (TFA)]) to afford the title compound (1.1 g, 54% yield) as a white solid. LC/MS (ESI) *m/z*: 1334.8 $[M+H]^+$.

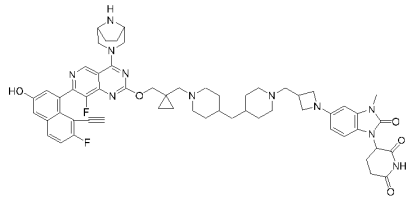
Step 10: Preparation of *tert*-butyl 3-[2-[[1-[[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]azetidin-3-yl]methyl]-4-piperidyl]methyl]-1-piperidyl]methyl]cyclopropyl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



A mixture of *tert*-butyl 3-[2-[[1-[[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]azetidin-3-yl]methyl]-4-piperidyl]methyl]-1-piperidyl]methyl]cyclopropyl]methoxy]-8-fluoro-7-[7-fluoro-3-(methoxymethoxy)-8-(2-triisopropylsilylethynyl)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.1 g, 0.82 mmol, 1 *eq*) and cesium fluoride (3.76 g, 24.72 mmol, 30 *eq*) in *N*,*N*-dimethylformamide (20 mL) was stirred at 25 °C for 3 h. The mixture was poured into ice-water

(w/w = 1/1) (50 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (30 mL × 4), and the combined organic extract was washed with brine (20 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum to afford the title compound (890 mg, crude) as a yellow solid. LC/MS (ESI) *m/z*: 1178.8 $[M+H]^+$.

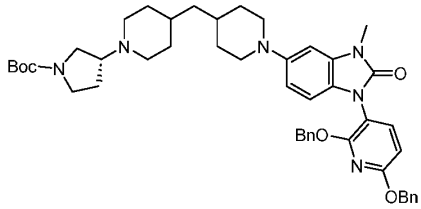
Step 11: Preparation of 3-[5-[3-[[4-[[1-[[1-[[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]methyl]-4-piperidyl]methyl]-1-piperidyl]methyl]azetidin-1-yl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



A mixture of *tert*-butyl 3-[2-[[1-[[4-[[1-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]azetidin-3-yl]methyl]-4-piperidyl]methyl]-1-piperidyl]methyl]cyclopropyl]methoxy]-7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (890 mg, 0.76 mmol, 1 *eq*) and trifluoroacetic acid (4.61 g, 40.39 mmol, 3 mL, 53.47 *eq*) in dichloromethane (6 mL) was stirred at 25 °C for 15 minutes. The mixture was concentrated under reduced pressure at 45 °C, and the residue was adjusted to pH 8 with *N,N*-diisopropylethylamine. The residue was purified by prep-HPLC (FA condition; column: Phenomenex luna C18 150 × 25 mm × 10 um; mobile phase: [10-30% CH_3CN in water (FA)]) to afford the title compound (134.7 mg, 16% yield, formic acid salt) as a white solid. LC/MS (ESI) *m/z*: 1034.8 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6 δ: 11.06 (s, 1H), 10.29 (br s, 1H), 9.13 (s, 1H), 8.15 (s, 1H), 8.00 (dd, J = 6.0, 9.2 Hz, 1H), 7.48 (t, J = 9.2 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.31 (d, J = 1.6 Hz, 1H), 6.12 (dd, J = 1.6, 8.4 Hz, 1H), 5.37 - 5.21 (m, 1H), 4.75 - 4.61 (m, 1H), 4.60 - 4.47 (m, 1H), 4.34 (br s, 2H), 4.20 (br s, 2H), 4.00 (t, J = 7.2 Hz, 2H), 3.94 - 3.81 (m, 3H), 3.52 (br t, J = 6.4 Hz, 2H), 3.40 - 3.36 (m, 2H), 3.29 (s, 7H), 3.18 - 3.10 (m, 2H), 2.96 - 2.75 (m, 4H), 2.71 - 2.58 (m, 3H), 2.06 - 1.93 (m, 5H), 1.77 (d, J = 12.8 Hz, 4H), 1.61 - 1.46 (m, 2H), 1.38 - 1.22 (m, 4H), 1.19 - 1.07 (m, 2H), 0.91 - 0.80 (m, 2H), 0.78 - 0.64 (m, 2H).

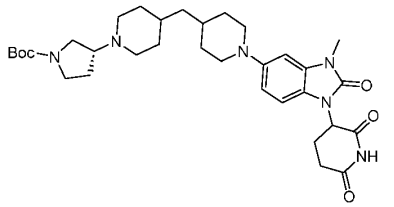
Example 157: Synthesis of 3-[5-[4-[[1-[(3R)-1-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]pyrrolidin-3-yl]-4-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione (**Compound 236**)

Step 1: Preparation of *tert*-butyl (3R)-3-[4-[[1-[1-(2,6-dibenzyloxy-3-pyridyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]pyrrolidine-1-carboxylate



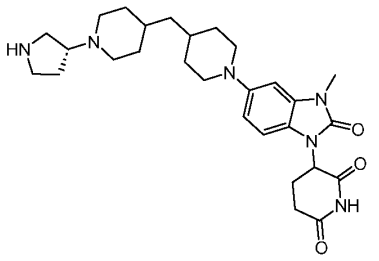
To a solution of 5-bromo-1-(2,6-dibenzyloxy-3-pyridyl)-3-methyl-benzimidazol-2-one (500 mg, 0.97 mmol, 1 *eq*) and *tert*-butyl (3R)-3-[4-(4-piperidylmethyl)-1-piperidyl]pyrrolidine-1-carboxylate (442 mg, 1.26 mmol, 1.3 *eq*) in dioxane (20 mL) were added cesium carbonate (946 mg, 2.90 mmol, 3 *eq*) and methanesulfonato(2-dicyclohexylphosphino-2,6-bis(dimethyl amino)-1,1-biphenyl)(2-amino-1,1-biphenyl-2 (78 mg, 0.09 mmol, 0.1 *eq*), and the reaction mixture was stirred at 100 °C for 16 h. The mixture was diluted with water (40 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1 to 1/10) to afford the title compound (452 mg, 59% yield) as a brown gum. LC/MS (ESI) *m/z*: 787.5 $[M+H]^+$.

Step 2: Preparation of (3R)-3-[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]pyrrolidine-1-carboxylate



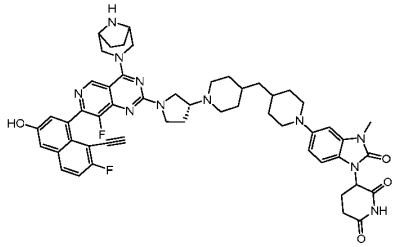
To a solution of *tert*-butyl (3R)-3-[4-[[1-[1-(2,6-dibenzyloxy-3-pyridyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]pyrrolidine-1-carboxylate (452 mg, 0.57 mmol, 1 *eq*) in tetrahydrofuran (20 mL) were added palladium on activated carbon catalyst (150 mg, 10% purity) and palladium hydroxide on activated carbon catalyst (150 mg, 20% purity) under nitrogen atmosphere, and the resulting mixture was degassed and purged with nitrogen for 3 times. The mixture was then stirred at 50 °C for 16 h under hydrogen (50 Psi) atmosphere. The mixture was filtered and concentrated in vacuum to afford the title compound (370 mg, crude) as a black gum. LC/MS (ESI) *m/z*: 609.4 $[M+H]^+$.

Step 3: Preparation of 3-[3-methyl-2-oxo-5-[4-[[1-[(3R)-pyrrolidin-3-yl]-4-piperidyl]methyl]-1-piperidyl]benzimidazol-1-yl]piperidine-2,6-dione



To *tert*-butyl (3R)-3-[4-[[1-[1-(2,6-dioxo-3-piperidyl)-3-methyl-2-oxo-benzimidazol-5-yl]-4-piperidyl]methyl]-1-piperidyl]pyrrolidine-1-carboxylate (370 mg, 0.61 mmol, 1 *eq*) in dichloromethane (8 mL) was added trifluoroacetic acid (4.61 g, 40.39 mmol, 3 mL, 66 *eq*), and the reaction mixture was stirred at 25 °C for 1 hours. The mixture was filtered and concentrated under vacuum, and the resulting residue was purified by prep-HPLC (column: Waters Atlantis T3 150*30 mm*5 um; mobile phase: [1-20% CH_3CN in water (FA)]) to afford the title compound (113 mg, 0.20 mmol, 33% yield, formic acid salt) as a colorless gum. LC/MS (ESI) *m/z*: 509.4 $[M+H]^+$.

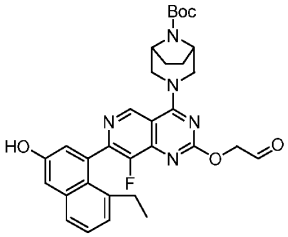
Step 4: Preparation of 3-[5-[4-[[1-[(3R)-1-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-2-yl]pyrrolidin-3-yl]-4-piperidyl]methyl]-1-piperidyl]-3-methyl-2-oxo-benzimidazol-1-yl]piperidine-2,6-dione



The title compound was prepared in an analogous manner to 3-(5-(4-((4-(((1-((3*R*)-1-(4-(3,8-diazabicyclo[3.2.1] octan-3-yl)-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-*d*] pyrimidin-2-yl)pyrrolidin-3-yl)piperidin-4-yl)methyl)piperidin-1-yl)methyl)piperidin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[*d*]imidazol-1-yl) piperidine-2,6-dione. (yellow solid, formic acid salt). LC/MS (ESI) *m/z*: 950.8 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 8.78 (s, 1H), 8.20 (s, 1H), 7.95 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.45 (t, *J* = 8.8 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.14 (d, *J* = 2.0 Hz, 1H), 6.92 (dd, *J* = 2.4, 8.0 Hz, 1H), 6.81 (s, 1H), 6.68 - 6.56 (m, 1H), 5.28 (dd, *J* = 3.6, 12.8 Hz, 1H), 4.49 - 4.36 (m, 1H), 4.28 - 4.18 (m, 1H), 3.94 (d, *J* = 7.2 Hz, 2H), 3.87 - 3.72 (m, 2H), 3.63 (s, 2H), 3.59 - 3.54 (m, 3H), 3.48 (s, 1H), 3.39 - 3.33 (m, 4H), 3.02 - 2.94 (m, 1H), 2.90 - 2.80 (m, 3H), 2.67 - 2.55 (m, 4H), 2.24 - 2.12 (m, 1H), 2.05 - 1.92 (m, 3H), 1.77 - 1.63 (m, 8H), 1.51 - 1.33 (m, 2H), 1.29 - 1.22 (m, 2H), 1.20 - 1.09 (m, 4H).

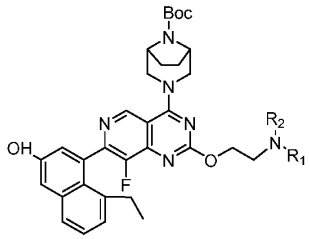
Example 158: Library Synthesis

Step 1:



To a solution of tert-butyl 3-[2-(2,2-dimethoxyethoxy)-7-[8-ethyl-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (295 umol) in acetone (1 mL) was added hydrochloric acid (12 M, 1 mL), the mixture was stirred at 20 °C for 10 min. Then aqueous sodium bicarbonate solution (27 mmol) and di-tert-butyl dicarbonate (354 umol) in THF (3 mL) was added at 20 °C. The mixture was stirred at 20 °C for 1 h under nitrogen atmosphere. The reaction was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (55 % ethyl acetate / petroleum ether) to afford product.

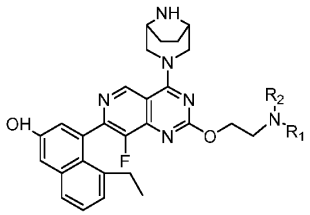
Step 2:



To a solution of tert-butyl 3-[7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-2-(2-oxoethoxy)pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (51 umol) in dichloromethane (1 mL) and isopropyl alcohol (0.1 mL) was added 2-(2,6-dioxo-3-piperidyl)-5-piperazin-1-yl-isoindoline-1,3-dione (54 umol), 2-methylpyridine borane complex (255 umol) and acetic acid (204 umol), the mixture was stirred at 20 °C for 1 h. The reaction mixture was filtered and concentrated. The residue was purified by

preparative thin layer chromatography (dichloromethane : methanol = 10:1) to afford product.

Step 3:



To a solution of tert-butyl 3-[2-[2-[4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-1-piperidyl]ethoxy]-7-(8-ethyl-3-hydroxy-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (44 umol) in hexafluoroisopropanol (1 mL) was added trifluoroacetic acid (0.2 mL) and stirred at 25 °C for 0.5 h. The reaction mixture was purified by preparative HPLC (Welch Xtimate C18 150x25mmx5μm; A: water with 0.225% v/v FA, B: acetonitrile; B%: 20-60; 25 min), lyophilized to afford product.

Compounds 225, 227, 231-233, and 237 were prepared according to the procedure in Example 158.

Characterization data for the compounds of the disclosure is presented below in Table 2.

Table 2.

Cmpd	LC/MS	NMR
1	923.1	
2	937.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 9.08 (s, 1H), 8.28 (s, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.36 (t, *J* = 8.4 Hz, 1H), 7.32-7.23 (m, 1H), 7.14-7.09 (m, 1H), 7.07-7.01 (m, 2H), 6.98-6.94 (m, 1H), 5.06-4.94 (m, 1H), 4.55-4.43 (m, 4H), 4.34-4.14 (m, 3H), 3.44 (br s, 3H), 3.29-3.21 (m, 5H), 3.01-2.81 (m, 4H), 2.75-2.55 (m, 6H), 2.42-2.11 (m, 4H), 2.06-1.92 (m, 3H), 1.82-1.68 (m, 8H), 1.67-1.59 (m, 2H), 1.49-1.37 (m, 1H), 1.20-1.07 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H)
3	937.1	
4	941.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 (s, 1H), 9.08 (s, 1H), 8.23 (s, 2H), 7.82 (d, J = 8.4 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.29-7.22 (m, 3H), 7.11 (d, J = 7.6 Hz, 1H), 6.97-6.93 (m, 1H), 5.13-5.05 (m, 1H), 4.96-4.88 (m, 1H), 4.56-4.44 (m, 4H), 3.92-3.79 (m, 7H), 3.19-3.08 (m, 2H), 2.74-2.65 (m, 1H), 2.68 (br d, *J* = 5.5 Hz, 4H), 2.46-2.36 (m, 9H), 2.33-2.15 (m, 5H), 2.13-2.09 (m, 3H), 2.06-2.00 (m, 1H), 1.83-1.69 (m, 4H), 0.80 (t, *J* = 7.6 Hz, 3H)
5	976.1	
6	901.1	
7	843.9	

8	926.1	
10	939.1	
11	926.1	
12	924.1	
13	939.1	
14	861.0	
15	915.0	
16	789.9	
17	903.0	
18	926.1	
19	882.0	
20	1008.2	
21	1010.1	
22	979.2	
25	979.2	
26	940.1	
27	896.0	
28	912.8	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.11 - 11.04 (m, 1H), 9.09 (s, 1H), 8.19 (s, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 6.4 Hz, 1H), 6.99 - 6.93 (m, 2H), 6.90 - 6.83 (m, 2H), 5.34 (dd, *J* = 5.2, 12.4 Hz, 1H), 4.50 - 4.39 (m, 4H), 3.67 (s, 1H), 3.63 (s, 1H), 3.61 (s, 3H), 3.45 (s, 1H), 3.11 - 3.05 (m, 3H), 2.94 (d, *J* = 9.2 Hz, 3H), 2.90 - 2.84 (m, 1H), 2.72 - 2.61 (m, 6H), 2.31 - 2.10 (m, 3H), 2.05 - 1.96 (m, 3H), 1.76 - 1.58 (m, 8H), 1.38 - 1.27 (m, 3H), 1.20 - 1.09 (m, 3H), 1.05 (t, *J* = 6.8 Hz, 2H), 0.82 (t, *J* = 7.2 Hz, 3H).
31	925.1	
32	911.0	
33	911.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.10 (s, 1H), 8.16 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.30-7.26 (m, 1H), 7.15-7.09 (m, 1H), 7.02-6.92 (m, 3H), 6.87-6.81 (m, 1H), 5.06-4.96 (m, 1H), 4.57-4.43 (m, 4H), 3.82-3.63 (m, 9H), 2.93-2.80 (m, 2H), 2.73-2.65 (m, 3H), 2.36-2.11 (m, 5H), 2.07 (s, 4H), 1.88-1.66 (m, 7H), 1.46-1.11 (m, 5H), 0.82 (t, *J* = 7.6 Hz, 3H)
34	812.9	
35	910.2	^{1}H NMR (400 MHz, DMSO-d_6) *δ* 10.98 (s, 1H), 10.45 - 9.82 (m, 1H), 9.07 (s, 1H), 8.15 (s, 1H), 7.98 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.57 - 7.36 (m, 3H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.19 - 6.96 (m, 2H), 5.11 (dd, *J* = 4.8, 13.2 Hz, 1H), 4.66 - 4.35 (m, 5H), 4.33 - 4.19 (m, 1H), 3.93 (s, 1H), 3.81 (br s, 2H), 3.71 (br d, *J* = 14.0 Hz, 2H), 3.04 - 2.93 (m, 3H), 2.92 - 2.84 (m, 1H), 2.80 - 2.63 (m, 7H), 2.14 - 1.92 (m, 4H), 1.84 - 1.69 (m, 6H), 1.67 - 1.59 (m, 2H), 1.56 - 1.43 (m, 1H), 1.42 - 1.32 (m, 1H), 1.29 - 1.19 (m, 2H), 1.19 - 1.05 (m, 4H)
36	798.9	^{1}H NMR (400 MHz, CD_3OD) δ 9.11 (s, 1H), 8.49 (s, 1H), 7.72 (s, 1H), 7.68-7.63 (m, 1H), 7.58-7.54 (m, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.32 (d, J = 2.8 Hz, 1H), 7.20-7.16 (m, 1H), 7.03 (d, *J* = 2.8 Hz, 1H), 5.20-5.14 (m, 1H), 4.77-4.70 (m, 4H), 4.62-4.60 (m, 2H), 4.52-4.42 (m, 2H), 4.01-3.93 (m, 2H), 3.91-3.79 (m, 2H), 3.60-3.49 (m, 2H), 2.99-2.86 (m, 2H), 2.85-2.74 (m, 3H), 2.59-2.45 (m, 1H), 2.44-2.24 (m, 2H), 2.23-2.15 (m, 1H), 2.09-1.92 (m, 8H), 0.90 (t, *J* = 7.6 Hz, 3H)
37	805.9	^{1}H NMR (400 MHz, CD_3OD) δ 9.09 (s, 1H), 8.43 (s, 1H), 7.76 (t, *J* = 8.8 Hz, 1H), 7.69-7.63 (m, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.34-7.30 (m, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.06-7.00 (m, 1H), 6.83 (dd, *J* = 2.4, 9.2 Hz, 1H), 6.76-6.68 (m, 1H), 4.76-4.62 (m, 6H), 4.19-4.07 (m, 2H), 3.96-3.81 (m, 2H), 3.42-3.36 (m, 4H), 3.00-2.93 (m, 2H), 2.87 (d, *J* = 5.6 Hz, 5H), 2.76-2.67 (m, 1H), 2.42-2.24 (m, 3H), 2.23-2.04 (m, 5H), 0.89 (s, 1H)

38	798.9	^{1}H NMR (400 MHz, CD_3OD) δ 9.11 (s, 1H), 8.49 (s, 1H), 7.76-7.74 (d, *J* = 8.0 Hz, 1H), 7.67-7.65 (d, *J* = 8.0 Hz, 1H), 7.48 (s, 1H), 7.46-7.41 (m, 1H), 7.41-7.36 (m, 1H), 7.33-7.31 (m, 1H), 7.19-7.15 (m, 1H), 7.03 (t, *J* = 2.0 Hz, 1H), 5.19-5.13 (m, 1H), 4.82-4.79 (m, 3H), 4.75 (d, *J* = 7.0 Hz, 2H), 4.49-4.44 (m, 2H), 4.03-3.94 (m, 2H), 3.92-3.78 (m, 2H), 3.57-3.48 (m, 2H), 3.29-3.22 (m, 2H), 2.98-2.85 (m, 2H), 2.84-2.69 (m, 3H), 2.53-2.41 (m, 1H), 2.41-2.24 (m, 2H), 2.23-2.13 (m, 1H), 2.07-1.92 (m, 8H), 0.91 (t, *J* = 7.4 Hz, 3H)
39	799.9	
40	813.9	
41	1007.7	^{1}H NMR (400 MHz, DMSO-d_6) *δ* 10.98 (s, 1H), 10.00 (s, 1H), 9.13 (s, 1H), 8.14 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.47 – 7.33 (m, 2H), 7.31 – 7.25 (m, 2H), 7.17 – 7.10 (m, 2H), 6.96 (d, *J* = 2.8 Hz, 1H), 5.15 – 5.05 (m, 1H), 4.65 – 4.54 (m, 2H), 4.52 – 4.37 (m, 3H), 4.33 – 4.23 (m, 1H), 3.80 – 3.66 (m, 3H), 3.28 –3.20 (m, 3H), 3.15 – 3.07 (m, 2H), 2.98 – 2.87 (m, 2H), 2.76 – 2.65 (m, 3H), 2.62 – 2.57 (m, 2H), 2.36 (s, 3H), 2.32 – 2.14 (m, 3H), 2.02 – 1.92 (m, 3H), 1.78 – 1.68 (m, 4H), 1.65 – 1.58 (m, 2H), 1.54 – 1.42 (m, 2H), 1.34 – 1.12 (m, 7H), 0.82 (t, *J* = 7.2 Hz, 3H)
42	1007.7	^{1}H NMR (400 MHz, DMSO-d_6) *δ* 10.98 (s, 1H), 9.09 (s, 1H), 8.16 (s, 1H), 8.14 (s, 1H), 7.67 (d, *J*=8.4 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.31 – 7.25 (m, 2H), 7.17 – 7.10 (m, 2H), 6.96 (d, *J*=2.4 Hz, 1H), 5.15 – 5.05 (m, 1H), 4.50 – 4.35 (m, 6H), 4.30 – 4.25 (m, 1H), 3.72 – 3.65 (m, 2H), 3.30 – 3.24 (m, 4H), 2.99 – 2.83 (m, 6H), 2.75 – 2.71 (m, 3H), 2.61 – 2.57 (m, 1H), 2.46 – 2.42 (m, 1H), 2.29 – 2.21 (m, 7H), 2.04– 1.91 (m, 6H), 1.82 – 1.74 (m, 2H), 1.63 – 1.53 (m, 6H), 1.36 – 1.18 (m, 5H), 1.10 – 1.04 (m, 6H), 0.81 (t, *J*=7.2 Hz, 3H)
43	1007.6	^{1}H NMR (400MHz, DMSO-d_6) *δ* 10.98 (s, 1H), 9.05 (s, 1H), 8.26 – 8.20 (m, 2H), 8.00 – 7.93 (m, 1H), 7.49 – 7.46 (m, 2H), 7.44 – 7.41 (m, 2H), 7.39 (d, *J*=2.4 Hz, 1H), 7.28 (d, *J*=7.2 Hz, 1H), 7.19 – 7.16 (m, 1H), 7.14 (d, *J*=8.0 Hz, 1H), 5.15 – 5.05 (m, 1H), 4.56 – 4.48 (m, 1H), 4.47 – 4.43 (m, 2H), 4.42 – 4.33 (m, 2H), 4.30 – 4.22 (m, 1H), 3.93 (s, 1H), 3.77 – 3.62 (m, 4H), 3.41 – 3.30 (m, 2H), 3.00 – 2.80 (m, 5H), 2.75 – 2.65 (m, 4H), 2.62 – 2.55 (m, 1H), 2.47 – 2.42 (m, 2H), 2.25 – 2.17 (m, 2H), 2.05 – 1.87 (m, 5H), 1.83 – 1.66 (m, 7H), 1.65 – 1.55 (m, 4H), 1.35 – 1.20 (m, 4H), 1.15 – 1.00 (m, 6H)
47	967.8	^{1}H NMR (400 MHz, CD_3OD) δ 9.14-9.04 (m, 1H), 8.41 (s, 1H), 7.64-7.60 (m, 2H), 7.38-7.36 (m, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.17-7.13 (m, 1H), 7.07-7.00 (m, 3H), 5.12-5.07 (m, 1H), 4.75-4.51 (m, 6H), 4.44-4.16 (m, 4H), 3.87-3.73 (m, 2H), 3.70-3.36 (m, 10H), 2.95-2.75 (m, 2H), 2.48 (s, 3H), 2.46-1.95 (m, 15H), 1.74 (d, *J* = 6.9 Hz, 2H), 0.92-0.80 (m, 3H)
48	967.8	^{1}H NMR (400 MHz, CD_3OD) δ 9.10 (s, 1H), 8.48 (s, 1H), 7.67-7.59 (m, 2H), 7.37-7.33 (m, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.09-7.00 (m, 3H), 5.15-5.05 (m, 1H), 4.71-4.34 (m, 10H), 4.17-4.16 (m, 1H), 3.86-3.58 (m, 7H), 3.50-3.39 (m, 4H), 2.91-2.73 (m, 2H), 2.43 (s, 3H), 2.41-1.97 (m, 15H), 1.71 (d, *J* = 7.6 Hz, 2H), 0.92-0.83 (m, 3H)
49	967.8	^{1}H NMR (400 MHz, CD_3OD) *δ* 9.13 - 8.95 (m, 1H), 8.41 (s, 1H), 7.61 (br d, *J* = 8.0 Hz, 1H), 7.33 (s, 3H), 7.31 - 7.26 (m, 1H), 7.23 - 6.98 (m, 3H), 5.18 - 5.09 (m, 1H), 4.72 (br d, *J* = 4.0 Hz, 5H), 4.49 (br d, *J* = 2.8 Hz, 2H), 4.45 - 4.33 (m, 2H), 4.32 - 4.25 (m, 1H), 3.88 - 3.77 (m, 2H), 3.63 (br s, 2H), 3.55 (br s, 1H), 3.49 (br s, 2H), 3.42 - 3.37 (m, 1H), 3.09 - 2.94 (m, 3H), 2.91 - 2.85 (m, 1H), 2.80 - 2.72 (m, 1H), 2.58 - 2.39 (m, 6H), 2.38 - 2.20 (m, 5H), 2.19 - 2.06 (m, 7H), 1.80 - 1.65 (m, 2H), 0.92 - 0.80 (m, 3H)
50	967.9	^{1}H NMR (400 MHz, CD_3OD) δ 9.10 (s, 1H), 8.46 (s, 1H), 7.67-7.59 (m, 2H), 7.38-7.34 (m, 1H), 7.29 (d, *J* = 2.4 Hz, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.07-7.05 (m, 2H), 7.01 (d, *J* = 2.4 Hz, 1H), 5.13-5.08 (m, 1H), 4.81-4.66 (m, 6H), 4.60-4.51 (m, 2H), 4.44-4.31 (m, 3H), 4.19 (s, 1H), 3.97-3.77 (m, 4H), 3.64 (s, 4H), 3.50 (d, *J* = 5.2 Hz, 1H), 3.13 (s, 3H), 2.98-2.85 (m, 2H), 2.52-1.65 (m, 18H), 0.94-0.77 (m, 3H)

51	967.4	^{1}H NMR (400 MHz, CD_3OD) δ 9.15-8.90 (m, 1H), 8.47 (s, 1H), 7.70-7.59 (m, 1H), 7.53-7.27 (m, 4H), 7.26-7.12 (m, 2H), 7.10-6.97 (m, 1H), 5.21-5.09 (m, 1H), 4.75-4.35 (m, 8H), 4.33-4.26 (m, 1H), 3.89-3.38 (m, 10H), 3.11-2.68 (m, 5H), 2.59-2.03 (m, 18H), 1.84-1.62 (m, 2H), 0.94-0.76 (m, 3H)
52	967.8	^{1}H NMR (400 MHz, CD_3OD) δ 9.10-9.07 (m, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.49-7.42 (m, 2H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.29 (s, 1H), 7.22-7.12 (m, 2H), 7.05-7.00 (m, 1H), 5.18-5.12 (m, 1H), 4.71-4.41 (m, 8H), 4.22 (s, 1H), 3.98 (s, 2H), 3.91-3.81 (m, 2H), 3.64-3.63 (m, 4H), 3.15 (s, 3H), 3.04-2.90 (m, 6H), 2.50-1.94 (m, 18H), 0.91-0.84 (m, 3H)
53	967.8	^{1}H NMR (400 MHz, CD_3OD) δ 9.10 (s, 1H), 8.48 (s, 1H), 7.63 (t, *J* = 8.4 Hz, 2H), 7.38-7.33 (m, 1H), 7.28 (d, *J* = 1.8 Hz, 1H), 7.15 (t, *J* = 7.0 Hz, 1H), 7.08-7.00 (m, 3H), 5.16-5.08 (m, 1H), 4.79-4.62 (m, 4H), 4.59-4.48 (m, 2H), 4.44-4.29 (m, 3H), 4.14 (s, 1H), 3.84-3.74 (m, 5H), 3.60-3.64 (m, 4H), 3.41-3.33 (m, 2H), 3.13 (s, 3H), 2.98-2.84 (m, 2H), 2.50-1.81 (m, 18H), 0.93-0.83 (m, 3H)
54	967.9	^{1}H NMR (400 MHz, CD_3OD) δ 9.14-9.01 (m, 1H), 8.46 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.51-7.40 (m, 2H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.30-7.27 (m, 1H), 7.25-7.10 (m, 2H), 7.05-6.98 (m, 1H), 5.21-5.12 (m, 1H), 4.80-4.71 (m, 2H), 4.66-4.50 (m, 3H), 4.50-4.34 (m, 3H), 4.26-4.13 (m, 1H), 3.97-3.76 (m, 4H), 3.72-3.46 (m, 5H), 3.16-3.10 (m, 3H), 3.09-2.80 (m, 6H), 2.58-1.80 (m, 17H), 0.94-0.79 (m, 3H)
55	993.5	^{1}H NMR (400 MHz, CD_3OD) δ 9.10 (s, 1H), 8.49 (s, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.52-7.42 (m, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.26 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 2.8 Hz, 1H), 5.21-5.11 (m, 1H), 4.81-4.77 (m, 2H), 4.75-4.64 (m, 2H), 4.55-4.41 (m, 2H), 4.03-3.93 (m, 2H), 3.91-3.78 (m, 2H), 3.62-3.39 (m, 6H), 3.36-3.32 (m, 2H), 3.07-2.67 (m, 10H), 2.59-2.45 (m, 1H), 2.42-2.13 (m, 3H), 2.09-1.82 (m, 11H), 1.77-1.58 (m, 2H), 1.57-1.36 (m, 6H), 1.33-1.20 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H)
56	896.8	^{1}H NMR (400 MHz, CD_3OD) δ 9.11 (s, 1H), 8.34 (s, 2H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.49-7.34 (m, 3H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 5.19-5.12 (m, 1H), 4.80-4.69 (m, 3H), 4.47 (d, *J* = 4.8 Hz, 2H), 4.03-3.94 (m, 2H), 3.90-3.78 (m, 2H), 3.69-3.58 (m, 2H), 3.53-3.46 (m, 2H), 3.43-3.36 (m, 2H), 3.03-2.86 (m, 3H), 2.84-2.72 (m, 3H), 2.60-2.46 (m, 1H), 2.41-2.23 (m, 2H), 2.21-2.13 (m, 1H), 2.07-1.92 (m, 6H), 1.87-1.69 (m, 3H), 1.59-1.26 (m, 8H), 0.90 (t, *J* = 7.6 Hz, 3H)
57	1007.5	^{1}H NMR (400 MHz, CD_3OD) δ 9.09 (s, 1H), 7.69-7.63 (m, 2H), 7.39-7.30 (m, 4H), 7.17 (d, *J* = 3.6 Hz, 1H), 7.01 (d, *J* = 1.6 Hz, 1H), 5.12-5.08 (m, 1H), 4.79-4.69 (m, 5H), 3.95 (s, 2H). 3.87-3.79 (m, 4H), 3.55-3.47 (m, 4H), 3.02-2.82 (m, 7H), 2.77-2.69 (m, 4H), 2.39-2.22 (m, 2H), 2.14-1.92 (m, 13H), 1.64-1.37 (m, 8H), 1.30-1.26 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H)
58	953.7	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 9.08 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.08 - 7.04 (m, 2H), 6.97 (d, *J* = 2.4 Hz, 1H), 5.04 (dd, *J* = 5.2, 13.2 Hz, 1H), 4.49 - 4.40 (m, 2H), 4.37 - 4.02 (m, 8H), 3.29 (br s, 9H), 2.95 - 2.70 (m, 5H), 2.58 (br d, *J* = 16.0 Hz, 1H), 2.39 - 2.15 (m, 4H), 2.12 - 1.88 (m, 3H), 1.80 - 1.63 (m, 10H), 1.56 - 1.50 (m, 1H), 0.81 (t, *J* = 7.2 Hz, 3H)
59	953.8	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 9.08 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.08 - 7.03 (m, 2H), 6.97 (d, *J* = 2.4 Hz, 1H), 5.04 (dd, *J* = 5.2, 13.2 Hz, 1H), 4.50 - 4.40 (m, 2H), 4.36 - 4.01 (m, 8H), 3.29 (br s, 9H), 3.08 - 2.63 (m, 5H), 2.58 (br d, *J* = 16.8 Hz, 1H), 2.47 - 2.13 (m, 4H), 2.12 - 1.81 (m, 3H), 1.81 - 1.62 (m, 10H), 1.56 - 1.48 (m, 1H), 0.81 (t, *J* = 7.2 Hz, 3H)

60	953.8	^{1}H NMR (400 MHz, CD_3OD) δ 9.18 - 9.04 (m, 1H), 8.54 - 8.37 (m, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.53 - 7.41 (m, 2H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.33 - 7.27 (m, 1H), 7.26 - 7.13 (m, 2H), 7.09 - 7.00 (m, 1H), 5.17 (td, *J* = 4.0, 13.2 Hz, 1H), 4.80 - 4.66 (m, 4H), 4.60 - 4.39 (m, 5H), 4.26 - 4.11 (m, 1H), 3.90 - 3.75 (m, 4H), 3.66 (d, *J* = 1.2 Hz, 4H), 3.54 - 3.47 (m, 1H), 3.17 - 2.97 (m, 4H), 2.95 - 2.75 (m, 2H), 2.57 - 2.31 (m, 4H), 2.26 - 2.05 (m, 7H), 2.01 - 1.84 (m, 4H), 1.31 (s, 1H), 0.94 - 0.85 (m, 3H)
61	953.7	^{1}H NMR (400 MHz, CD3OD) δ 9.16 - 9.07 (m, 1H), 8.55 - 8.39 (m, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.53 - 7.41 (m, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.33 - 7.28 (m, 1H), 7.27 - 7.11 (m, 2H), 7.08 - 7.00 (m, 1H), 5.23 - 5.12 (m, 1H), 4.77 - 4.65 (m, 4H), 4.59 - 4.38 (m, 5H), 4.16 (dt, J = 3.6, 7.6 Hz, 1H), 3.87 - 3.73 (m, 4H), 3.72 - 3.55 (m, 4H), 3.52 - 3.45 (m, 1H), 3.18 - 2.97 (m, 4H), 2.94 - 2.71 (m, 2H), 2.53 - 2.29 (m, 4H), 2.24 - 2.02 (m, 7H), 2.00 - 1.84 (m, 4H), 1.31 (s, 1H), 0.94 - 0.85 (m, 3H)
62	967.4	^{1}H NMR (400 MHz, CD_3OD) δ 9.09 (s, 1H), 8.50 (s, 1H), 7.69 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.39-7.31 (m, 2H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.18-7.13 (m, 1H), 7.01 (d, *J* = 2.8 Hz, 1H), 5.11-5.04 (m, 1H), 4.76-4.65 (m, 2H), 4.54-4.47 (m, 2H), 4.44-4.36 (m, 1H), 4.16-4.00 (m, 1H), 3.87-3.55 (m, 9H), 3.52-3.39 (m, 5H), 2.93-2.81 (m, 1H), 2.79-2.68 (m, 2H), 2.44-2.21 (m, 4H), 2.19-1.77 (m, 12H), 0.92-0.85 (m, 3H)
63	967.4	^{1}H NMR (400 MHz, CD_3OD) δ 9.10 (s, 1H), 8.49 (s, 1H), 7.69 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.39-7.32 (m, 2H), 7.28 (d, *J* = 2.8 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.16 (t, *J* = 5.6 Hz, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 5.11-5.05 (m, 1H), 4.75-4.66 (m, 2H), 4.56-4.48 (m, 2H), 4.44-4.37 (m, 1H), 4.20-4.04 (m, 1H), 3.89-3.53 (m, 9H), 3.50-3.38 (m, 5H), 2.93-2.81 (m, 1H), 2.78-2.65 (m, 2H), 2.42-2.23 (m, 4H), 2.22-1.78 (m, 12H), 0.93-0.84 (m, 3H)
64	967.8	^{1}H NMR (400 MHz, CD_3OD) δ 9.13 (s, 1H), 8.49 (s, 1H), 7.73 - 7.61 (m, 2H), 7.43 (dd, *J* = 3.2, 7.2 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.33 - 7.28 (m, 2H), 7.17 (t, *J* = 6.8 Hz, 1H), 7.03 (s, 1H), 5.11 (dd, *J* = 5.2, 12.4 Hz, 1H), 4.79 (t, *J* = 12.0 Hz, 2H), 4.73 - 4.66 (m, 2H), 4.61 - 4.52 (m, 2H), 4.46 - 4.39 (m, 1H), 4.21 (s, 1H), 3.94 - 3.78 (m, 4H), 3.78 - 3.64 (m, 4H), 3.51 (d, *J* = 4.8 Hz, 1H), 3.41 - 3.35 (m, 1H), 3.31 - 3.26 (m, 2H), 2.92 - 2.81 (m, 1H), 2.80 - 2.65 (m, 2H), 2.48 - 2.20 (m, 6H), 2.19 - 1.85 (m, 10H), 0.89 (q, *J* = 7.6 Hz, 3H)
65	967.8	^{1}H NMR (400 MHz, CD_3OD) δ 9.10 (s, 1H), 8.48 (s, 1H), 7.70 - 7.58 (m, 2H), 7.41 (dd, *J* = 3.2, 7.2 Hz, 1H), 7.38 - 7.32 (m, 1H), 7.31 - 7.26 (m, 2H), 7.15 (t, *J* = 6.8 Hz, 1H), 7.01 (s, 1H), 5.09 (dd, *J* = 5.2, 12.4 Hz, 1H), 4.82 - 4.73 (m, 2H), 4.72 - 4.65 (m, 2H), 4.60 - 4.50 (m, 2H), 4.40 (dd, *J* = 9.2, 12.4 Hz, 1H), 4.24 - 4.14 (m, 1H), 3.93 - 3.76 (m, 4H), 3.75 - 3.62 (m, 4H), 3.49 (d, *J* = 5.4 Hz, 1H), 3.35 (s, 1H), 3.29 - 3.25 (m, 2H), 2.91 - 2.78 (m, 1H), 2.77 - 2.62 (m, 2H), 2.46 - 2.18 (m, 6H), 2.17 - 1.85 (m, 10H), 0.87 (q, *J* = 7.6 Hz, 3H)
66	910.3	^{1}H NMR (400 MHz, CD_3OD) δ 9.11 (s, 1H), 8.47 (s, 1H), 7.67 - 7.60 (m, 2H), 7.41 - 7.27 (m, 4H), 7.18 (d, *J* = 6.8 Hz, 1H), 7.01 (d, *J* = 2.8 Hz, 1H), 5.09 (dd, *J* = 5.6, 12.4 Hz, 1H), 4.75 (dd, *J* = 13.6, 19.2 Hz, 4H), 4.07 - 3.98 (m, 2H), 3.88 (dd, *J* = 13.6, 18.4 Hz, 2H), 3.74 (d, *J* = 12.0 Hz, 2H), 3.63 (d, *J* = 9.6 Hz, 2H), 3.48 (d, *J* = 4.4 Hz, 2H), 2.97 (t, *J* = 12.0 Hz, 2H), 2.91 - 2.81 (m, 3H), 2.78 - 2.65 (m, 2H), 2.41 - 2.23 (m, 2H), 2.13 - 1.93 (m, 7H), 1.84 - 1.71 (m, 3H), 1.63 - 1.41 (m, 5H), 1.29 (t, *J* = 6.8 Hz, 2H), 0.90 (t, *J* = 7.2 Hz, 3H)
67	910.7	^{1}H NMR (400 MHz, CD_3OD) δ 9.10 (s, 1H), 8.42 (s, 1H), 7.69 - 7.60 (m, 2H), 7.40 - 7.34 (m, 1H), 7.31 (dd, *J* = 2.4, 8.8 Hz, 2H), 7.22 - 7.14 (m, 2H), 7.01 (d, *J* = 2.8 Hz, 1H), 5.06 (dd, *J* = 5.6, 12.4 Hz, 1H), 4.80 (d, *J* = 5.6 Hz, 2H), 4.70 (d, *J* = 15.2 Hz, 2H), 4.03 (d, *J* = 12.8 Hz, 2H), 3.92 (s, 2H), 3.82 (t, *J* = 14.8 Hz, 2H), 3.58 (d, *J* = 11.2 Hz, 2H), 3.43 (s, 2H), 3.03 - 2.80 (m, 5H), 2.79 - 2.63 (m, 2H), 2.45 - 2.21 (m, 2H), 2.14 - 2.05 (m, 1H), 2.03 - 1.87 (m, 6H), 1.86 - 1.78 (m, 2H), 1.77 - 1.63 (m, 2H), 1.52 - 1.37 (m, 2H), 1.32 - 1.22 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H)

69	1025.7	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.06 (s, 1H), 8.23 - 8.18 (m, 1H), 8.18 - 8.14 (m, 1H), 8.01 - 7.94 (m, 1H), 7.50 - 7.37 (m, 3H), 7.21 - 7.10 (m, 2H), 5.06 (dd, *J* = 5.1, 13.1 Hz, 1H), 4.60 - 4.41 (m, 6H), 4.35 - 4.26 (m, 2H), 3.01 - 2.86 (m, 6H), 2.80 - 2.71 (m, 4H), 2.63 - 2.54 (m, 2H), 2.32 - 2.21 (m, 4H), 2.14 - 1.94 (m, 6H), 1.86 - 1.67 (m, 8H), 1.63 - 1.53 (m, 4H), 1.39 - 1.24 (m, 4H), 1.19 - 1.05 (m, 6H).
79	1061.2	^{1}H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.06 (s, 1H), 8.21 (s, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.52 - 7.43 (m, 2H), 7.40 (d, J = 2.4 Hz, 1H), 7.20 - 7.13 (m, 2H), 5.07 (dd, J = 5.2, 13.2 Hz, 1H), 4.56 - 4.44 (m, 4H), 4.38 - 4.29 (m, 2H), 3.93 (s, 1H), 3.72 - 3.62 (m, 4H), 3.54 - 3.40 (m, 3H), 3.02 (d, J = 10.4 Hz, 2H), 2.95 - 2.85 (m, 3H), 2.82 - 2.67 (m, 4H), 2.64 - 2.56 (m, 1H), 2.46 - 2.37 (m, 1H), 2.17 (d, J = 6.8 Hz, 2H), 2.07 - 1.94 (m, 3H), 1.92 - 1.59 (m, 16H), 1.43-1.37 (m, 4H), 1.32 - 1.22 (m, 2H)
80	1050.3	
81	1041.6	^{1}H NMR (400 MHz, CD3OD-d4) δ 9.00 (s, 1H), 7.85 (dd, J = 5.6, 9.2 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.36-7.16 (m, 4H), 5.12 (dd, J = 5.2, 13.2 Hz, 1H), 4.67-4.54 (m, 4H), 4.50-4.36 (m, 2H), 3.75-3.62 (m, 4H), 3.50-3.43 (m, 2H), 3.36 (s, 1H), 3.08 (dd, J = 1.6, 4.0 Hz, 2H), 2.98-2.82 (m, 5H), 2.81-2.70 (m, 3H), 2.57-2.43 (m, 1H), 2.28-2.10 (m, 5H), 1.99 (s, 2H), 1.89-1.67 (m, 10H), 1.65-1.53 (m, 2H), 1.49-1.36 (m, 3H), 1.25 (d, J = 6.8 Hz, 6H)
82	1022.2	
83	994.1	^{1}H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.05 (s, 1H), 8.21 (s, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.47 (t, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.01 - 6.93 (m, 1H), 6.92 - 6.83 (m, 2H), 5.35 (br dd, J = 5.6, 12.4 Hz, 1H), 4.54 - 4.43 (m, 3H), 4.35 (br d, J = 11.6 Hz, 1H), 3.94 (s, 1H), 3.70 - 3.57 (m, 9H), 3.10 (br d, J = 8.4 Hz, 2H), 2.93 - 2.83 (m, 1H), 2.76 - 2.61 (m, 6H), 2.46 (br s, 4H), 2.35 (br s, 4H), 2.26 - 2.19 (m, 2H), 2.03 - 1.96 (m, 1H), 1.84 - 1.76 (m, 2H), 1.71 (br s, 4H), 1.66 - 1.58 (m, 1H), 1.42 (br s, 8H), 1.35 - 1.25 (m, 2H)
84	1020.2	
85	999.2	^{1}H NMR (400 MHz, DMSO-d6) δ 10.94 (s, 1H), 9.13 (s, 1H), 8.17 (s, 2H), 7.82 - 7.70 (m, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.09 - 6.96 (m, 3H), 5.04 (dd, J = 5.2, 13.2 Hz, 1H), 4.62 - 4.47 (m, 2H), 4.44 - 4.36 (m, 1H), 4.34 - 4.25 (m, 2H), 4.23 - 4.09 (m, 2H), 3.95 - 3.67 (m, 7H), 3.39 - 3.23 (m, 2H), 2.96 - 2.70 (m, 6H), 2.59 (d, J = 16.4 Hz, 1H), 2.43 - 2.29 (m, 6H), 2.28 - 2.04 (m, 7H), 1.96 - 1.88 (m, 2H), 1.85 - 1.72 (m, 9H), 1.53 - 1.34 (m, 2H), 1.21 - 1.09 (m, 2H), 0.77 - 0.67 (m, 3H)
86	1011.2	^{1}H NMR (400 MHz, DMSO-d6) δ 10.94 (s, 1H), 9.14 - 9.06 (m, 1H), 8.19 (s, 3H), 7.76 (dd, J = 6.0, 9.2 Hz, 1H), 7.49 (d, J = 9.2 Hz, 1H), 7.39 - 7.30 (m, 2H), 7.09 - 6.99 (m, 3H), 5.03 (dd, J = 5.2, 13.2 Hz, 1H), 4.51 - 4.40 (m, 4H), 4.33 - 4.28 (m, 1H), 4.16 (s, 1H), 3.85 (br d, J = 12.8 Hz, 4H), 2.96 - 2.88 (m, 3H), 2.87 - 2.75 (m, 5H), 2.73 - 2.66 (m, 2H), 2.61 - 2.55 (m, 1H), 2.41 - 2.31 (m, 2H), 2.20 - 2.08 (m, 3H), 2.06 - 1.84 (m, 6H), 1.80 - 1.64 (m, 7H), 1.58 (br d, J = 11.6 Hz, 4H), 1.39 - 1.21 (m, 3H), 1.20 - 0.99 (m, 8H), 0.72 (t, J = 7.2 Hz, 3H)
87	1007.2	
88	1025.2	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.06 (s, 1H), 8.20 (s, 3H), 8.01 - 7.92 (m, 1H), 7.51 - 7.41 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.21 - 7.10 (m, 2H), 5.07 (dd, J = 5.2, 13.2 Hz, 1H), 4.59 - 4.42 (m, 4H), 4.41 - 4.26 (m, 2H), 3.93 (s, 1H), 3.80 - 3.64 (m, 4H), 3.47 (d, J = 1.2 Hz, 2H), 2.99 - 2.82 (m, 5H), 2.80 - 2.69 (m, 4H), 2.64 - 2.53 (m, 2H), 2.45 - 2.30 (m, 2H), 2.23 - 2.14 (m, 2H), 2.08 - 1.92 (m, 5H), 1.81 - 1.69 (m, 6H), 1.64 (t, J = 11.6 Hz, 4H), 1.51 (d, J = 1.6 Hz, 2H), 1.42 - 1.32 (m, 1H), 1.31 - 1.22 (m, 2H), 1.21 - 1.03 (m, 6H)
89	925.0	

90	1025.2	^{1}H NMR (400 MHz, DMSO-d6) δ 10.94 (s, 1H), 8.99 (s, 1H), 8.20 (s, 3H), 7.97 (dd, J = 6.0, 8.8 Hz, 1H), 7.53 - 7.42 (m, 2H), 7.39 (s, 1H), 7.22 - 7.08 (m, 1H), 7.07 - 6.93 (m, 2H), 5.04 (dd, J = 5.2, 13.2 Hz, 1H), 4.36 - 4.13 (m, 5H), 3.90 - 3.81 (m, 5H), 3.62 (s, 10H), 2.94 - 2.75 (m, 6H), 2.64 - 2.52 (m, 4H), 2.39 - 2.28 (m, 2H), 2.18 - 2.08 (m, 4H), 2.02 - 1.91 (m, 2H), 1.80 - 1.62 (m, 9H), 1.60 - 1.34 (m, 7H), 1.25 - 1.07 (m, 3H)
91	1025.2	
92	997.1	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.05 (s, 1H), 8.21 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.55 - 7.42 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.21 - 7.11 (m, 2H), 5.07 (dd, J = 5.2, 13.2 Hz, 1H), 4.56 - 4.41 (m, 5H), 4.40 - 4.23 (m, 3H), 3.94 (s, 1H), 3.73 - 3.59 (m, 4H), 3.09 (b s, 4H), 2.99 - 2.86 (m, 3H), 2.71 (t, J = 4.8 Hz, 2H), 2.58 (d, J = 16.8 Hz, 1H), 2.46 - 2.31 (m, 5H), 2.19 (d, J = 6.8 Hz, 2H), 2.11 - 1.89 (m, 3H), 1.74 (s, 4H), 1.65 (d, J = 11.2 Hz, 2H), 1.60 - 1.39 (m, 9H), 1.20 - 0.99 (m, 2H)
93	979.1	^{1}H NMR (400 MHz, DMSO-d6) δ 10.94 (s, 1H), 9.04 (s, 1H), 8.20 (s, 2H), 7.96 (dd, J = 6.0, 9.2 Hz, 1H), 7.58 - 7.42 (m, 2H), 7.38 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 7.07 - 6.95 (m, 2H), 5.03 (dd, J = 5.2, 13.2 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.44 (t, J = 5.6 Hz, 2H), 4.39 - 4.31 (m, 2H), 4.28 (s, 1H), 4.17 (d, J = 16.8 Hz, 2H), 3.93 (s, 1H), 3.70 (s, 2H), 3.67 - 3.60 (m, 2H), 3.28 (d, J = 0.8 Hz, 4H), 2.98 - 2.82 (m, 3H), 2.70 (t, J = 5.2 Hz, 2H), 2.62 - 2.53 (m, 1H), 2.43 - 2.26 (m, 5H), 2.21 - 2.12 (m, 2H), 2.08 - 1.88 (m, 3H), 1.73 (s, 4H), 1.68 - 1.59 (m, 2H), 1.48 (d, J = 4.4 Hz, 9H), 1.17 - 0.94 (m, 2H)
94	1050.3	^{1}H NMR (400 MHz, DMSO-d6) δ 11.06 (s, 1H), 9.06 (s, 1H), 8.16 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 7.02 - 6.91 (m, 1H), 6.90 - 6.76 (m, 2H), 5.66 - 5.54 (m, 1H), 5.28 (br dd, J = 5.2, 12.8 Hz, 1H), 4.54 (br d, J = 12.4 Hz, 1H), 4.47 (br t, J = 5.2 Hz, 2H), 4.39 (br d, J = 12.8 Hz, 1H), 3.93 (s, 1H), 3.83 (br s, 2H), 3.71 (br s, 3H), 3.08 (br d, J = 10.4 Hz, 2H), 3.00 - 2.82 (m, 6H), 2.76 - 2.70 (m, 2H), 2.69 - 2.56 (m, 4H), 2.30 (br d, J = 6.0 Hz, 2H), 2.10 - 1.92 (m, 5H), 1.85 - 1.72 (m, 6H), 1.69 - 1.55 (m, 5H), 1.45 (dd, J = 6.8, 10.8 Hz, 6H), 1.37 - 1.20 (m, 4H), 1.19 - 1.03 (m, 6H)
95	1038.2	
96	1010.1	
97	1021.2	
98	1050.3	
99	950.1	^{1}H NMR (400 MHz, CD3OD-d4) δ 9.01 (s, 1H), 7.89-7.83 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.36-7.29 (m, 2H), 7.21 (d, J = 2.4 Hz, 1H), 7.07-7.02 (m, 2H), 5.13-5.07 (m, 1H), 4.63 (br t, J = 13.6 Hz, 3H), 4.51-4.47 (m, 1H), 4.40-4.32 (m, 3H), 3.88 (br d, J = 11.6 Hz, 2H), 3.75-3.65 (m, 4H), 3.37 (s, 1H), 3.23-3.13 (m, 2H), 2.91-2.74 (m, 4H), 2.62-2.39 (m, 3H), 2.18-2.07 (m, 2H), 1.90-1.69 (m, 8H), 1.64-1.53 (m, 1H), 1.51-1.40 (m, 1H), 1.29-1.14 (m, 6H), 0.80-0.71 (m, 2H), 0.56 (br s, 2H)
100	1020.2	^{1}H NMR (400 MHz, CD3OD-d4) δ 9.02 (s, 1H), 7.87 - 7.85 (m, 1H), 7.62 (dd, J = 2.4, 8.8 Hz, 1H), 7.40 - 7.26 (m, 2H), 7.21 (t, J = 2.0 Hz, 1H), 7.10 - 7.00 (m, 2H), 5.09 (d, J = 4.8 Hz, 1H), 4.68 - 4.54 (m, 4H), 4.48 - 4.28 (m, 5H), 3.90 (d, J = 12.4 Hz, 2H), 3.77 - 3.60 (m, 5H), 3.36 (s, 1H), 2.91 - 2.78 (m, 5H), 2.64 - 2.43 (m, 9H), 2.29 - 2.17 (m, 4H), 1.95 - 1.69 (m, 14H), 1.33 - 1.22 (m, 2H)
101	1026.2	
102	1022.2	
103	916.0	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.06 (s, 1H), 8.12 (s, 1H), 8.01 – 7.93 (m, 1H), 7.50 – 7.42 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.19 - 7.12 (m, 2H), 7.24 - 7.17 (m, 1H), 7.07 - 6.97 (m, 2H), 5.05 (dd, J = 5.2, 9.2 Hz, 1H), 4.56 - 4.51 (m, 1H), 4.50 - 4.45 (m, 1H), 4.42 - 4.35 (m, 2H), 4.33 – 4.28 (m, 1H), 4.25 – 4.15 (m, 2H), 3.96 – 3.93 (m, 1H), 3.79 – 3.64 (m, 5H), 3.56 –

		3.48 (m, 2H), 3.41 - 3.26 (m, 4H), 2.96 - 2.87 (m, 3H), 2.85 - 2.76 (m, 1H), 2.62 - 2.55 (m, 1H), 2.44 - 2.38 (m, 1H), 2.37 (s, 3H), 2.25 – 2.19 (m, 1H), 1.99 – 1.86 (m, 5H), 1.77 – 1.74 (m, 3H), 1.63 – 1.53 (m, 2H)
104	898.0	
105	1038.2	
106	1027.1	^{1}H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.05 (s, 1H), 8.21 (s, 2H), 7.98 (dd, J = 5.8, 9.2 Hz, 1H), 7.51 - 7.42 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.20 - 7.10 (m, 2H), 5.07 (dd, J = 5.2, 13.2 Hz, 1H), 4.55 - 4.43 (m, 4H), 4.39 - 4.27 (m, 3H), 3.94 (s, 1H), 3.76 - 3.71 (m, 2H), 3.69 - 3.62 (m, 2H), 3.52 - 3.44 (m, 2H), 3.39 (s, 2H), 3.16 (s, 2H), 2.97 - 2.85 (m, 1H), 2.83 - 2.64 (m, 8H), 2.62 - 2.54 (m, 1H), 2.44 - 2.31 (m, 1H), 2.17 (d, J = 6.4 Hz, 3H), 2.08 - 1.94 (m, 3H), 1.75 (s, 9H), 1.69 - 1.59 (m, 1H), 1.47 - 1.32 (m, 4H), 1.31 - 1.17 (m, 2H)
107	1007.2	
108	1006.2	
109	1041.6	
110	1007.2	^{1}H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.08 (s, 1H), 8.21 (s, 3H), 7.99 (dd, J = 6.0, 9.2 Hz, 1H), 7.47 (t, J = 9.2 Hz, 1H), 7.44 - 7.37 (m, 2H), 7.25 (dd, J = 2.0, 8.4 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.15 (d, J = 1.6 Hz, 1H), 5.10 (dd, J = 5.2, 13.2 Hz, 1H), 4.57 (d, J = 12.4 Hz, 1H), 4.52-4.48 (m, 2H), 4.42 (d, J = 12.4 Hz, 1H), 4.37 - 4.30 (m, 1H), 4.24 - 4.17 (m, 1H), 3.95 (s, 1H), 3.90-3.88 (m, 2H), 3.81 - 3.69 (m, 4H), 3.05 - 2.87 (m, 5H), 2.82 - 2.68 (m, 4H), 2.63-2.57 (m, 2H), 2.43 - 2.29 (m, 4H), 2.13-2.07 (m, 4H), 2.01 - 1.94 (m, 1H), 1.87 - 1.71 (m, 7H), 1.63-1.57 (m, 4H), 1.41 - 1.29 (m, 2H), 1.27 - 1.04 (m, 8H)
111	1008.2	
112	1031.1	^{1}H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.04 (s, 1H), 8.20 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.50 - 7.43 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.24 - 7.15 (m, 2H), 5.07 (dd, J = 4.8, 13.2 Hz, 1H), 4.52 - 4.45 (m, 2H), 4.41 - 4.29 (m, 3H), 4.24 - 4.20 (m, 1H), 4.14 - 4.09 (m, 1H), 3.94 (d, J = 2.0 Hz, 1H), 3.59 (s, 5H), 3.05 - 2.97 (m, 3H), 2.94 (s, 2H), 2.81 - 2.73 (m, 4H), 2.60 (d, J = 2.8 Hz, 2H), 2.37 - 2.31 (m, 5H), 2.24 - 2.13 (m, 4H), 2.02 - 1.93 (m, 3H), 1.92 - 1.85 (m, 3H), 1.78 (d, J = 8.4 Hz, 4H), 1.72 - 1.65 (m, 4H), 1.45 - 1.34 (m, 2H)
113	1029.6	
114	941.0	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 - 10.89 (m, 1H), 9.02 (t, J = 2.8 Hz, 1H), 8.16 (d, J = 3.2 Hz, 1H), 7.96 (dd, J = 6.0, 9.6 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 8.8 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.08 - 7.00 (m, 2H), 5.06 - 5.00 (m, 1H), 4.49 - 4.39 (m, 2H), 4.31 (d, J = 16.8 Hz, 2H), 4.24 - 4.16 (m, 2H), 4.04 (t, J = 5.2 Hz, 2H), 3.92 (s, 1H), 3.66 - 3.58 (m, 6H), 3.51 (d, J = 1.6 Hz, 6H), 3.19 - 3.14 (m, 4H), 2.95 - 2.83 (m, 2H), 2.60 - 2.56 (m, 2H), 2.35 (d, J = 4.0 Hz, 1H), 2.02 - 1.90 (m, 3H), 1.67 (s, 5H), 1.63 - 1.58 (m, 1H)
115	995.1	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.06 (s, 1H), 8.17 (s, 2H), 7.98 (dd, J = 6.0, 9.2Hz, 1H), 7.50 - 7.37 (m, 3H), 7.32 - 7.26 (m, 1H), 7.21 - 7.11 (m, 2H), 5.11 (dd, J = 5.2, 9.2Hz, 1H), 4.61 - 4.51 (m, 1H), 4.46 - 4.36 (m, 3H), 4.33 - 4.24 (m, 2H), 4.16 - 4.10 (m, 1H), 3.95 - 3.92 (m, 1H), 3.83 (s, 2H), 3.77 - 3.69 (m, 2H), 3.40 - 3.25 (m, 4H), 2.99 - 2.86 (m, 1H), 2.85 - 2.78 (m, 1H), 2.75 - 2.66 (m, 4H), 2.62 - 2.54 (m, 2H), 2.36 (s, 3H), 2.23 - 2.16 (m, 3H), 2.11 - 1.99 (m, 3H), 1.94 - 1.73 (m, 11H), 1.69 - 1.60 (m, 1H), 1.48 - 1.36 (m, 2H), 1.34 - 1.19 (m, 2H)
116	995.1	
117	941.0	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.08 - 8.97 (m, 1H), 8.17 (s, 1H), 7.97 (dd, J = 5.6, 9.2 Hz, 1H), 7.50 - 7.40 (m, 2H), 7.39 (d, J = 2.4 Hz,

		1H), 7.34 (d, J = 7.6 Hz, 1H), 7.20 - 7.14 (m, 2H), 5.12 (dd, J = 5.2, 13.2 Hz, 1H), 4.52 - 4.40 (m, 3H), 4.37 - 4.27 (m, 2H), 4.26 - 4.19 (m, 1H), 4.11 - 4.03 (m, 2H), 3.92 (s, 1H), 3.64 (s, 4H), 3.53 (s, 2H), 3.24 - 3.22 (m, 2H), 3.16 (d, J = 2.0 Hz, 2H), 3.06 - 3.00 (m, 4H), 2.92 - 2.87 (m, 1H), 2.64 - 2.54 (m, 2H), 2.51 - 2.51 (m, 3H), 2.45 - 2.40 (m, 1H), 2.04 - 1.95 (m, 3H), 1.70 (s, 6H)
118	884.0	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.09 (s, 1H), 8.18 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.45 - 7.33 (m, 2H), 7.32 - 7.26 (m, 2H), 7.14 (dd, J = 7.6, 14.4 Hz, 2H), 6.97 (d, J = 2.4 Hz, 1H), 5.10 (dd, J = 5.2, 13.2 Hz, 1H), 4.48 - 4.36 (m, 4H), 4.33 - 4.23 (m, 2H), 4.22 - 4.13 (m, 1H), 3.66 (d, J = 1.2 Hz, 1H), 3.61 - 3.57 (m, 3H), 3.54 - 3.47 (m, 5H), 2.95 - 2.77 (m, 5H), 2.68 - 2.59 (m, 1H), 2.36 (s, 3H), 2.29 - 2.17 (m, 3H), 2.01 - 1.89 (m, 5H), 1.69 - 1.54 (m, 6H), 0.81 (t, J = 7.6 Hz, 3H)
119	987.1	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.08 (s, 1H), 8.14 (s, 2H), 7.98 (dd, J = 5.6, 9.2 Hz, 1H), 7.56 - 7.43 (m, 2H), 7.40 (d, J = 2.6 Hz, 1H), 7.27 - 7.13 (m, 2H), 5.07 (dd, J = 4.6, 13.4 Hz, 1H), 4.60 (d, J = 13.2 Hz, 1H), 4.54 - 4.40 (m, 4H), 4.31 (d, J = 16.8 Hz, 1H), 3.99 (s, 2H), 3.93 (s, 1H), 3.79 - 3.70 (m, 2H), 3.53 - 3.40 (m, 3H), 3.04 (s, 4H), 3.00 - 2.82 (m, 3H), 2.72 (d, J = 12.4 Hz, 3H), 2.65 (s, 1H), 2.62 - 2.53 (m, 3H), 2.47 - 2.34 (m, 4H), 1.98 (dd, J = 6.0, 11.2 Hz, 1H), 1.91 - 1.81 (m, 6H), 1.80 - 1.71 (m, 2H), 1.68 (s, 3H)
120	1015.1	^{1}H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.07 (s, 1H), 8.15 (s, 2H), 7.98 (dd, J = 6.0, 9.0 Hz, 1H), 7.50 - 7.44 (m, 2H), 7.40 (d, J = 2.4 Hz, 1H), 7.23 - 7.15 (m, 2H), 5.07 (dd, J = 5.2, 13.2 Hz, 1H), 4.65 - 4.36 (m, 6H), 4.31 (d, J = 16.8 Hz, 1H), 3.96 - 3.87 (m, 4H), 3.74 (t, J = 12.8 Hz, 4H), 3.02 (dd, J = 10.0, 11.2 Hz, 4H), 2.96 - 2.88 (m, 2H), 2.81 (s, 3H), 2.60 (s, 1H), 2.55 (s, 4H), 2.02 - 1.88 (m, 4H), 1.87 - 1.68 (m, 6H), 1.49 - 1.35 (m, 8H)
121	997.1	^{1}H NMR (400 MHz, DMSO-d6) δ 11.00 (s, 1H), 9.11 (s, 1H), 8.16 (s, 1H), 7.99 (dd, J = 6.0, 9.2 Hz, 1H), 7.57 - 7.38 (m, 3H), 7.32 (d, J = 7.6 Hz, 1H), 7.24 - 7.11 (m, 2H), 5.12 (dd, J = 5.2, 13.2 Hz, 1H), 4.65 (br d, J = 12.8 Hz, 1H), 4.56 - 4.48 (m, 3H), 4.44 (br d, J = 17.6 Hz, 1H), 4.29 (br d, J = 17.2 Hz, 1H), 4.16 (br s, 2H), 3.95 (s, 1H), 3.83 (br d, J = 13.6 Hz, 2H), 3.45 - 3.33 (m, 4H), 3.23 (br d, J = 9.2 Hz, 2H), 2.97 - 2.89 (m, 1H), 2.81 (br d, J = 6.0 Hz, 4H), 2.75 (br d, J = 12.0 Hz, 3H), 2.60 (br d, J = 16.0 Hz, 2H), 2.53 (br d, J = 2.0 Hz, 1H), 2.49 - 2.34 (m, 4H), 2.05 - 1.92 (m, 5H), 1.82 (br t, J = 11.6 Hz, 6H), 1.71 (br d, J = 10.0 Hz, 2H), 1.62 - 1.48 (m, 3H), 1.45 - 1.26 (m, 4H)
122	1013.1	
123	1025.2	
124	1025.2	^{1}H NMR (400 MHz, DMSO-d6) δ 11.00 (s, 1H), 9.11 (s, 1H), 8.16 (s, 1H), 7.99 (dd, J = 6.0, 9.2 Hz, 1H), 7.57 - 7.38 (m, 3H), 7.32 (d, J = 7.6 Hz, 1H), 7.24 - 7.11 (m, 2H), 5.12 (dd, J = 5.2, 13.2 Hz, 1H), 4.65 (br d, J = 12.8 Hz, 1H), 4.56 - 4.48 (m, 3H), 4.44 (br d, J = 17.6 Hz, 1H), 4.29 (br d, J = 17.2 Hz, 1H), 4.16 (br s, 2H), 3.95 (s, 1H), 3.83 (br d, J = 13.6 Hz, 2H), 3.45 - 3.33 (m, 4H), 3.23 (br d, J = 9.2 Hz, 2H), 2.97 - 2.89 (m, 1H), 2.81 (br d, J = 6.0 Hz, 4H), 2.75 (br d, J = 12.0 Hz, 3H), 2.60 (br d, J = 16.0 Hz, 2H), 2.53 (br d, J = 2.0 Hz, 1H), 2.49 - 2.34 (m, 4H), 2.05 - 1.92 (m, 5H), 1.82 (br t, J = 11.6 Hz, 6H), 1.71 (br d, J = 10.0 Hz, 2H), 1.62 - 1.48 (m, 3H), 1.45 - 1.26 (m, 4H)
125	1025.2	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.06 (s, 1H), 8.17 (s, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.52 - 7.37 (m, 3H), 7.31 (d, J = 7.6 Hz, 1H), 7.22 - 7.13 (m, 2H), 5.12 (dd, J = 5.2, 13.2 Hz, 1H), 4.56 - 4.36 (m, 5H), 4.29 (d, J = 17.2 Hz, 1H), 3.93 (s, 1H), 3.78 (s, 3H), 3.71 (d, J = 14.8 Hz, 5H), 3.44 (dd, J = 3.2, 7.6 Hz, 3H), 3.25 - 3.20 (m, 2H), 3.02 - 2.91 (m, 5H), 2.87 (d, J = 10.4 Hz, 2H), 2.72 (t, J = 5.8 Hz, 2H), 2.59 (s, 1H), 2.05 (t, J = 10.4 Hz, 4H), 2.00 - 1.88 (m, 3H), 1.88 - 1.82 (m, 1H), 1.77 (s, 4H), 1.57 (t, J = 13.2 Hz, 3H), 1.35 - 1.22 (m, 2H), 1.15 - 1.03 (m, 5H)
126	1007.2	^{1}H NMR (400 MHz, CD3OD-d4) δ 9.00 (s, 1H), 7.88 - 7.84 (m, 1H), 7.45 - 7.42 (m, 2H), 7.35 - 7.30 (m, 2H), 7.24 - 7.21 (m, 2H), 5.16 - 5.12 (m, 1H),

		4.66 - 4.56 (m, 5H), 4.48 - 4.47 (m, 2H), 3.73 - 3.66 (m, 4H), 3.40 (s, 1H), 3.38 (s, 2H), 3.13 - 3.10 (m, 2H), 3.01 - 2.99 (m, 2H), 2.92 - 2.86 (m, 3H), 2.80 - 2.73 (m, 3H), 2.58 - 2.50 (m, 1H), 2.34 - 2.31 (m, 2H), 2.24 - 2.07 (m, 5H), 1.87 - 1.72 (m, 10H), 1.48 - 1.22 (m, 10H)
127	969.1	
128	924.1	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.04 (s, 1H), 8.17 - 8.15 (m, 1H), 7.97 (dd, J1 = 6.0 Hz, J2 = 9.2 Hz, 1H), 7.51 - 7.36 (m, 3H), 7.28 (d, J = 7.2 Hz, 1H), 7.20 - 7.11 (m, 2H), 5.15 - 5.06 (m, 1H), 4.57 - 4.20 (m, 8H), 3.92 (s, 1H), 3.65-3.61 (m, 4H), 2.99 - 2.88 (m, 4H), 2.75 - 2.65 (m, 6H), 2.06 - 1.94 (m, 3H), 1.78 - 1.61 (m, 8H), 1.31 - 1.06 (m, 10H)
129	925.0	^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.05 (s, 1H), 8.18 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 6.99 - 6.92 (m, 1H), 6.90 - 6.82 (m, 2H), 5.38 - 5.30 (m, 1H), 4.52 - 4.42 (m, 3H), 4.39 - 4.33 (m, 1H), 3.93 (s, 1H), 3.69 (s, 2H), 3.64 (s, 1H), 3.61 (s, 3H), 3.58 (s, 1H), 3.08 (d, J = 9.6 Hz, 2H), 2.96 (d, J = 10.4 Hz, 2H), 2.89 - 2.83 (m, 1H), 2.74 - 2.62 (m, 6H), 2.45 (s, 1H), 2.07 - 1.96 (m, 3H), 1.72 (s, 6H), 1.66 - 1.59 (m, 2H), 1.50 - 1.41 (m, 1H), 1.37 - 1.25 (m, 3H), 1.19 - 1.06 (m, 4H)
130	1025.2	^{1}H NMR (400 MHz, DMSO-d6) δ 11.00 (s, 1H), 9.07 (s, 1H), 8.22 (s, 3H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.99 (dd, J = 2.0, 7.2 Hz, 1H), 6.92 (dd, J = 2.0, 12.0 Hz, 1H), 5.10 (dd, J = 5.2, 13.2 Hz, 3H), 5.00 - 4.78 (m, 3H), 4.56 (d, J = 12.8 Hz, 1H), 4.51 - 4.36 (m, 4H), 4.33 - 4.22 (m, 1H), 3.93 (s, 1H), 3.86 (s, 2H), 3.74 (t, J = 12.4 Hz, 2H), 3.54 - 3.36 (m, 2H), 3.05 - 2.94 (m, 2H), 2.89 (d, J = 11.2 Hz, 2H), 2.83 - 2.68 (m, 4H), 2.63 - 2.52 (m, 2H), 2.47 - 2.40 (m, 1H), 2.26 (d, J = 6.4 Hz, 2H), 2.15 - 1.93 (m, 5H), 1.87 - 1.68 (m, 6H), 1.60 (d, J = 11.6 Hz, 3H), 1.31 (d, J = 4.0 Hz, 2H), 1.26 - 1.18 (m, 2H), 1.18 - 1.02 (m, 5H)
131	1025.2	^{1}H NMR (400 MHz, DMSO-d6) δ 11.00 (s, 1H), 9.79 - 9.48 (m, 2H), 9.42 - 9.26 (m, 1H), 9.16 (s, 1H), 8.00 (dd, J = 6.0, 9.2 Hz, 1H), 7.55 - 7.39 (m, 3H), 7.33 (d, J = 7.6 Hz, 1H), 7.23 - 7.14 (m, 2H), 5.13 (dd, J = 5.2, 13.2 Hz, 1H), 4.90 - 4.53 (m, 4H), 4.50 - 4.38 (m, 1H), 4.35 - 4.19 (m, 3H), 3.73 - 3.34 (m, 10H), 3.19 - 2.87 (m, 7H), 2.84 - 2.70 (m, 2H), 2.69 - 2.57 (m, 2H), 2.21 - 1.71 (m, 16H), 1.71 - 1.27 (m, 6H)
132	979.1	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.05 (s, 1H), 8.19 (s, 3H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.52 - 7.37 (m, 3H), 7.28 (d, J = 7.2 Hz, 1H), 7.20 - 7.12 (m, 2H), 5.11 (dd, J = 5.2, 13.2 Hz, 1H), 4.51 (d, J = 12.4 Hz, 1H), 4.47 - 4.43 (m, 2H), 4.41 - 4.34 (m, 2H), 4.27 (d, J = 17.2 Hz, 2H), 3.93 (s, 1H), 3.70 (s, 2H), 3.64 (s, 2H), 3.40 - 3.32 (m, 4H), 2.98 - 2.85 (m, 2H), 2.75 - 2.68 (m, 4H), 2.58 (d, J = 17.2 Hz, 2H), 2.46 - 2.43 (m, 2H), 2.35 (s, 4H), 2.22 (d, J = 7.2 Hz, 2H), 2.03 - 1.94 (m, 1H), 1.79 (d, J = 12.4 Hz, 2H), 1.72 (s, 4H), 1.41 (s, 8H), 1.28 - 1.19 (m, 2H)
133	1022.2	^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.05 (s, 1H), 8.18 (s, 3H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 7.02 - 6.92 (m, 1H), 6.91 - 6.82 (m, 2H), 5.36 - 5.31 (m, 1H), 4.51 - 4.48 (m, 1H), 4.45 (t, J = 5.2 Hz, 2H), 4.36 - 4.33 (m, 1H), 3.92 (s, 1H), 3.65 (s, 2H), 3.61 (s, 3H), 3.10 (d, J = 8.4 Hz, 4H), 2.97 - 2.81 (m, 7H), 2.73 - 2.63 (m, 6H), 2.20 (dd, J = 1.2, 4.0 Hz, 2H), 2.04 - 1.96 (m, 3H), 1.93 - 1.85 (m, 2H), 1.81 - 1.76 (m, 2H), 1.71 (s, 3H), 1.60 - 1.57 (m, 5H), 1.29 (d, J = 6.4 Hz, 4H), 1.15 - 1.04 (m, 6H)
134	979.1	
135	951.1	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.11 - 9.02 (m, 1H), 8.19 (s, 2H), 8.01 - 7.92 (m, 1H), 7.49 - 7.37 (m, 3H), 7.31 - 7.27 (m, 1H), 7.19 - 7.11 (m, 2H), 5.15 - 5.06 (m, 1H), 4.51 - 4.24 (m, 7H), 3.90 (d, J = 5.2 Hz, 1H), 3.63 (d, J = 6.0 Hz, 4H), 3.34 (s, 4H), 3.02 (s, 3H), 2.95 - 2.89 (m, 1H), 2.73

		- 2.55 (m, 7H), 2.43 - 2.35 (m, 5H), 2.02 - 1.95 (m, 1H), 1.75 (d, J = 12.4 Hz, 2H), 1.71 - 1.63 (m, 7H), 1.49 - 1.41 (m, 1H), 1.30 - 1.21 (m, 2H)
136	1008.2	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (br s, 1H), 9.05 (s, 1H), 8.20 (s, 3H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.57 - 7.35 (m, 3H), 7.28 (d, J = 7.6 Hz, 1H), 7.20 - 7.06 (m, 2H), 5.11 (br dd, J = 5.2, 13.2 Hz, 1H), 4.56 - 4.41 (m, 3H), 4.40 - 4.20 (m, 3H), 3.93 (s, 1H), 3.72 - 3.59 (m, 2H), 3.36 (t, J = 12.0 Hz, 2H), 3.01 - 2.83 (m, 3H), 2.77 - 2.65 (m, 4H), 2.58 (br d, J = 17.6 Hz, 4H), 2.49 - 2.43 (m, 4H), 2.41 - 2.23 (m, 6H), 2.16 (br d, J = 7.2 Hz, 2H), 2.12 - 1.93 (m, 5H), 1.83 - 1.71 (m, 5H), 1.64 (d, J = 11.2 Hz, 3H), 1.38 (s, 1H), 1.34 - 1.16 (m, 2H), 1.15 - 0.98 (m, 2H)
137	1011.2	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.13 (s, 1H), 8.17 (s, 2H), 7.80 - 7.72 (m, 1H), 7.42 (t, J=7.6 Hz, 1H), 7.37 - 7.32 (m, 2H), 7.29 (d, J=7.6 Hz, 1H), 7.15 (d, J=8.0 Hz, 1H), 7.02 (d, J=2.4 Hz, 1H), 5.15 - 5.08 (m, 1H), 4.62 – 4.47 (m, 5H), 4.45 – 4.39 (m, 1H), 4.31 – 4.25 (m, 1H), 3.96 – 3.88 (m, 2H), 2.86 - 2.72 (m, 3H), 3.42 - 3.31 (m, 2H), 3.05 - 2.89 (m, 5H), 2.82 - 2.76 (m, 2H), 2.74 - 2.65 (m, 2H), 2.63 - 2.55 (m, 1H), 2.39 - 2.30 (m, 3H), 2.19 - 2.07 (m, 5H), 2.04 - 1.95 (m, 1H), 1.88 - 1.72 (m, 7H), 1.66 - 1.58 (m, 4H),1.42 - 1.17 (m, 6H), 1.15 - 1.05(m, 4H), 0.72 (t, J=7.2 Hz, 3H)
138	1007.2	
139	981.2	^{1}H NMR (400 MHz, DMSO-d6) δ 11.00 - 10.96 (m, 1H), 9.10 (s, 1H), 8.15 (s, 2H), 7.67 (d, J = 8.0 Hz, 1H), 7.47 - 7.34 (m, 2H), 7.31 - 7.26 (m, 2H), 7.13 (t, J = 7.6 Hz, 2H), 6.96 (d, J = 2.4 Hz, 1H), 5.11 (dd, J = 5.2, 13.2 Hz, 1H), 4.52 - 4.43 (m, 2H), 4.41 - 4.35 (m, 2H), 4.31 - 4.24 (m, 2H), 4.14 - 4.09 (m, 1H), 3.70 (d, J = 11.6 Hz, 4H), 3.65 - 3.62 (m, 1H), 3.36 (s, 2H), 3.24 (d, J = 5.6 Hz, 2H), 2.94 - 2.88 (m, 1H), 2.81 - 2.77 (m, 1H), 2.73 - 2.67 (m, 4H), 2.61 - 2.56 (m, 2H), 2.35 (s, 3H), 2.30 - 2.23 (m, 2H), 2.22 - 2.19 (m, 1H), 2.16 (d, J = 7.6 Hz, 2H), 2.04 - 1.96 (m, 3H), 1.92 - 1.85 (m, 2H), 1.83 - 1.76 (m, 4H), 1.74 - 1.67 (m, 4H), 1.66 - 1.58 (m, 1H), 1.43 - 1.34 (m, 2H), 1.29 - 1.19 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H)
140	951.1	^{1}H NMR (400 MHz, DMSO-d6) δ 11.03 - 10.96 (m, 1H), 9.06 (s, 1H), 8.19 (s, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.49 - 7.42 (m, 2H), 7.40 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.19 - 7.12 (m, 2H), 5.11 (dd, J = 5.2, 13.2 Hz, 1H), 4.54 (d, J = 12.4 Hz, 1H), 4.45 (d, J = 6.0 Hz, 2H), 4.41 - 4.37 (m, 2H), 4.29 - 4.26 (m, 1H), 3.94 (s, 1H), 3.82 (s, 2H), 3.71 (s, 2H), 3.35 (s, 2H), 2.95 (d, J = 6.0 Hz, 8H), 2.88 (d, J = 5.4 Hz, 1H), 2.73 - 2.70 (m, 2H), 2.61 (s, 2H), 2.56 (s, 1H), 2.46 - 2.42 (m, 1H), 2.06 - 1.96 (m, 4H), 1.84 (s, 4H), 1.78 (s, 4H), 1.64 (d, J = 10.8 Hz, 2H), 1.40 (dd, J = 2.4, 7.6 Hz, 1H), 1.20 - 1.10 (m, 2H)
141	840.0	
142	1007.6	
143	1004.2	
144	979.1	
145	907.0	
146	907.0	
147	1004.2	
148	1040.2	^{1}H NMR (400 MHz, DMSO-d6) δ 11.00 - 10.90 (m, 1H), 9.06 (s, 1H), 8.18 (s, 2H), 8.01 - 7.94 (m, 1H), 7.46 (t, J = 8.8 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.1 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 5.02 (dd, J = 5.2, 13.2 Hz, 1H), 4.53 (d, J = 12.8 Hz, 1H), 4.46 (s, 2H), 4.42 - 4.33 (m, 2H), 4.23 (d, J = 17.2 Hz, 1H), 3.93 (s, 1H), 3.76 (s, 2H), 3.73 - 3.64 (m, 2H), 3.47 (dd, J = 2.4, 9.2 Hz, 2H), 2.99 - 2.88 (m, 3H), 2.79 - 2.65 (m, 5H), 2.63 - 2.55 (m, 2H), 2.53 (s, 3H), 2.43 - 2.24 (m, 9H), 2.16 (d, J = 7.2 Hz, 2H), 2.09 (d, J = 7.2

		Hz, 2H), 2.06 - 2.00 (m, 2H), 1.97 - 1.92 (m, 1H), 1.81 - 1.72 (m, 6H), 1.65 (d, J = 12.0 Hz, 3H), 1.53 - 1.41 (m, 1H), 1.30 - 1.18 (m, 2H), 1.15 - 1.01 (m, 2H)
149	1039.2	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.05 (s, 1H), 8.21 (s, 3H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.50 - 7.34 (m, 2H), 7.18 (d, J = 2.4 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 5.02 (dd, J = 4.8, 13.2 Hz, 1H), 4.56 - 4.33 (m, 5H), 4.22 (d, J = 16.8 Hz, 1H), 3.93 (s, 1H), 3.79 - 3.60 (m, 4H), 3.47 (dd, J = 3.2, 4.4 Hz, 2H), 3.01 - 2.81 (m, 5H), 2.79 - 2.65 (m, 4H), 2.65 - 2.51 (m, 5H), 2.49 - 2.31 (m, 3H), 2.25 - 2.17 (m, 2H), 2.10 - 1.85 (m, 5H), 1.83 - 1.64 (m, 7H), 1.59 (d, J = 11.2 Hz, 4H), 1.39 - 1.19 (m, 4H), 1.16 - 1.00 (m, 6H)
150	983.1	
151	1027.1	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.07 (s, 1H), 8.19 (s, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 5.02 (dd, J = 5.2, 13.2 Hz, 1H), 4.57 (br d, J = 12.8 Hz, 1H), 4.45 - 4.33 (m, 3H), 4.30 - 4.19 (m, 2H), 4.13 (quin, J = 5.6 Hz, 1H), 3.95 (d, J = 2.8 Hz, 1H), 3.89 (br s, 2H), 3.81 - 3.69 (m, 2H), 3.47 (br d, J = 8.8 Hz, 2H), 3.37 - 3.22 (m, 2H), 2.96 - 2.77 (m, 2H), 2.77 - 2.64 (m, 4H), 2.63 - 2.54 (m, 1H), 2.52 (s, 3H), 2.47 - 2.38 (m, 1H), 2.36 (s, 3H), 2.25 - 2.16 (m, 3H), 2.14 - 2.02 (m, 2H), 1.99 - 1.85 (m, 3H), 1.85 - 1.73 (m, 8H), 1.66 (br s, 2H), 1.50 - 1.36 (m, 2H), 1.30 - 1.18 (m, 2H)
152	1024.2	
153	1011.1	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.06 (s, 1H), 8.18 (s, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 5.02 (dd, J = 5.2, 13.2 Hz, 1H), 4.58 - 4.44 (m, 3H), 4.39 (d, J = 16.8 Hz, 2H), 4.22 (d, J = 16.8 Hz, 1H), 3.94 (s, 1H), 3.81 (s, 2H), 3.72 (t, J = 14.0 Hz, 2H), 3.47 (d, J = 6.4 Hz, 2H), 2.95 - 2.84 (m, 1H), 2.79 - 2.69 (m, 4H), 2.61 - 2.54 (m, 2H), 2.53 (s, 3H), 2.49 - 2.38 (m, 8H), 2.35 - 2.19 (m, 3H), 1.99 - 1.91 (m, 1H), 1.83 - 1.60 (m, 8H), 1.44 (s, 8H), 1.30 - 1.20 (m, 2H)
154	983.1	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 10.28 (br s, 1H), 9.13 (s, 1H), 8.14 (s, 1H), 7.99 (dd, J = 6.0, 9.2 Hz, 1H), 7.48 (t, J = 9.2 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 6.89 (br d, J = 7.2 Hz, 1H), 5.03 (br dd, J = 5.0, 13.2 Hz, 1H), 4.74 - 4.57 (m, 3H), 4.53 (br d, J = 13.6 Hz, 1H), 4.39 (br d, J = 16.8 Hz, 1H), 4.26 - 4.14 (m, 3H), 3.95 - 3.83 (m, 6H), 3.16 - 2.97 (m, 8H), 2.94 - 2.85 (m, 1H), 2.61 - 2.52 (m, 7H), 2.45 - 2.37 (m, 3H), 1.95 (br d, J = 9.6 Hz, 10H), 1.85 - 1.67 (m, 3H), 1.46 - 1.19 (m, 2H)
155	953.1	
156	981.1	
157	991.2	
158	914.1	
159	1069.2	
160	1037.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (br s, 1H), 9.06 (s, 1H), 8.21 (s, 2H), 8.05 - 7.92 (m, 1H), 7.47 (t, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.83 - 6.77 (m, 1H), 6.62 (dd, J = 2.0, 8.8 Hz, 1H), 5.29 (dd, J = 5.6, 12.8 Hz, 1H), 4.53 (br d, J = 12.4 Hz, 1H), 4.47 (br t, J = 5.2 Hz, 2H), 4.38 (br d, J = 12.4 Hz, 1H), 3.94 (s, 2H), 3.74 (br d, J = 10.0 Hz, 4H), 3.67 (br d, J = 14.4 Hz, 3H), 3.56 (br d, J = 11.6 Hz, 2H), 3.30 (s, 4H), 2.95 - 2.84 (m, 1H), 2.76 (br s, 2H), 2.63 - 2.62 (m, 1H), 2.69 - 2.57 (m, 6H), 2.47 (br s, 3H), 2.40 - 2.31 (m, 6H), 2.14 (br d, J = 6.8 Hz, 2H), 2.09 (s, 2H), 2.03 - 1.95 (m, 1H), 1.76 (br s, 6H), 1.65 - 1.55 (m, 1H), 1.47 - 1.47 (m, 1H), 1.47 (br d, J = 9.2 Hz, 2H), 1.22 (br d, J = 11.2 Hz, 4H), 0.85 (s, 3H)

161	1036.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (br s, 1H), 9.05 (s, 1H), 8.21 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 6.61 (dd, J = 2.0, 8.8 Hz, 1H), 5.27 (dd, J = 5.6, 12.8 Hz, 1H), 4.51 (br d, J = 13.2 Hz, 1H), 4.46 (br t, J = 5.6 Hz, 2H), 4.35 (br d, J = 10.8 Hz, 1H), 3.92 (s, 1H), 3.55 - 3.51 (m, 5H), 3.29 (s, 3H), 2.93 - 2.84 (m, 1H), 2.79 (br d, J = 11.6 Hz, 2H), 2.73 (br t, J = 5.2 Hz, 2H), 2.70 - 2.66 (m, 1H), 2.65 - 2.60 (m, 2H), 2.58 (br d, J = 9.2 Hz, 3H), 2.52 (br s, 2H), 2.42 - 2.31 (m, 3H), 2.18 (br d, J = 6.8 Hz, 2H), 2.02 - 1.88 (m, 3H), 1.80 - 1.69 (m, 6H), 1.60 (br d, J = 12.4 Hz, 3H), 1.43 - 1.28 (m, 5H), 1.27 - 1.17 (m, 4H), 1.14 (br d, J = 4.4 Hz, 2H)
162	1051.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.04 (s, 1H), 8.23 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 1.6 Hz, 1H), 6.65 - 6.57 (m, 1H), 5.28 (dd, J = 5.2, 12.8 Hz, 1H), 4.52 - 4.46 (m, 1H), 4.38 - 4.29 (m, 3H), 3.91 (s, 1H), 3.65 (s, 8H), 3.56 (d, J = 12.4 Hz, 5H), 3.29 (s, 3H), 2.89 - 2.79 (m, 3H), 2.67 - 2.56 (m, 6H), 2.18 (d, J = 6.8 Hz, 2H), 2.03 - 1.94 (m, 4H), 1.89 (t, J = 11.2 Hz, 2H), 1.77 (d, J = 11.2 Hz, 2H), 1.72 - 1.57 (m, 7H), 1.44 (d, J = 4.0 Hz, 1H), 1.28 - 1.17 (m, 2H), 1.15 - 1.03 (m, 2H), 0.98 (s, 6H)
163	1025.2	
164	967.1	^{1}H NMR (400 MHz, CD_3OD-d_4) δ 9.01 (s, 1H), 7.87 - 7.84 (m, 1H), 7.59 - 7.56 (m,1H), 7.35 - 7.29 (m,2H), 7.21 - 7.20 (m,1H), 6.50 - 6.48 (m, 2H), 5.09 - 5.05 (m, 1H), 4.65 - 4.56 (m, 2H), 4.49 - 4.47 (m, 2H), 4.36 - 4.34 (m, 2H), 4.25 - 4.23 (m, 1H), 4.12 - 4.08 (m, 2H), 3.73 - 3.61 (m, 6H), 3.48 - 3.43 (m, 1H), 3.39 - 3.35 (m, 2H), 3.05 - 2.99 (m, 2H), 2.92 - 2.84 (m, 1H), 2.79 - 2.74 (m, 3H), 2.70 - 2.67 (m, 2H), 2.52 (s, 3H), 2.46 - 2.37 (m, 2H), 2.27 - 2.21 (m, 2H), 2.15 - 2.00 (m, 3H), 1.92 - 1.79 (m, 6H), 1.62 - 1.57 (m, 2H)
165	1009.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 - 10.91 (m, 1H), 9.06 (s, 1H), 8.16 (s, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.52 - 7.44 (m, 2H), 7.40 (d, J = 2.4 Hz, 1H), 7.18 (s, 1H), 7.06 - 7.00 (m, 2H), 5.07 - 5.00 (m, 1H), 4.54 (br d, J = 12.8 Hz, 1H), 4.42 - 4.34 (m, 2H), 4.31 (br d, J = 17.2 Hz, 1H), 4.22 - 4.12 (m, 3H), 3.94 (s, 1H), 3.86 (br d, J = 12.0 Hz, 2H), 3.79 (br s, 2H), 3.75 - 3.64 (m, 3H), 3.31 - 3.26 (m, 2H), 2.98 (br dd, J = 4.0, 10.0 Hz, 1H), 2.92 (td, J = 5.2, 8.0 Hz, 2H), 2.80 (br t, J = 11.6 Hz, 2H), 2.72 - 2.66 (m, 2H), 2.60 (br s, 1H), 2.37 (br d, J = 5.2 Hz, 1H), 2.21 - 2.12 (m, 3H), 2.03 (br dd, J = 8.4, 12.0 Hz, 2H), 1.98 - 1.93 (m, 1H), 1.90 - 1.84 (m, 2H), 1.82 - 1.70 (m, 9H), 1.45 - 1.35 (m, 2H), 1.21 - 1.12 (m, 2H), 1.03 - 0.96 (m, 3H)
166	1040.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H), 9.04 (s, 1H), 7.99 - 7.95 (m, 1H), 7.54 - 7.35 (m, 2H), 7.17 (d, J = 2.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.71 (t, J = 8.0 Hz, 1H), 5.37 - 5.24 (m, 1H), 4.54 - 4.42 (m, 3H), 4.35 (d, J = 12.0 Hz, 1H), 3.93 (s, 1H), 3.66 (s, 5H), 3.20 (d, J = 10.8 Hz, 4H), 2.97 - 2.79 (m, 6H), 2.72 - 2.57 (m, 7H), 2.26 (s, 1H), 2.13 (br d, J = 6.4 Hz, 2H), 2.06 - 1.96 (m, 3H), 1.88 (t, J = 10.8 Hz, 2H), 1.71 (s, 5H), 1.62 (t, J = 11.8 Hz, 4H), 1.52 - 1.39 (m, 2H), 1.36 - 1.21 (m, 3H), 1.19 - 1.02 (m, 6H)
167	1068.2	^{1}H NMR (400 MHz, CD_3OD-d_4) δ 9.01 (s, 1H), 7.86 (dd, J = 5.6, 9.2 Hz, 1H), 7.36 - 7.29 (m, 2H), 7.21 (d, J = 2.4 Hz, 1H), 6.89 - 6.80 (m, 2H), 5.28 (dd, J = 5.2, 12.4 Hz, 1H), 4.67 - 4.55 (m, 5H), 3.74 - 3.64 (m, 4H), 3.37 (s, 1H), 3.14 - 3.08 (m, 2H), 2.99 (br d, J = 11.2 Hz, 2H), 2.93 - 2.85 (m, 3H), 2.83 - 2.75 (m,

		2H), 2.74 - 2.67 (m, 2H), 2.31 (br d, J = 6.4 Hz, 2H), 2.26 - 2.19 (m, 2H), 2.18 - 2.10 (m, 2H), 2.09 - 2.00 (m, 2H), 1.90 - 1.84 (m, 2H), 1.83 - 1.77 (m, 6H), 1.73 (br d, J = 13.2 Hz, 2H), 1.69 - 1.58 (m, 2H), 1.51 (br d, J = 6.8 Hz, 6H), 1.41 (br d, J = 11.6 Hz, 2H), 1.33 - 1.23 (m, 8H)
168	1054.2	^{1}H NMR (400 MHz, CD_3OD-d_4) δ 9.02 (d, J = 1.2 Hz, 1H), 7.87 (dd, J = 8.8, 5.6 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.24 - 7.13 (m, 2H), 5.11 (dd, J = 13.2, 5.2 Hz, 1H), 4.71 - 4.42 (m, 7H), 3.79 - 3.64 (m, 4H), 3.63 - 3.55 (m, 2H), 3.45 - 3.34 (m, 2H), 2.95 - 2.73 (m, 5H), 2.61 - 2.39 (m, 9H), 2.33 - 2.25 (m, 2H), 2.20 - 2.11 (m, 3H), 1.94 - 1.70 (m, 10H), 1.65 - 1.57 (m, 1H), 1.48 - 1.32 (m, 2H), 1.29 - 1.03 (m, 8H)
169	1054.2	^{1}H NMR (400 MHz, CD_3OD-d_4) δ 9.03 (s, 1H), 7.89 -7.86 (m, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.38 - 7.31 (m, 2H), 7.25 - 7.15 (m, 2H), 5.15 - 5.10 (m, 1H), 4.72 - 4.56 (m, 5H), 4.54 - 4.43 (m, 2H), 3.78 - 3.65 (m, 4H), 3.63 - 3.57 (m, 2H), 3.38 (s, 1H), 3.18 - 3.08 (m, 2H), 2.96 - 2.75 (m, 6H), 2.69 - 2.59 (m, 2H), 2.55 - 2.42 (m, 2H), 2.33 - 2.10 (m, 8H), 1.96 - 1.78 (m, 8H), 1.65 - 1.54 (m, 2H), 1.40 - 1.21 (m, 5H), 1.06 (s, 6H)
170	1039.2	^{1}H NMR (400 MHz, CD_3OD-d_4) δ 9.01 (s, 1H), 7.86 (dd, J = 5.6, 9.2 Hz, 1H), 7.38 - 7.29 (m, 2H), 7.21 (d, J = 2.4 Hz, 1H), 6.87 (br d, J = 7.2 Hz, 1H), 5.06 (dd, J = 5.2, 13.2 Hz, 1H), 4.67 - 4.56 (m, 5H), 4.51 - 4.30 (m, 3H), 3.76 - 3.63 (m, 4H), 3.56 (br d, J = 9.2 Hz, 2H), 3.15 - 3.08 (m, 2H), 3.01 (br d, J = 10.0 Hz, 2H), 2.92 - 2.85 (m, 3H), 2.81 - 2.73 (m, 3H), 2.58 (s, 3H), 2.48 (br dd, J = 4.8, 13.2 Hz, 1H), 2.32 (br d, J = 6.4 Hz, 2H), 2.28 - 2.00 (m, 6H), 1.88 - 1.70 (m, 10H), 1.42 - 1.22 (m, 9H)
171	998.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.11 (s, 1H), 8.20 (s, 3H), 7.76 (dd, J = 6.0, 9.2 Hz, 1H), 7.40 - 7.30 (m, 2H), 7.01 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 2.0, 8.8 Hz, 1H), 5.28 (dd, J = 5.2, 12.8 Hz, 1H), 4.54 - 4.39 (m, 5H), 3.83 - 3.62 (m, 5H), 3.56 (d, J = 12.0 Hz, 2H), 3.29 (s, 3H), 2.94 - 2.83 (m, 1H), 2.78 - 2.66 (m, 3H), 2.64 - 2.56 (m, 3H), 2.47 (s, 3H), 2.43 - 2.31 (m, 5H), 2.24 (d, J = 6.8 Hz, 2H), 2.18 - 2.09 (m, 1H), 2.02 - 1.94 (m, 1H), 1.82 - 1.58 (m, 7H), 1.42 (s, 8H), 1.30 - 1.15 (m, 3H), 0.72 (t, J = 7.2 Hz, 3H)
172	1026.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (br s, 1H), 9.13 (s, 1H), 8.26 (s, 3H), 7.77 (dd, J = 6.0, 9.2 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.03 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 2.0, 8.8 Hz, 1H), 5.29 (dd, J = 5.2, 12.8 Hz, 1H), 4.63 - 4.39 (m, 4H), 3.92 - 3.66 (m, 4H), 3.57 (br d, J = 11.6 Hz, 2H), 3.03 - 2.84 (m, 5H), 2.80 - 2.57 (m, 6H), 2.42 - 2.26 (m, 3H), 2.21 - 1.93 (m, 6H), 1.84 - 1.72 (m, 6H), 1.70 - 1.55 (m, 5H), 1.40 - 1.02 (m, 10H), 0.73 (t, J = 7.6 Hz, 3H)
173	1023.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.05 (s, 1H), 8.21 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 2.0, 8.8 Hz, 1H), 5.28 (dd, J = 5.2, 12.8 Hz, 1H), 4.52 (d, J = 12.4 Hz, 1H), 4.45 (t, J = 5.6 Hz, 2H), 4.41 - 4.34 (m, 1H), 3.92 (s, 1H), 3.77 - 3.60 (m, 4H), 3.56 (d, J = 11.6 Hz, 2H), 3.30 (s, 3H), 2.95 - 2.80 (m, 3H), 2.72 - 2.67 (m, 2H), 2.66 - 2.54 (m, 4H), 2.49-2.47 (m, 4H), 2.33 (d, J = 1.6 Hz, 4H), 2.22 (d, J = 6.8 Hz, 2H), 2.10 (d, J = 6.8 Hz, 2H), 2.00 - 1.88 (m, 3H), 1.65 (d, J = 10.4 Hz, 3H), 1.85 - 1.57 (m, 6H), 1.47 (s, 1H), 1.31 - 1.18 (m, 2H), 1.15 - 1.05 (m, 2H)

174	1054.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 10.24 - 10.06 (m, 1H), 9.03 (s, 1H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.50 - 7.42 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.20 - 7.11 (m, 2H), 5.06 (dd, J = 5.2, 13.2 Hz, 1H), 4.52 - 4.42 (m, 2H), 4.37 - 4.26 (m, 4H), 3.91 (s, 1H), 3.66 - 3.55 (m, 4H), 3.52 - 3.41 (m, 3H), 2.96 - 2.71 (m, 6H), 2.61 (br s, 3H), 2.56 (br d, J = 1.6 Hz, 1H), 2.47 - 2.35 (m, 2H), 2.15 (br d, J = 4.0 Hz, 2H), 2.09 - 1.93 (m, 5H), 1.92 - 1.71 (m, 5H), 1.71 - 1.60 (m, 7H), 1.48 - 1.38 (m, 1H), 1.30 - 1.19 (m, 2H), 1.16 - 1.03 (m, 2H), 0.97 (s, 6H)
175	953.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.08 (s, 1H), 8.15 (s, 2H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.47 (t, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.94 - 6.84 (m, 2H), 6.64 - 6.57 (m, 1H), 5.26 (dd, J = 5.6, 13.1 Hz, 1H), 4.61 - 4.54 (m, 2H), 4.53 - 4.46 (m, 2H), 4.42 (d, J = 13.2 Hz, 1H), 3.94 (s, 1H), 3.90 (s, 2H), 3.75 (t, J = 12.4 Hz, 3H), 3.52 (d, J = 11.6 Hz, 4H), 3.01 (s, 3H), 2.90 - 2.83 (m, 1H), 2.78 (s, 2H), 2.68 - 2.60 (m, 2H), 2.58 (s, 1H), 2.54 (s, 1H), 2.12 (t, J = 10.8 Hz, 2H), 2.01 - 1.92 (m, 1H), 1.82 (s, 4H), 1.71 (d, J = 12.4 Hz, 2H), 1.67 - 1.61 (m, 2H), 1.44 (d, J = 6.8 Hz, 6H), 1.29 - 1.20 (m, 2H), 1.19 - 1.08 (m, 4H)
176	940.1	^{1}H NMR (400 MHz, CD_3OD-d_4) δ 9.02 (s, 1H), 7.86 (dd, J = 5.6, 9.2 Hz, 1H), 7.36 - 7.28 (m, 2H), 7.21 (d, J = 2.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.76 (br d, J = 8.8 Hz, 1H), 5.26 (dd, J = 5.6, 12.4 Hz, 1H), 4.68 - 4.56 (m, 5H), 4.54 - 4.48 (m, 1H), 3.75 - 3.65 (m, 4H), 3.49 - 3.41 (m, 1H), 3.38 (s, 1H), 3.14 (br t, J = 4.0 Hz, 4H), 2.94 - 2.86 (m, 1H), 2.82 - 2.74 (m, 2H), 2.71 - 2.64 (m, 8H), 2.36 (dd, J = 7.6, 12.4 Hz, 1H), 2.17 - 2.08 (m, 3H), 1.90 - 1.74 (m, 6H), 1.57 - 1.51 (m, 6H)
177	1033.6	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.12 (s, 1H), 8.18 (s, 2H), 7.76 (dd, J = 6.0, 9.2 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.42 - 7.30 (m, 2H), 7.25 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 5.09 (dd, J = 5.2, 13.2 Hz, 1H), 4.53 (br t, J = 15.2 Hz, 3H), 4.45 - 4.35 (m, 3H), 4.32 - 4.27 (m, 2H), 4.22 (s, 1H), 4.16 - 4.09 (m, 2H), 3.87 (br d, J = 10.8 Hz, 2H), 3.80 (br d, J = 13.2 Hz, 1H), 3.73 (br d, J = 13.6 Hz, 1H), 3.42 - 3.31 (m, 3H), 3.26 (br dd, J = 6.0, 9.2 Hz, 1H), 2.96 - 2.86 (m, 1H), 2.82 (br t, J = 5.2 Hz, 1H), 2.78 - 2.66 (m, 4H), 2.59 (br d, J = 16.8 Hz, 1H), 2.44 (br dd, J = 4.8, 13.6 Hz, 1H), 2.36 (s, 4H), 2.28 - 2.18 (m, 3H), 2.16 - 2.05 (m, 3H), 1.98 (br dd, J = 5.2, 10.4 Hz, 1H), 1.89 (br d, J = 5.2 Hz, 1H), 1.85 - 1.76 (m, 7H), 1.72 - 1.59 (m, 1H), 1.51 - 1.37 (m, 2H), 1.29 (q, J = 10.4 Hz, 2H), 0.72 (t, J = 7.2 Hz, 3H)
178	1017.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (br s, 1H), 9.11 (s, 1H), 8.21 (s, 1H), 7.76 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.39 - 7.29 (m, 2H), 7.14 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 5.07 (br dd, J = 5.2, 13.3 Hz, 1H), 4.47 (br d, J = 16.8 Hz, 3H), 4.41 - 4.37 (m, 1H), 4.34 - 4.23 (m, 4H), 4.14 - 4.10 (m, 1H), 3.80 - 3.65 (m, 5H), 3.47 (br s, 2H), 3.35 - 3.19 (m, 2H), 2.98 - 2.84 (m, 1H), 2.83 - 2.64 (m, 5H), 2.63 - 2.55 (m, 1H), 2.48 - 2.38 (m, 1H), 2.35 (s, 3H), 2.22 - 2.16 (m, 3H), 2.15 - 2.10 (m, 1H), 2.05 (br t, J = 9.6 Hz, 2H), 2.00 - 1.94 (m, 1H), 1.92 - 1.84 (m, 2H), 1.83 - 1.63 (m, 8H), 1.49 - 1.34 (m, 2H), 1.32 - 1.15 (m, 2H), 0.72 (t, J = 7.6 Hz, 3H)
179	1040.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 - 10.94 (m, 1H), 9.10 (s, 1H), 8.22 (s, 2H), 7.76 (dd, J = 6.0, 9.2 Hz, 1H), 7.39 - 7.27 (m, 2H), 7.01 (d, J = 2.4 Hz, 1H), 6.96 - 6.87 (m, 1H), 6.84 - 6.75 (m, 1H), 6.67 - 6.55 (m, 1H), 5.27 (br dd, J = 5.6, 12.8 Hz, 1H), 4.54 - 4.39 (m, 4H), 3.55 (br d, J = 12.0 Hz, 7H), 3.31 - 3.27 (m, 3H), 2.95 - 2.83 (m, 1H), 2.79 (br d, J = 10.8 Hz, 2H), 2.72 (br t, J =

		5.6 Hz, 2H), 2.69 - 2.65 (m, 1H), 2.64 - 2.54 (m, 5H), 2.52 (br d, J = 2.0 Hz, 2H), 2.42 - 2.31 (m, 3H), 2.21 - 2.09 (m, 3H), 2.03 - 1.88 (m, 3H), 1.76 (br d, J = 12.8 Hz, 2H), 1.72 - 1.65 (m, 3H), 1.59 (br d, J = 11.2 Hz, 3H), 1.41 - 1.16 (m, 8H), 1.13 (br d, J = 4.4 Hz, 2H), 0.87 (s, 3H), 0.72 (t, J = 7.6 Hz, 3H)
180	1041.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (br s, 1H), 9.12 (s, 1H), 8.22 (s, 2H), 7.77 (dd, J = 6.0, 9.2 Hz, 1H), 7.39 - 7.31 (m, 2H), 7.02 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 2.0, 8.8 Hz, 1H), 5.29 (dd, J = 5.2, 12.8 Hz, 1H), 4.55 - 4.39 (m, 4H), 3.77 - 3.66 (m, 3H), 3.56 (br d, J = 11.6 Hz, 2H), 3.30 (s, 3H), 3.00 - 2.67 (m, 2H), 2.55 (s, 4H), 2.47 (br d, J = 4.0 Hz, 7H), 2.41 - 2.27 (m, 8H), 2.20 - 2.03 (m, 6H), 2.01 - 1.94 (m, 1H), 1.79 - 1.68 (m, 6H), 1.63 - 1.54 (m, 1H), 1.51 - 1.42 (m, 2H), 1.22 (br d, J = 8.0 Hz, 4H), 0.85 (s, 3H), 0.73 (t, J = 7.2 Hz, 3H)
181	1045.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.10 (s, 1H), 8.22 - 8.17 (m, 2H), 7.76 (dd, J = 6.0, 9.2 Hz, 1H), 7.38 - 7.31 (m, 2H), 7.02 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 6.61 (dd, J = 2.0, 8.8 Hz, 1H), 5.28 (dd, J = 5.2, 12.8 Hz, 1H), 4.51 - 4.41 (m, 4H), 3.70 - 3.60 (m, 5H), 3.56 (d, J = 12.0 Hz, 3H), 3.29 (s, 3H), 2.92 - 2.83 (m, 1H), 2.76 - 2.65 (m, 5H), 2.64 - 2.55 (m, 4H), 2.46 (s, 3H), 2.40 (s, 2H), 2.36 - 2.28 (m, 6H), 2.13 (d, J = 7.2 Hz, 3H), 2.02 - 1.94 (m, 1H), 1.82 - 1.71 (m, 5H), 1.68 (s, 4H), 1.62 - 1.51 (m, 2H), 1.22 (d, J = 10.0 Hz, 2H), 0.72 (t, J = 7.6 Hz, 3H)
182	1044.2	
183	1040.2	^{1}H NMR (400 MHz, CD_3OD-d_4) δ 9.01 (s, 1H), 7.88 - 7.84 (m, 1H), 7.35 - 7.30 (m, 2H), 7.21 - 7.20 (m, 1H), 6.99 - 6.96 (m, 1H), 6.87 - 6.86 (m, 1H), 6.81 - 6.78 (m, 1H), 5.30 - 5.25 (m, 1H), 4.69 - 4.57 (m, 4H), 3.73 - 3.67 (m, 4H), 3.58 - 3.54 (m, 2H), 3.40 (s, 3H), 3.37 (s, 1H), 2.95 - 2.87 (m, 7H), 2.81 - 2.75 (m, 2H), 2.70 - 2.65 (m, 2H), 2.52 - 2.44 (m, 4H), 2.18 - 2.09 (m, 3H), 1.90 - 1.79 (m, 9H), 1.70 - 1.61 (m, 3H), 1.55 - 1.46 (m, 1H), 1.39 - 1.34 (m, 3H), 1.25 - 1.19 (m, 4H)
184	1064.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 10.30 - 9.99 (m, 1H), 9.03 (s, 1H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.17 (s, 1H), 6.95 - 6.81 (m, 2H), 6.61 (dd, J = 1.6, 8.8 Hz, 1H), 5.25 (dd, J = 5.2, 12.8 Hz, 1H), 4.63 - 4.53 (m, 1H), 4.52 - 4.42 (m, 2H), 4.30 (d, J = 12.4 Hz, 1H), 4.16 (dd, J = 6.0, 10.8 Hz, 1H), 3.91 (d, J = 5.2 Hz, 1H), 3.62 (d, J = 11.8 Hz, 1H), 3.58 - 3.46 (m, 5H), 3.03 - 2.94 (m, 1H), 2.89 - 2.74 (m, 5H), 2.65 - 2.55 (m, 4H), 2.31 - 2.19 (m, 2H), 2.11 (d, J = 6.8 Hz, 2H), 2.01 - 1.92 (m, 1H), 1.84 - 1.72 (m, 4H), 1.68 - 1.62 (m, 4H), 1.60 - 1.52 (m, 5H), 1.44 (d, J = 6.8 Hz, 6H), 1.34 - 1.13 (m, 5H), 1.12 - 0.96 (m, 9H)
185	1039.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 10.49 - 9.89 (m, 1H), 9.03 (s, 1H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.50 - 7.43 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.21 - 7.09 (m, 2H), 5.06 (dd, J = 5.2, 13.2 Hz, 1H), 4.56 - 4.42 (m, 3H), 4.30 (d, J = 16.4 Hz, 2H), 4.16 (dd, J = 5.6, 10.4 Hz, 1H), 3.91 (d, J = 5.2 Hz, 1H), 3.62 (d, J = 12.0 Hz, 1H), 3.58 - 3.51 (m, 3H), 3.47 (s, 2H), 3.01 - 2.71 (m, 9H), 2.62 - 2.56 (m, 1H), 2.44 - 2.34 (m, 1H), 2.25 (q, J = 10.0 Hz, 2H), 2.12 (d, J = 6.8 Hz, 2H), 2.01 - 1.91 (m, 1H), 1.84 - 1.74 (m, 4H), 1.69 - 1.62 (5H), 1.56 (d, J = 9.2 Hz, 4H), 1.30 - 1.20 (m, 4H), 1.10 - 0.95 (m, 9H)
186	985.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.03 (s, 1H), 8.21 (s, 1H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.8 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.29 - 7.21 (m, 1H), 7.17 (d, J = 2.4 Hz, 1H), 5.09 (dd, J = 5.2, 13.6 Hz, 1H), 4.56 - 4.47 (m, 1H), 4.45 - 4.36 (m, 1H), 4.34 - 4.20

		(m, 4H), 3.94 (s, 1H), 3.71 - 3.54 (m, 6H), 3.39 - 3.34 (m, 2H), 2.94 - 2.85 (m, 1H), 2.75 2.65 (m, 2H), 2.62 - 2.56 (m, 1H), 2.47 - 2.22 (m, 10H), 2.18 - 2.11 (m, 2H), 2.04 - 1.93 (m, 1H), 1.84 - 1.75 (m, 2H), 1.74 - 1.56 (m, 5H), 1.36 - 1.18 (m, 2H), 0.69 - 0.58 (m, 2H), 0.47 - 0.35 (m, 2H)
187	985.5	
188	966.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.04 (s, 1H), 8.21 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 6.61 (dd, J = 2.0, 8.8 Hz, 1H), 5.27 (dd, J = 5.2, 12.8 Hz, 1H), 4.53 (d, J = 12.4 Hz, 1H), 4.37 - 4.27 (m, 3H), 3.93 (s, 1H), 3.69 (s, 5H), 3.61 (d, J = 13.2 Hz, 4H), 3.55 (d, J = 11.6 Hz, 4H), 3.29 (s, 3H), 2.91 - 2.83 (m, 1H), 2.70 - 2.64 (m, 1H), 2.62 (d, J = 2.4 Hz, 1H), 2.61 - 2.55 (m, 2H), 2.36 - 2.26 (m, 5H), 2.12 (d, J = 7.2 Hz, 2H), 2.02 - 1.94 (m, 1H), 1.81 - 1.68 (m, 6H), 1.65 - 1.53 (m, 1H), 1.27 - 1.15 (m, 2H), 0.64 (s, 2H), 0.41 (s, 2H)
189	966.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.03 (s, 1H), 8.20 (s, 1H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.46 (t, J = 9.6 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 6.96 - 6.90 (m, 1H), 6.83 - 6.79 (m, 1H), 6.60 (dd, J = 1.6, 8.4 Hz, 1H), 5.28 (dd, J = 5.2, 12.4 Hz, 1H), 4.51 (d, J = 11.6 Hz, 1H), 4.35 - 4.23 (m, 3H), 3.93 (s, 1H), 3.70 - 3.58 (m, 5H), 3.29 (s, 3H), 3.08 - 3.01 (m, 4H), 2.99 - 2.92 (m, 2H), 2.90 - 2.84 (m, 1H), 2.72 - 2.57 (m, 2H), 2.47 - 2.43 (m, 4H), 2.34 - 2.29 (m, 2H), 2.13 (d, J = 6.8 Hz, 2H), 2.01 - 1.94 (m, 1H), 1.92 - 1.84 (m, 2H), 1.74 - 1.62 (m, 6H), 1.52 - 1.44 (m, 1H), 1.12 - 1.00 (m, 2H), 0.64 (s, 2H), 0.41 (s, 2H)
190	984.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 10.56 - 9.64 (m, 1H), 9.07 (s, 1H), 8.15 (s, 1H), 7.98 (dd, J = 6.0, 9.2 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 5.09 (dd, J = 5.2, 13.2 Hz, 1H), 4.59 (d, J = 12.4 Hz, 1H), 4.45 - 4.36 (m, 2H), 4.33 - 4.20 (m, 3H), 3.93 (s, 3H), 3.76 (dd, J = 13.2, 17.6 Hz, 2H), 3.13 - 3.02 (m, 3H), 2.97 - 2.83 (m, 2H), 2.74 - 2.66 (m, 2H), 2.63 - 2.56 (m, 1H), 2.49 - 2.42 (m, 3H), 2.13 - 1.94 (m, 3H), 1.85 (s, 4H), 1.76 - 1.62 (m, 4H), 1.55 - 1.37 (m, 2H), 1.37 - 1.21 (m, 3H), 1.20 - 1.06 (m, 4H), 0.69 (s, 2H), 0.49 (s, 2H)
191	993.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 10.24 (s, 1H), 9.13 (s, 1H), 8.14 (s, 1H), 8.03 – 7.95 (m, 1H), 7.47 (t, J = 8.8 Hz, 1H), 7.42 - 7.39 (m, 1H), 7.20 - 7.15 (m, 1H), 6.95 - 6.84 (m, 2H), 6.64 – 6.57 (m, 1H), 5.32- 5.21 (m, 1H), 4.71 - 4.50 (m, 3H), 4.42 - 4.30 (m, 2H), 4.23 – 4.15 (m, 2H), 3.90 (s, 1H), 3.89 – 3.82 (m, 2H), 3.61 – 3.45 (m, 4H), 2.94 – 2.83 (m, 2H), 2.70 – 2.55 (m, 5H), 2.04 – 1.90 (m, 6H), 1.88 – 1.79 (m, 2H), 1.73 – 1.53 (m, 4H), 1.44 (d, J = 6.8 Hz, 9H), 1.27 – 1.07 (m, 5H), 0.87 – 0.63 (m, 4H)
192	968.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.04 (s, 1H), 8.19 (s, 2H), 7.97 (dd, J = 6.0, 9.2 Hz, 1H), 7.49 - 7.42 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.19 - 7.10 (m, 2H), 5.07 (dd, J = 5.2, 13.2 Hz, 1H), 4.54 - 4.44 (m, 2H), 4.34 - 4.26 (m, 4H), 3.95 - 3.91 (m, 1H), 3.66 (s, 3H), 3.59 (d, J = 12.4 Hz, 2H), 3.45 (s, 3H), 3.00 - 2.88 (m, 4H), 2.77 - 2.70 (m, 2H), 2.32 (s, 2H), 2.00 - 1.93 (m, 1H), 1.91 - 1.83 (m, 2H), 1.76 - 1.67 (m, 6H), 1.60 (d, J = 10.8 Hz, 2H), 1.51 - 1.44 (m, 1H), 1.36 - 1.18 (m, 4H), 1.16 - 1.04 (m, 4H), 0.67 - 0.59 (m, 2H), 0.41 (s, 2H)
193	1034.2	
194	1039.2	

195	1064.3	
196	1062.3	
197	1012.1	
198	1040.2	
199	1058.2	
200	1041.2	
201	1046.1	
202	1022.2	
203	1040.2	
204	1035.2	
205	1026.2	
206	1040.2	
207	1014.2	
208	1063.3	
209	1042.2	
210	965.1	
211	1037.2	
212	1054.3	
213	1028.1	
214	1025.2	
215	1007.2	
216	1007.2	
217	1068.2	
218	994.1	
219	1042.6	
220	1013.6	
221	1023.2	
222	1051.2	
223	1026.2	
224	1056.2	
225	985.6	^{1}H NMR (400MHz, DMSO-d_6) δ 11.10 (s, 1H), 8.19 (s, 1H), 7.96 (dd, *J* = 6.0, 8.8 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.46 (t, *J* = 8.8 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.22 (dd, *J* = 6.8, 8.4 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.72 (t, *J* = 8.0 Hz, 1H), 5.32 (dd, *J* = 5.2, 12.4 Hz, 1H), 4.48 - 4.40 (m, 2H), 4.38 - 4.33 (m, 1H), 4.29 - 4.24 (m, 1H), 3.86 - 3.84 (m, 1H), 3.81 (s, 2H), 3.60 (s, 1H), 3.57 (s, 1H), 3.47 - 3.46 (m, 3H), 3.45 - 3.43 (m, 1H), 3.23 - 3.18 (m, 2H), 2.91 - 2.84 (m, 1H), 2.78 - 2.71 (m, 2H), 2.69 - 2.57 (m, 4H), 2.49 - 2.46 (m, 4H), 2.44 - 2.35 (m, 4H), 2.29 - 2.22 (m, 2H), 2.04 - 1.95 (m, 1H), 1.91 - 1.73 (m, 6H), 1.69 - 1.56 (m, 1H), 1.52 - 1.36 (m, 8H), 1.32 - 1.21 (m, 2H)
227	1051.6	^{1}H NMR (400MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.18 (s, 2H), 7.96 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.21 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.62 (dd, *J* = 2.0, 8.8 Hz, 1H), 5.28 (dd, *J* = 5.6, 12.8 Hz, 1H), 4.38 - 4.25 (m, 4H), 3.86 (s, 2H), 3.83 (d, *J* = 0.8 Hz, 1H), 3.62 - 3.55 (m, 8H), 3.30 (s, 3H), 2.93 - 2.84 (m, 3H), 2.73 - 2.56 (m, 7H), 2.29 - 2.21 (m, 3H), 2.09 - 1.93 (m, 6H), 1.91 - 1.74 (m, 6H), 1.71 - 1.59 (m, 3H), 1.55 - 1.40 (m, 1H), 1.31 - 1.06 (m, 4H), 0.98 (s, 6H)

231	1039.5	^{1}H NMR (400MHz, DMSO-d_6) δ 11.10 (br s, 1H), 8.22 (s, 2H), 7.96 (dd, *J* = 9.2, 6.0 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.45 (t, *J* = 9.2 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.75 - 6.64 (m, 1H), 5.36 - 5.26 (m, 1H), 4.47 - 4.38 (m, 2H), 4.38 - 4.20 (m, 3H), 3.85 (s, 1H) 3.80 - 3.70 (m, 2H), 3.55 (d, *J* = 12.4 Hz, 2H), 3.46 (s, 3H), 3.25 - 3.15 (m, 2H), 3.00 - 2.78 (m, 5H), 2.75 - 2.56 (m, 7H), 2.20 - 2.10 (m, 2H), 2.08 - 1.96 (m, 3H), 1.94 - 1.75 (m, 5H), 1.74 - 1.57 (m, 6H), 1.54 - 1.39 (m, 2H), 1.38 - 1.21 (m, 3H), 1.19 - 1.02 (m, 5H)
232	1039.7	^{1}H NMR (400 MHz, CD_3OD) δ 7.85 - 7.72 (m, 2H), 7.38 - 7.18 (m, 3H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.82 (d, *J* = 2.4 Hz, 2H), 5.28 (dd, *J* = 5.6, 12.4 Hz, 1H), 4.68 - 4.54 (m, 3H), 4.49 (br dd, *J* = 6.8, 12.0 Hz, 2H), 3.64 - 3.54 (m, 6H), 3.20 (s, 1H), 3.16 - 3.03 (m, 2H), 3.00 - 2.92 (m, 2H), 2.92 - 2.83 (m, 3H), 2.82 - 2.64 (m, 4H), 2.29 (br d, *J* = 6.8 Hz, 2H), 2.25 - 2.11 (m, 3H), 2.04 - 1.93 (m, 2H), 1.91 - 1.77 (m, 6H), 1.69 (br t, *J* = 9.6 Hz, 5H), 1.48 - 1.37 (m, 6H), 1.34 - 1.22 (m, 4H), 1.21 - 1.14 (m, 2H)
233	1021.5	^{1}H NMR (400MHz, DMSO-d_6) δ 11.05 (s, 1H), 10.16 (s, 1H), 7.96 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.45 (t, *J* = 9.2 Hz, 1H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.16 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.61 (dd, *J* = 2.0, 8.4 Hz, 1H), 5.27 (dd, *J* = 5.6, 12.8 Hz, 1H), 4.39 (m, 2H), 4.31 - 4.15 (m, 2H), 3.84 (s, 1H), 3.60 - 3.46 (m, 6H), 3.29 (s, 3H), 2.90 (m, *J* = 10.0 Hz, 3H), 2.76 (m, 2H), 2.69 - 2.54 (m, 7H), 2.08 - 1.95 (m, 5H), 1.77 - 1.55 (m, 12H), 1.50 - 1.39 (m, 2H), 1.29 - 1.04 (m, 9H)
234	1019.5	^{1}H NMR (400MHz, MeOD-d_4) δ 9.04 (s, 1H), 8.14 - 8.06 (m, 2H), 7.68 - 7.63 (m, 2H), 7.43 (dt, *J* = 3.6, 9.2 Hz, 1H), 6.98 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.79 (br d, *J* = 8.8 Hz, 1H), 5.37 - 5.24 (m, 1H), 4.62 (br t, *J* = 10.8 Hz, 2H), 4.49 - 4.41 (m, 1H), 4.35 (br d, *J* = 11.6 Hz, 1H), 3.76 - 3.65 (m, 4H), 3.56 (br d, *J* = 12.0 Hz, 2H), 3.43 (s, 1H), 3.40 (d, *J* = 1.6 Hz, 3H), 3.16 - 3.05 (m, 1H), 2.98 - 2.86 (m, 2H), 2.83 - 2.73 (m, 3H), 2.71 - 2.60 (m, 4H), 2.56 (br d, *J* = 6.8 Hz, 2H), 2.53 - 2.43 (m, 4H), 2.24 (br d, *J* = 7.2 Hz, 3H), 2.19 - 2.13 (m, 1H), 2.09 - 2.03 (m, 1H), 1.99 - 1.92 (m, 2H), 1.88 (br d, *J* = 11.2 Hz, 6H), 1.82 - 1.77 (m, 3H), 1.70 - 1.63 (m, 1H), 1.47 - 1.25 (m, 4H), 0.92 (dd, *J* = 2.8, 7.6 Hz, 1H)
238	1022.4	^{1}H NMR (400MHz, MeOD-d_4) δ 9.05 (s, 1H), 8.19 - 8.06 (m, 2H), 7.72 - 7.62 (m, 2H), 7.53 (dd, *J* = 3.2, 8.0 Hz, 1H), 7.46 (dt, *J* = 2.0, 9.2 Hz, 1H), 7.17 (dt, *J* = 3.6, 8.0 Hz, 1H), 5.12 (dd, *J* = 5.2, 13.4 Hz, 1H), 4.64 (t, *J* = 11.2 Hz, 2H), 4.58 - 4.34 (m, 4H), 3.76 - 3.66 (m, 4H), 3.58 (d, *J* = 10.8 Hz, 2H), 3.45 (s, 1H), 3.29 - 3.03 (m, 2H), 2.95 - 2.88 (m, 2H), 2.83 - 2.61 (m, 6H), 2.60 - 2.42 (m, 7H), 2.30 - 2.22 (m, 3H), 2.21 - 1.93 (m, 5H), 1.93 - 1.62 (m, 11H), 1.45 - 1.34 (m, 2H)

Example 159: Biological Assays

Reagents

AsPC-1 (CRL-1682) cells were purchased from ATCC and are homozygous for the G12D mutation in KRas. AsPC-1 cells were cultured in GIBCO RPMI-1640 (ThermoFisher Scientific, catalog# 61870-036, with Glutamax, no HEPES, no Na Pyruvate) supplemented with 10% FBS (ThermoFisher Scientific, catalog# 2060357) and 1X Penicillin-Streptomycin

(ThermoFisher Scientific, catalog# 15140122, 10000 U/ml, 100X). For degradation assays, 384 well plates were used. Alamar blue was purchased from ThermoFisher Scientific (A50101) and used according to manufacturer instructions. The Nano-Glo® HiBiT Lytic Detection System and Nano-Glo® HiBiT Blotting System were purchased from Promega (#N3050 and #N2410) and used according to manufacturer instructions.

To create the AsPC-1 HiBiT-KRasG12D cell line, CRISPR-Cas9 was used to insert the HiBiT tag onto the N-terminus of one or more of the endogenous KRas alleles. See Schwinn, M.K. et al. (2018) CRISPR-mediated tagging of endogenous proteins with a luminescent peptide, ACS Chem. Biol. 13(2), 467-474. After knock-in of the tag, individual clones were isolated by single cell dilution and screened for HiBiT insertion by PCR. A clone was identified that contained the desired HiBiT-KRasG12D sequence at one allele while the remaining two KRasG12D alleles were untagged. This clone was used in further studies.

HiBiT degradation assays (G12D)

AsPC-1 HiBiT-KRasG12D cells were plated at 9000 or 15,000 cells/well in a 384 well plate (Corning #3770). Compounds of the present disclosure and positive controls were diluted in the appropriate cell media and applied to the plated cells resulting in a final concentration titration of 10 µM to 508 pM in 0.5% DMSO. Gambogic acid was used as a positive control for cytotoxicity and titrated from 10 µM to 78 nM. All assays were performed in triplicate. Cells were treated with compounds for 24 hr at 37 °C in an incubator containing 5% CO2. Following treatment, alamar blue was used to determine if any compounds led to a loss in cell viability after 24 hr. The 10X alamar blue reagent was added to a final concentration of 1X as recommended by the manufacturer and cells were returned to the incubator for 4 hr. Plates were then allowed to equilibrate to RT and fluorescence was measured using a Perkin-Elmer EnVision. After completion of the fluorescence read, the liquid from each well was removed and the cells were washed with PBS. The Nano-Glo® HiBiT detection reagent was prepared according to the manufacturer's instructions and added to each well after the PBS wash was removed. Following incubation at room temperature for 45 min, the luminescence was read using the ultra-sensitive luminescence aperture on the Envision instrument.

Data analysis

Fluorescence values from the alamar blue treatment were normalized to the DMSO-only control for each compound titration. HiBiT luminescence was normalized to the DMSO-only control and the fractional HiBiT signal was plotted versus the log of the PROTAC concentration and fit to a 4-parameter dose-response model to obtain the concentration of the compound that leads to half maximal degradation (DC_{50}) as well as the maximum degradation observed (D_{max}, conventionally expressed as a percentage of control).

Degradation data is presented below in Table 3.

Table 3. Degradation of KRas-G12D in AsPC-1 cells at 24h with compounds of the disclosure

DC_{50}: A, B, C, or D. According to the code, A represents a DC_{50} value ≤100.0 nM; B represents a DC_{50} value >100.0 nM and ≤250.0 nM; C represents a DC_{50} value >250.0 nM and ≤1000.0 nM; D represents an DC_{50} value >1000 nM.

D_{max}: A, B, C, or D. According to the code, A represents a D_{max} value >70%; B represents a D_{max} value >50% and ≤70%; C represents a D_{max} value >25% and ≤50%; D represents a D_{max} value ≤25%.

Compound	KRas Degradation DC_{50}	KRas Degradation D_{max}
1	B	C
2	A	A
3	C	B
4	D	nd*
5	D	nd*
6	D	nd*
7	D	nd*
8	C	C
9	C	C
10	C	C
11	C	C
12	D	C
13	C	C
14	C	D
15	C	C
16	D	nd*
17	C	D
18	D	D
19	C	B
20	B	B
21	C	C
22	B	C
23	C	C
24	B	C
25	A	B
26	C	C
27	C	C
28	C	B
29	C	B
30	D	C
31	B	C
32	C	B
33	C	B
34	C	B
35	B	A
36	C	C

37	D	C
38	B	B
39	C	D
40	D	D
41	D	nd*
42	D	nd*
43	A	A
44	D	nd*
45	C	C
46	D	nd*
47	C	D
48	D	nd*
49	D	nd*
50	A	D
51	D	nd*
52	C	D
53	B	C
54	C	D
55	A	B
56	C	B
57	B	C
58	A	B
59	A	B
60	B	C
61	C	B
62	A	C
63	C	C
64	B	C
65	C	B
66	C	D
67	D	C
68	A	A
69	A	A
70	A	A
71	A	A
72	A	A
73	nd*	nd*
74	A	A
75	A	B
76	A	A
77	A	A
78	nd*	nd*
79	A	A
80	A	A
81	A	A
82	A	A
83	A	A

84	A	A
85	A	A
86	A	A
87	A	A
88	A	A
89	A	A
90	D	C
91	A	A
92	A	A
93	A	A
94	A	A
95	A	A
96	A	A
97	D	nd*
98	A	A
99	A	A
100	A	A
101	A	A
102	A	A
103	A	A
104	A	A
105	A	D
106	A	A
107	D	nd*
108	A	D
109	A	A
110	A	A
111	A	A
112	A	A
113	A	A
114	A	C
115	A	A
116	A	A
117	C	C
118	D	B
119	A	B
120	A	A
121	A	A
122	A	A
123	A	A
124	A	A
125	A	B
126	A	A
127	A	B
128	B	A
129	A	A
130	A	A

131	A	A
132	A	A
133	A	A
134	A	A
135	C	B
136	A	A
137	A	B
138	A	A
139	A	A
140	C	B
141	D	nd*
142	A	A
143	A	B
144	A	C
145	B	A
146	C	B
147	A	A
148	A	A
149	A	A
150	A	B
151	A	A
152	A	B
153	A	A
154	A	A
155	D	nd*
156	D	nd*
157	D	nd*
158	D	D
159	A	A
160	A	A
161	A	A
162	A	A
163	A	A
164	A	A
165	A	A
166	A	A
167	A	B
168	A	A
169	A	A
170	A	A
171	A	A
172	A	A
173	A	A
174	A	A
175	A	A
176	A	A
177	A	A

178	A	A
179	A	A
180	A	A
181	A	A
182	A	A
183	A	A
184	A	A
185	A	A
186	A	A
187	A	A
188	A	A
189	A	A
190	A	A
191	A	A
192	A	A
193	A	A
194	A	A
195	A	A
196	A	A
197	A	A
198	A	A
199	A	A
200	A	A
201	A	A
202	A	A
203	A	A
204	A	A
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215	A	A
216	A	A
217	A	A
218	A	A
219	A	A
220	A	A
221	A	A
222	A	A
223	A	A
224	A	A

225	A	A
226	A	A
227	A	B
228	A	B
229	A	A
230	A	B
231	A	A
232	A	A
233	A	A
234	A	A
235	A	A
236	A	A
237	A	A
238	A	A
239	A	A

*nd = not determined

Example 160: Treatment with Compounds 69 and 102 and Results in Tumor Growth Inhibition In Vivo

The effect on tumor growth of treatment with Compound 69 and 102 was assessed in the GP2d (95090714 Millipore Sigma, USA) and LS180 (CL-187 ATCC, USA) colorectal cancer models, and the AsPC-1 (CRL-1682 ATCC, USA), SW1990 (CRL-2172, ATCC, USA), HPAC (CRL-2119 ATCC, USA), and Panc04.03 (CRL-2555 ATCC, USA) pancreatic cancer models. Briefly, cells were grown in HYPER flasks (Corning) and harvested and prepared for implant by preparing a suspension with a final concentration of 25 x 10^6 cells/ml in 50% matrigel (Corning) and 50% phenol red-free media (Gibco DMEM or RPMI-1640, depending on cell line). For Panc04.03, 6-7 week NOD/SCID female mice (GemPharmatech Co. Ltd) were inoculated with 200µl of the cell suspension (10 million cells/mouse) subcutaneously on the left flank under sterile conditions. For all other cell lines, 6-8 weeks old CB17 SCID female mice (Charles River Laboratories) were inoculated with 200µl of the cell suspension (5 million cells/mouse) subcutaneously on the left flank under sterile conditions. Studies were initiated when tumors reached an average of approximately 200 mm^3. Compound 69 and Compound 102 were prepared in 30% HPbCD in 10mM citrate buffer, pH 4.0, and dosed intravenously (IV). Tumor growth inhibition (TGI) was calculated using the formula % TGI = $(V_C-V_T)/(V_C-V_0)$ x 100 where V_C, V_T are the average of control and treated groups at the end of the study, and V_0 is the average tumor volume at randomization. Treatment with Compound 69 and Compound 102 resulted in robust TGI in multiple models, including GP2d (Figure 7A and 7B), LS180 (Figure 8), SW1990 (Figure 10A and 10B), HPAC (Figure 11), and Panc04.03 (Figure 12). More moderate response was observed with Compound 69 in AsPC-1 (Figure 9A), whereas Compound 102 led to 100% TGI (Figure 9B). Compound treatment in LS180 resulted in moderate TGI of 30-50% (Figure 8).

Tumor lysate preparation and Western blot methods

Cold RIPA buffer was added to frozen tumor pieces at a volume of 1µl/mg of tumor tissue in a 2ml tube. A single metal bead (5mm) was added to each tube and tumors were lysed by rapid shaking in a Tissuelyser for 4 minutes at 24 Hz at 4°C. Beads were removed from tubes and lysates were centrifuged for 15 minutes at 4°C at 15000 rpm in a benchtop microcentrifuge. The supernatants (lysates) were collected and used to make 1:30 dilutions in RIPA buffer. The concentrated and diluted lysates were frozen at -80°C.

Protein Quantification, BCA assay

The BCA assay was run according to manufacturer's protocol (ThermoFisher) with provided bovine serum albumin (BSA) standard curve (range = 2mg/ml - 0.1 mg/ml) in a 96 well plate. The previously prepared 1:30 lysate dilutions were used for the BCA assay and for preparation of gel samples. Plates were read (OD562) using a BioTek Cytation3 plate reader running Gen5 3.11 software. Protein concentration of tumor lysates was determined with GraphPad Prism by interpolating sample ODs with BCA assay standard curve.

SDS-PAGE gel samples

Lysates were diluted by combing an appropriate volume of lysate, sample buffer, reducing agent, and ultrapure water. Gel samples were prepared to allow equal volume loading of 8-10µg of total protein/lane for all tumor samples.

Electrophoresis and Transfer

Gels were loaded with 8µg of total protein per well on 26 well, 4-12% Bis-Tris gels (ThermoFisher). BioRad Precision Plus molecular weight markers were loaded into lanes 1 and 26 (4µl per lane). Gels were run in MOPS/SDS running buffer for 65 minutes at 150 volts. Protein was transferred to nitrocellulose membranes using the BioRad Trans Blot Turbo semi-dry system. Transfer conditions were midi gel format at 25 volts, 2.5 amps, for 7 minutes.

Blocking and antibody hybridization

Membranes were cut into strips at desired molecular weights and then blocked for 1 hour in 3% BSA/TBS-T. Primary antibodies were diluted as per manufacturer's instructions in 3% BSA/TBS-T and incubated overnight at 4°C with gentle rocking. Membranes were then washed 5 x 5 minutes with TBS-T at room temperature. Secondary antibodies were diluted 1:20000 in 3% BSA/TBS-T and incubated at room temperature for 1 hour. Membranes were then washed 5 x 5 minutes with TBS-T.

Chemiluminescent Development and densitometry

Membranes were developed for 2 minutes with SuperSignal™ West Femto Maximum Sensitivity Substrate and then imaged with a BioRad ChemiDoc imager running Image Lab software v 5.2.1. Densitometry analysis was done using ImageJ software, all samples were normalized to vinculin loading control and then graphed as a percent of control as compared to vehicle treated tumors.

Reagents for Cell culture / implantation

DMEM – Gibco / ThermoFisher # 10566016
RPMI-1640 – Gibco / ThermoFisher # 61870036
DMEM/F12 - Gibco / ThermoFisher # 10565018
DMEM (phenol red-free) - Gibco/ThermoFisher #21063029
RPMI-1640 (phenol red-free) Gibco/ThermoFisher #11835030
DPBS – Gibco/ThermoFisher #14190144
Trypsin/EDTA - Gibco/ThermoFisher #25200056
FBS – Gibco/ThermoFisher #26140079
Penicillin-Streptomycin (PenStrep) - Gibco/ThermoFisher #15140122
Human EGF recombinant protein – Gibco/ThermoFisher #PHG0315
EMEM – ATCC #302003
RPMI-1640 – ATCC #302001
Hydrocortisone – Millipore Sigma #H0135-1mg
Insulin solution, human – Millipore Sigma #19278-5ml
ITS supplement – R&D Systems #AR013
Matrigel – Corning #354234
HYPER flask – Corning# 10034

Reagents for Tumor Western Blots

RIPA buffer - ThermoFisher #89900
HALT protease inhibitor - ThermoFisher #78437
HALT phosphatase inhibitor - Thermofisher #78420
EDTA, 0.5M - Thermofisher #1861275
BCA Protein Assay kit - ThermoFisher #23225
NuPAGE 4x LDS sample buffer – ThermoFisher #NP0007
Bolt 10x sample reducing agent – Thermofisher #B0009
NuPAGE 4-12% Bis-Tris Midi gel, 26 well – ThermoFisher #WG1403BX10
BioRad Precision Plus Dual Color ladder - BioRad #1610374
Trans-blot midi Nitrocellulose transfer pack - Biorad #1704159
MOPS/SDS running buffer - Thermofisher #NP0001-02

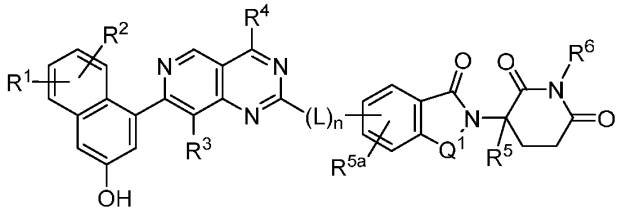
SuperSignal™ West Femto - ThermoFisher #34095
TBS-T (1X TBS with 0.1% tween-20)
BSA, bovine serum albumin, fraction V - AmericanBio #AB00440-01000
5 mm stainless steel bead - Qiagen #69989
Ras (G12D mutant specific)(D8H7) Rabbit mAb – Cell Signaling Technology #14429S
Vinculin (E1E9V) XP Rabbit mAb – Cell Signaling Technology #13901S
Anti-rabbit IgG, HRP-linked Antibody – Cell Signaling Technology #7074P2

The disclosed subject matter is not to be limited in scope by the specific embodiments and examples described herein. Indeed, various modifications of the disclosure in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

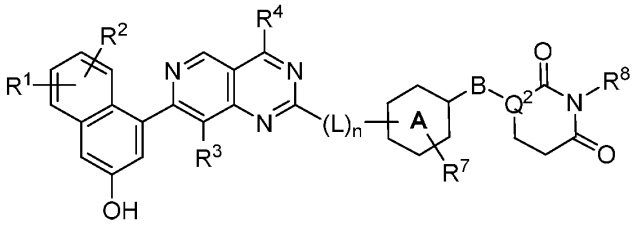
All references (*e.g.,* publications or patents or patent applications) cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual reference (*e.g.,* publication or patent or patent application) was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. Other embodiments are within the following claims.

CLAIMS

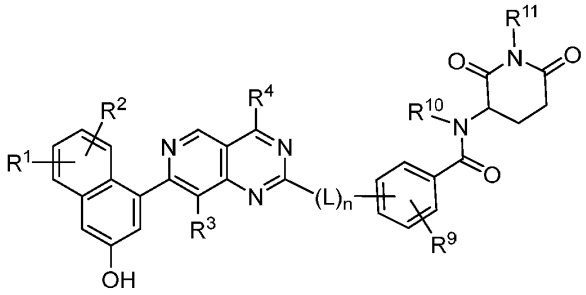
1. A compound of any one of Formula I–IV:



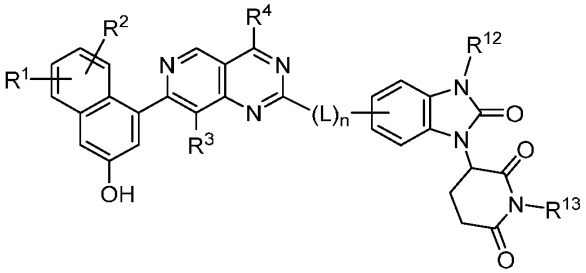
(I),



(II),



(III),



or

(IV),

or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is selected from $C(R^{14})_2$, C(O), and NR^{14};

Q^2 is CR^{14} or N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl,

R^3 is selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^4 is selected from C_{3-11} cycloalkyl, 3-10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl, wherein C_{3-11} cycloalkyl, 3-10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl are optionally substituted with R^{4a};

R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{5a}, R^5, R^6, R^8, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

Ring A is selected from phenyl, 6-membered heteroaryl, C_6 cycloalkyl, and 6-membered heterocycloalkyl;

B is a bond or C_{1-6} alkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

2. The compound of claim 1, wherein:

Q^1 is $C(R^{14})_2$ or C(O);

Q^2 is N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^3 is selected from H, halo, and CN;

R^4 is C_{3-11} cycloalkyl or 3-10 membered heterocycloalkyl, wherein C_{3-11} cycloalkyl and 3-10 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{5a}, R^5, R^6, R^8, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

Ring A is selected from phenyl, 6-membered heteroaryl, and 6-membered heterocycloalkyl;

B is a bond or C_{1-6} alkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, and 5-10 membered heteroaryl,

wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

3. The compound of claim 1 or 2, wherein:

Q^1 is $C(R^{14})_2$ or C(O);

Q^2 is N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6-8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6-8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^{5a}, R^5, R^6, R^8, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

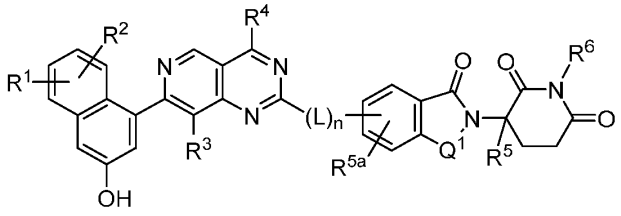
Ring A is phenyl or 6-membered heterocycloalkyl;

B is a bond or C_{1-6} alkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

4. The compound of any one of claims 1–3, wherein the compound has a structure of Formula I,



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is $C(R^{14})_2$ or C(O);

R^1 and R^2 are each independently selected from halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6-8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6-8 membered heterocycloalkyl are optionally substituted with R^{4a};

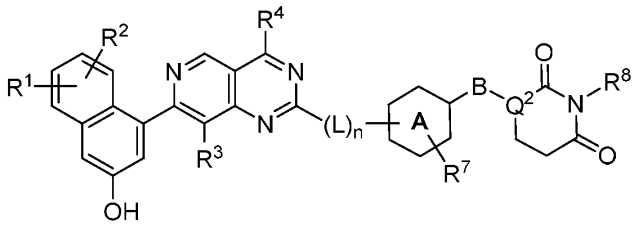
R^{4a} is H or C_{1-6} alkyl;

R^{5a}, R^5, R^6, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

5. The compound of any one of claims 1–3, wherein the compound has a structure of Formula II,



(II)

or a pharmaceutically acceptable salt thereof,

wherein:

Q^2 is N;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6-8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6-8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

R^8 and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^7 is selected from H, =O, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

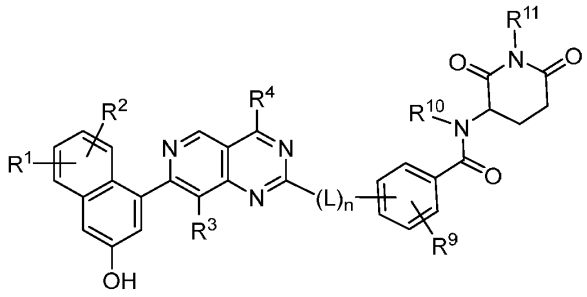
Ring A is phenyl or 6-membered heterocycloalkyl;

B is a bond or C_{1-6} alkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

6. The compound of any one of claims 1–3, wherein the compound has a structure of Formula III,



(III)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6-8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6-8 membered heterocycloalkyl are optionally substituted with R^{4a};

R^{4a} is H or C_{1-6} alkyl;

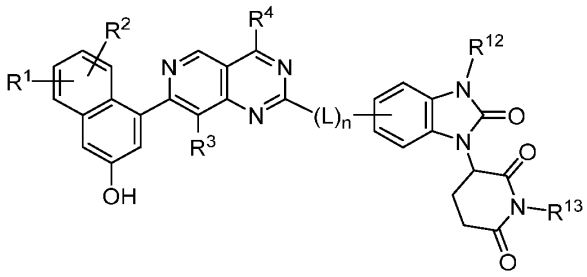
R^{10} and R^{11} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^9 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

7. The compound of any one of claims 1–3, wherein the compound has a structure of Formula IV,



(IV)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C≡CH;

R^3 is selected from H, halo, and CN;

R^4 is C_{6-8} cycloalkyl or 6-8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6-8 membered heterocycloalkyl are optionally substituted with R^{4a};

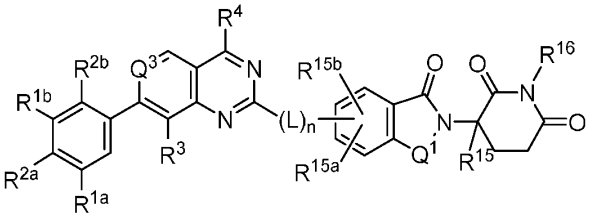
R^{4a} is H or C_{1-6} alkyl;

R^{12} and R^{13} and are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

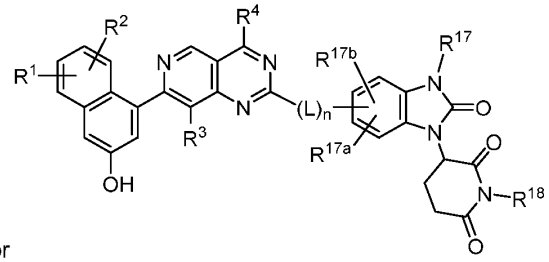
each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

8. A compound of Formula V or VI:



(V),



or

(VI)

or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is selected from $C(R^{14})_2$, C(O), and NR^{14};

Q^3 is CR^{14} or N;

R^{1a} and R^{2a} are each independently selected from OH, H, and halo;

R^{1b} and R^{2b} are each independently selected from halo and C_{3-6} cycloalkyl,

or R^{1b} and R^{2b}, together with the phenyl to which they attach, form C_{8-12} aryl, wherein C_{8-12} aryl is optionally substituted with R^1 and R^2;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^3 is selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^4 is selected from C_{3-11} cycloalkyl, 3–10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl, wherein C_{3-11} cycloalkyl, 3–10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl are optionally substituted with 1 or 2 R^{4a};

each R^{4a} is independently selected from H, OH, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{14}, R^{15a}, R^{15b}, R^{15}, R^{16}, R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3–12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3–12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

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

9. The compound of claim 8, wherein:

Q^1 is $C(R^{14})_2$ or C(O);

Q^3 is CR^{14} or N;

R^{1a} and R^{2a} are each independently selected from OH, H, and halo;

R^{1b} and R^{2b}, together with the phenyl to which they attach, form C_{8-12} aryl, wherein C_{8-12} aryl is optionally substituted with R^1 and R^2;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^3 is selected from H, halo, and CN;

R^4 is selected from C_{3-11} cycloalkyl and 3–10 membered heterocycloalkyl, wherein C_{3-11} cycloalkyl and 3–10 membered heterocycloalkyl are optionally substituted with 1 or 2 R^{4a};

each R^{4a} is independently selected from H, OH, and C_{1-6} alkyl;

R^{14}, R^{15a}, R^{15}, R^{15b}, R^{16}, R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

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

10. The compound of claim 8 or 9, wherein:

Q^1 is $C(R^{14})_2$ or C(O);

Q^3 is CH or N;

R^{1a} and R^{2a} are each independently selected from H, OH, and halo;

R^{1b} and R^{2b}, together with the phenyl to which they attach, form naphthyl substituted with R^1 and R^2;

R^1 and R^2 are each independently selected from H, halo, C_{1-3} alkyl, C_{3-5} cycloalkyl, and C≡CH;

R^3 is H or halo;

R^4 is selected from C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with 1 or 2 R^{4a};

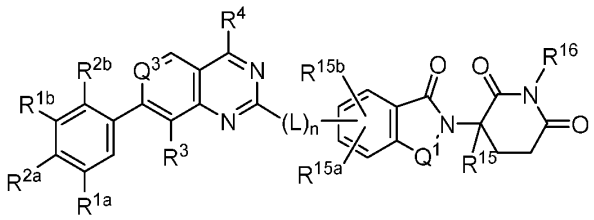
each R^{4a} is independently selected from H, OH, and C_{1-6} alkyl;

R^{14}, R^{15a}, R^{15b}, R^{15}, R^{16}, R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-3} alkyl, and C_{1-3} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

11. The compound of any one of claims 8–10, wherein the compound has a structure of Formula V,



(V)

or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is $C(R^{14})_2$ or C(O);

Q^3 is CH or N;

R^{1a} and R^{2a} are each independently selected from H, OH, and halo;

R^{1b} and R^{2b}, together with the phenyl to which they attach, form naphthyl substituted with R^1 and R^2;

R^1 and R^2 are each independently selected from H, halo, C_{1-3} alkyl, C_{3-5} cycloalkyl and C≡CH;

R^3 is H or halo;

R^4 is selected from C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with 1 or 2 R^{4a};

each R^{4a} is independently selected from H, OH, and C_{1-6} alkyl;

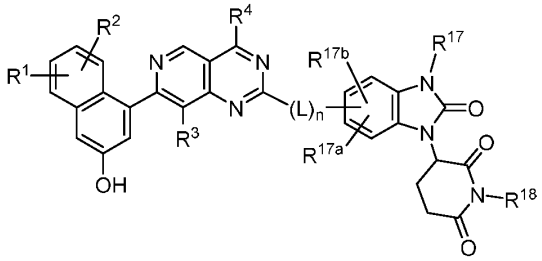
R^{14}, R^{15}, and R^{16} are each independently selected from H, halo, C_{1-3} alkyl, and C_{1-3} alkoxy;

R^{15a} and R^{15b} are each independently selected from halo, C_{1-3} alkyl, and C_{1-3} alkoxy;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

12. The compound of any one of claims 8–10, wherein the compound has a structure of Formula VI,



(VI)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 are each independently selected from H, halo, C_{1-3} alkyl, C_{3-5} cycloalkyl, and C≡CH;

R^3 is H or halo;

R^4 is selected from C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl, wherein C_{6-8} cycloalkyl and 6–8 membered heterocycloalkyl are optionally substituted with 1 or 2 R^{4a};

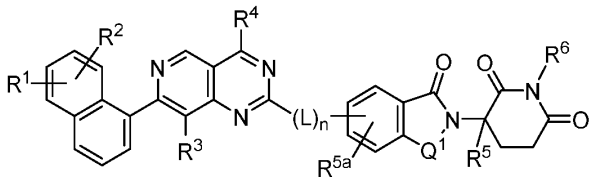
each R^{4a} is independently selected from H, OH, and C_{1-6} alkyl;

R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-3} alkyl, and C_{1-3} alkoxy;

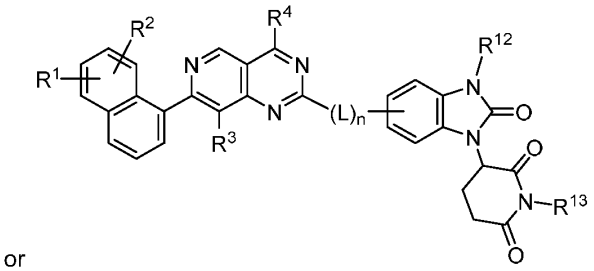
each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, O, C(O), N(H), N(C_{1-6} alkyl), C_{4-7} cycloalkyl, 5-12 membered heterocycloalkyl, and 6-7 membered heteroaryl, wherein 5-12 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from halo, CN, and C_{1-6} alkyl; and

n is 1, 2, 3, 4, 5, or 6.

13. A compound of Formula AI or AIV:



(AI)



or

(AIV)

or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is selected from $C(R^{14})_2$, C(O), and NR^{14};

R^1 and R^2 are each independently halo or C_{2-6} alkynyl;

R^3 is selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^4 is selected from C_{3-11} cycloalkyl, 3-10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl, wherein C_{3-11} cycloalkyl, 3-10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl are optionally substituted with R^{4a};

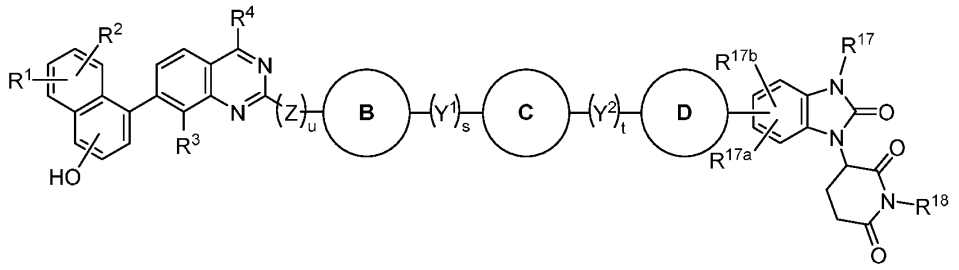
R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^{5a}, R^5, R^6, R^{12}, R^{13}, and R^{14} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each L is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, O, C(O), N(H), $N(C_{1-6}$ alkyl), C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl; and

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

14. A compound of Formula VII:



(VII)

or a pharmaceutically acceptable salt thereof,

wherein:

Ring B and Ring C are each independently selected from 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl;

Ring D is selected from a bond, C_{3-11} cycloalkyl, 3-12 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein 3-12 membered heterocycloalkyl is optionally substituted with halo, CN, and C_{1-6} alkyl, provided that when Ring D is a bond, then Y^2 is also a bond and t is 0;

Y^1 and Y^2 are each independently selected from a bond, O, C(O), N(H), N(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

Z is selected from N(H), N(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^3 is selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

R^4 is selected from C_{3-11} cycloalkyl, 3-10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl, wherein C_{3-11} cycloalkyl, 3-10 membered heterocycloalkyl, C_{6-10} aryl, and 3-10 membered heteroaryl are optionally substituted with R^{4a};

R^{4a} is selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

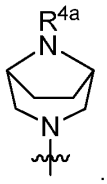
R^{17a}, R^{17b}, R^{17}, and R^{18} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

s and t are each independently 0, 1, 2, or 3; and

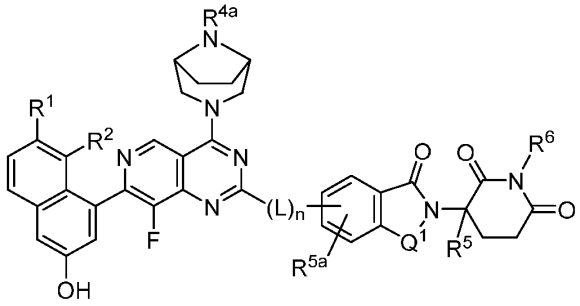
u is 1 or 2.

15. The compound of any one of claims 1–14, wherein R^4 is bridged 8-membered heterocycloalkyl optionally substituted with R^{4a}.

16. The compound of any one of claims 1–15, wherein R^4 is:



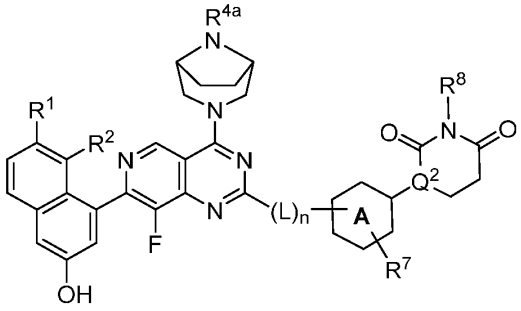
17. The compound of any one of claims 1–4 and 15, wherein the compound has a structure of Formula IA:



(IA)

or a pharmaceutically acceptable salt thereof.

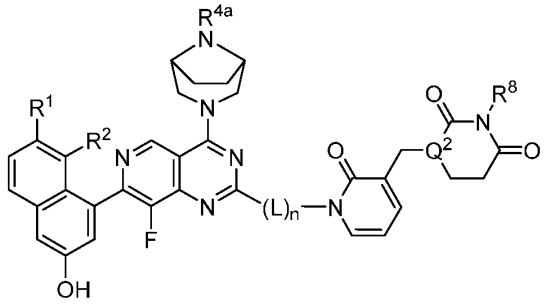
18. The compound of any one of claims 1–3, 5, and 15, wherein the compound has a structure of Formula IIA:



(IIA)

or a pharmaceutically acceptable salt thereof.

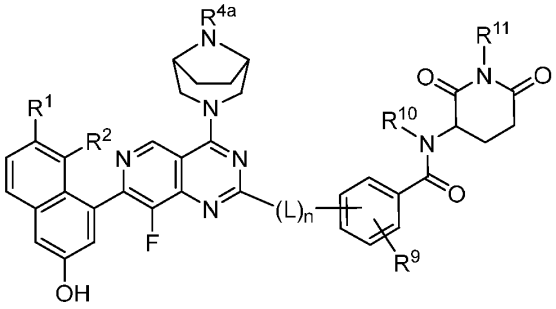
19. The compound of any one of claims 1–3, 5, and 15, wherein the compound has a structure of Formula IIB:



(IIB)

or a pharmaceutically acceptable salt thereof.

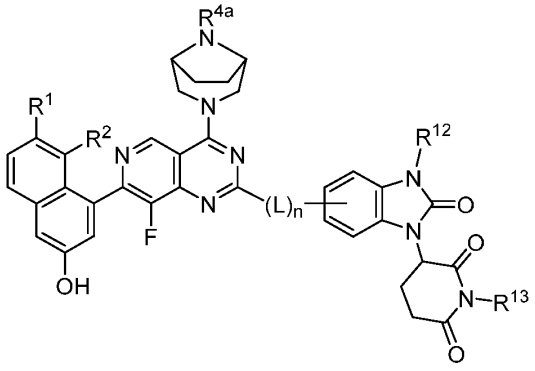
20. The compound of any one of claims 1–3, 6, and 15, wherein the compound has a structure of Formula IIIA:



(IIIA)

or a pharmaceutically acceptable salt thereof.

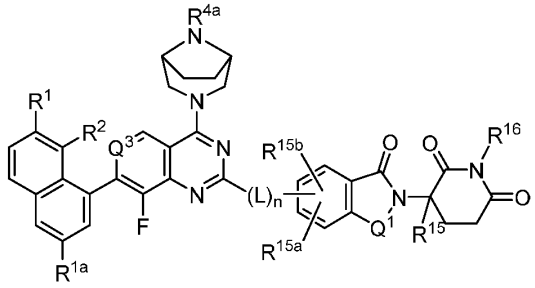
21. The compound of any one of claims 1–3, 7, and 15, wherein the compound has a structure of Formula IVA:



(IVA)

or a pharmaceutically acceptable salt thereof.

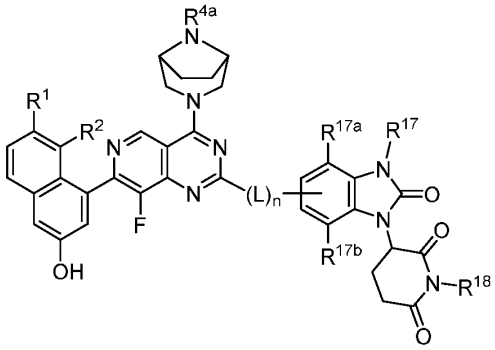
22. The compound of any one of claims 8–11, wherein the compound has a structure of Formula VA:



(VA)

or a pharmaceutically acceptable salt thereof.

23. The compound of any one of claims 8–10 and 12, wherein the compound has a structure of Formula VIA:



(VIA)

or a pharmaceutically acceptable salt thereof.

24. The compound of any one of claims 1–4, 8–11, 13, 15–17, and 22, wherein Q^1 is CH_2 or C(O).

25. The compound of any one of claims 1–3, 5, 15, 16, 18, and 19, wherein Q^2 is N.

26. The compound of any one of claims 1–25, wherein R^1 is selected from H, halo, and C_{1-6} alkyl.

27. The compound of any one of claims 1–25, wherein R^1 is H.

28. The compound of any one of claims 1–25, wherein R^1 is halo.

29. The compound of any one of claims 1–25, wherein R^1 is C_{1-6} alkyl.

30. The compound of any one of claims 1–29, wherein R^2 is selected from H, C_{1-6} alkyl, and C≡CH.

31. The compound of any one of claims 1–30, wherein R^2 is H.

32. The compound of any one of claims 1–30, wherein R^2 is C_{1-6} alkyl.

33. The compound of any one of claims 1–30, wherein R^2 is C≡CH.

34. The compound of any one of claims 1–16 and 24–33, wherein R^3 is halo.

35. The compound of any one of claims 1 and 8–34, wherein R^{4a} is H or C_{1-6} alkyl.

36. The compound of any one of claims 1 and 8–34, wherein each R^{4a} is selected from OH and C_{1-6} alkyl.

37. The compound of any one of claims 1-4, 13, 15–17, and 24–36, wherein R^{5a} is H, halo, or C_{1-6} alkoxy.

38. The compound of any one of claims 1–4, 13, 15–17, and 24–37, wherein R^5 is H or C_{1-6} alkyl.

39. The compound of any one of claims 1–4, 13, 15–17, and 24–37, 35, wherein R^6 is H or C_{1-6} alkyl.

40. The compound of any one of claims 1–3, 5, 15, 16, 18, and 24–36, wherein R^7 is selected from H, =O, halo, and C_{1-6} alkoxy.

41. The compound of any one of claims 1–3, 5, 15, 16, 18, 24–36, and 40, wherein R^7 is =O.

42. The compound of any one of claims 1–3, 5, 15, 16, 18, 24–36, and 40, wherein R^7 is halo.

43. The compound of any one of claims 1–3, 5, 15, 16, 18, 24–36, and 40, wherein R^7 is C_{1-6} alkoxy.

44. The compound of any one of claims 1–3, 5, 15, 16, 18, 24–36, and 40–43, wherein R^8 is H or C_{1-6} alkyl.

45. The compound of any one of claims 1–3, 5, 15, 16, 18, 24–36, and 40–44, wherein R^8 is H.

46. The compound of any one of claims 1–3, 6, 15, 16, 20, and 26–36, wherein R^9 is selected from H, halo, and C_{1-6} alkoxy.

47. The compound of any one of claims 1–3, 6, 15, 16, 20, 26–36, and 46, wherein R^9 is halo.

48. The compound of any one of claims 1–3, 6, 15, 16, 18, 26–36, 46, and 47, wherein R^9 is C_{1-6} alkoxy.

49. The compound of any one of claims 1–3, 6, 15, 16, 18, 26–36, and 46–48, wherein R^{10} is H.

50. The compound of any one of claims 1–3, 6, 15, 16, 18, 26–36, and 46–49, wherein R^{11} is H.

51. The compound of any one of claims 1–3, 7, 15, 16, 21, and 26–36, wherein R^{12} is C_{1-6} alkyl.

52. The compound of any one of claims 1–3, 7, 15, 16, 21, 26–36, and 51, wherein R^{13} is H.

53. The compound of any one of claims 1–5, 8–11, 13–19, 22, and 24–45, wherein R^{14} is H or C_{1-6} alkyl.

54. The compound of any one of claims 1–5, 8–11, 13–19, 22, 24–45, and 53, wherein R^{14} is H.

55. The compound of any one of claims 1–5, 8–11, 13–19, 22, 24–45, and 53, wherein R^{14} is C_{1-6} alkyl.

56. The compound of any one of claims 1–3, 5, 15, 16, 18, 25–36, 40–45, and 53–55, wherein Ring A is phenyl.

57. The compound of any one of claims 1–3, 5, 15, 16, 18, 25–36, 40–45, and 53–55, wherein Ring A is 6-membered heterocycloalkyl.

58. The compound of any one of claims 1–3, 5, 15, 16, 18, 25–36, 40–45, 53–55, and 57, wherein Ring A is dihydropyridinyl.

59. The compound of any one of claims 1–3, 5, 15, 16, 18, 25–36, 40–45, and 53–58, wherein B is a bond.

60. The compound of any one of claims 1–3, 5, 15, 16, 18, 25–36, 40–45, and 53–58, wherein B is C_{1-6} alkyl.

61. The compound of any one of claims 8–11, 15, 16 22, 24, and 26–36, wherein Q^3 is N.

62. The compound of any one of claims 8–11, 15, 22, 24, 26–36, 56, and 61, wherein R^{1a} is H or OH.

63. The compound of any one of claims 8–11, 15, 22, 26–36, 56, 61, and 62, wherein R^{1a} is H.

64. The compound of any one of claims 8–11, 15, 22, 26–36, 56, 61, and 62, wherein R^{1a} is OH.

65. The compound of any one of claims 8–11, 15, 22, 26–36, 56, and 61–64, wherein R^{2a} is H.

66. The compound of any one of claims 8–11, 15, 22, 26–36, 56, and 61–65, wherein R^{15a} is H, halo, or C_{1-6} alkoxy.

67. The compound of any one of claims 8–11, 15, 22, 26–36, 56, and 61–66, wherein R^{15b} is H or C_{1-6} alkyl.

68. The compound of any one of claims 8–11, 15, 22, 26–36, 56, and 61–67, wherein R^{15} is H or C_{1-6} alkyl.

69. The compound of any one of claims 8–11, 15, 22, 26–36, 56, and 61–68, wherein R^{16} is H or C_{1-6} alkyl.

70. The compound of any one of claims 8–10, 12, 14–16, and 26–36, wherein R^{17a} and R^{17b} are each independently H or halo.

71. The compound of any one of claims 8–10, 12, 14–16, 26–36, and 70, wherein R^{17} is C_{1-6} alkyl.

72. The compound of any one of claims 8–10, 12, 14–16, 26–36, 70, and 71, wherein R^{18} is H.

73. The compound of any one of claims 1–13 and 15–72, wherein each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C(O), 5-12 membered heterocycloalkyl, wherein 5-12 membered heterocycloalkyl is optionally substituted with halo.

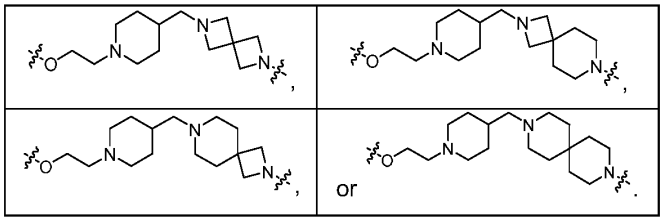
74. The compound of claim 73, wherein 5–12 membered heterocycloalkyl is fused 8 membered heterocycloalkyl.

75. The compound of any one of claims 1–13 and 15–72, wherein each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, and 6-12 membered heterocycloalkyl, wherein 6-12 membered heterocycloalkyl is optionally substituted with halo or C_{1-6} alkyl.

76. The compound of any one of claims 1–13 and 15–72, wherein each L is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, 6-8 membered heterocycloalkyl, and 5-6 membered heteroaryl, wherein 6-8 membered heterocycloalkyl is optionally substituted with halo.

77. The compound of any one of claims 1–13, 15–72, and 75, wherein n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(6-12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-12 membered heterocycloalkyl).

78. The compound of claim 77, wherein each L forms the linker:



79. The compound of any one of claims 1–13 and 15–72, wherein each L is independently selected from O, C_{1-6} alkyl, C_{1-6} alkoxy, and 5-12 membered heterocycloalkyl, wherein 5-12 membered heterocycloalkyl is optionally substituted with C_{1-6} alkyl.

80. The compound of any one of claims 1–13, 15–72 and 79, wherein n is 6, and each L forms the following linker: (C_{1-6} alkoxy)-(6-12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl).

81. The compound of any one of claims 1–13, 15–72, 79, and 80, wherein n is 6, and each L forms the following linker: (C_{1-6} alkoxy)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl).

82. The compound of any one of claims 1–13, 15–72, and 79, wherein n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(5-12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(5-12 membered heterocycloalkyl).

83. The compound of any one of claims 1–13, 15–72, 79, and 82, wherein n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(11-membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl).

84. The compound of any one of claim 83, wherein 11-membered heterocycloalkyl is spirocyclic 11-membered heterocycloalkyl.

85. The compound of any one of claims 1–13, 15–72, and 79, wherein n is 6, and each L forms the following linker: (C_{1-6} alkoxy)-(5-12 membered heterocycloalkyl)-(O)-(5-12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(5-12 membered heterocycloalkyl), wherein 5-12 membered heterocycloalkyl is optionally substituted with C_{1-6} alkyl.

86. The compound of any one of claims 1–13, 15–72, 79, and 85, wherein n is 6, and each L forms the following linker: (C_{1-6} alkoxy)-(5-membered heterocycloalkyl)-(O)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(6-membered heterocycloalkyl), wherein 5 membered heterocycloalkyl is optionally substituted with C_{1-6} alkyl.

87. The compound of any one of claims 1–13, 15–72, and 79, wherein n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(5-12 membered heterocycloalkyl)-(C_{1-6} alkyl)-(5-12 membered heterocycloalkyl).

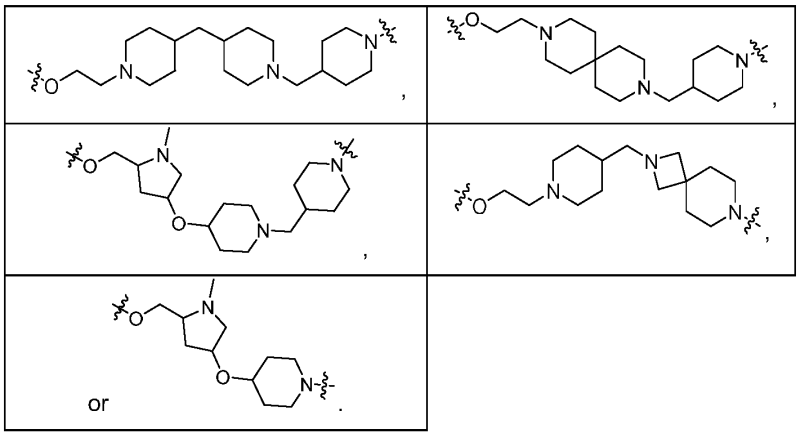
88. The compound of any one of claims 1–13, 15–72, 79, and 87, wherein n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(6-membered heterocycloalkyl)-(C_{1-6} alkyl)-(9-membered heterocycloalkyl).

89. The compound of claim 88, wherein 9-membered heterocycloalkyl is spirocyclic 9-membered heterocycloalkyl.

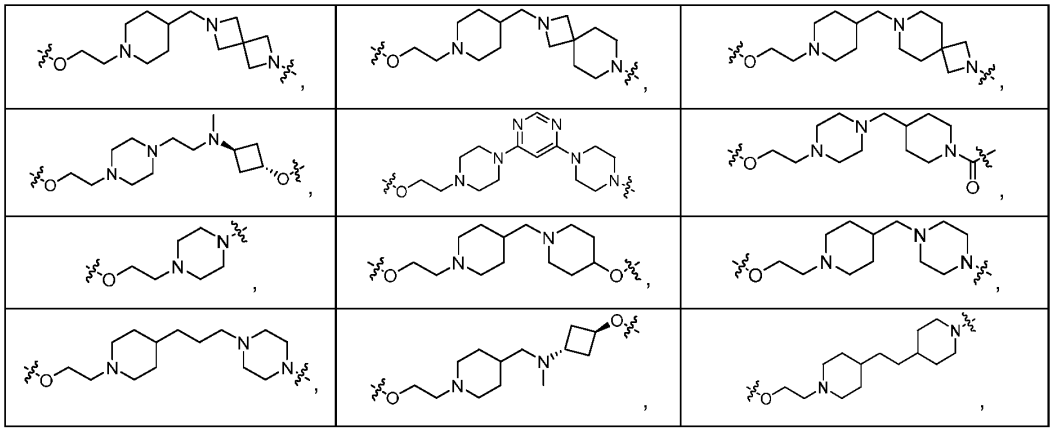
90. The compound of any one of claims 1–13, 15–72, and 79, wherein n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(5-12 membered heterocycloalkyl)-(O)-(5-12 membered heterocycloalkyl), wherein 5-12 membered heterocycloalkyl is optionally substituted with C_{1-6} alkyl.

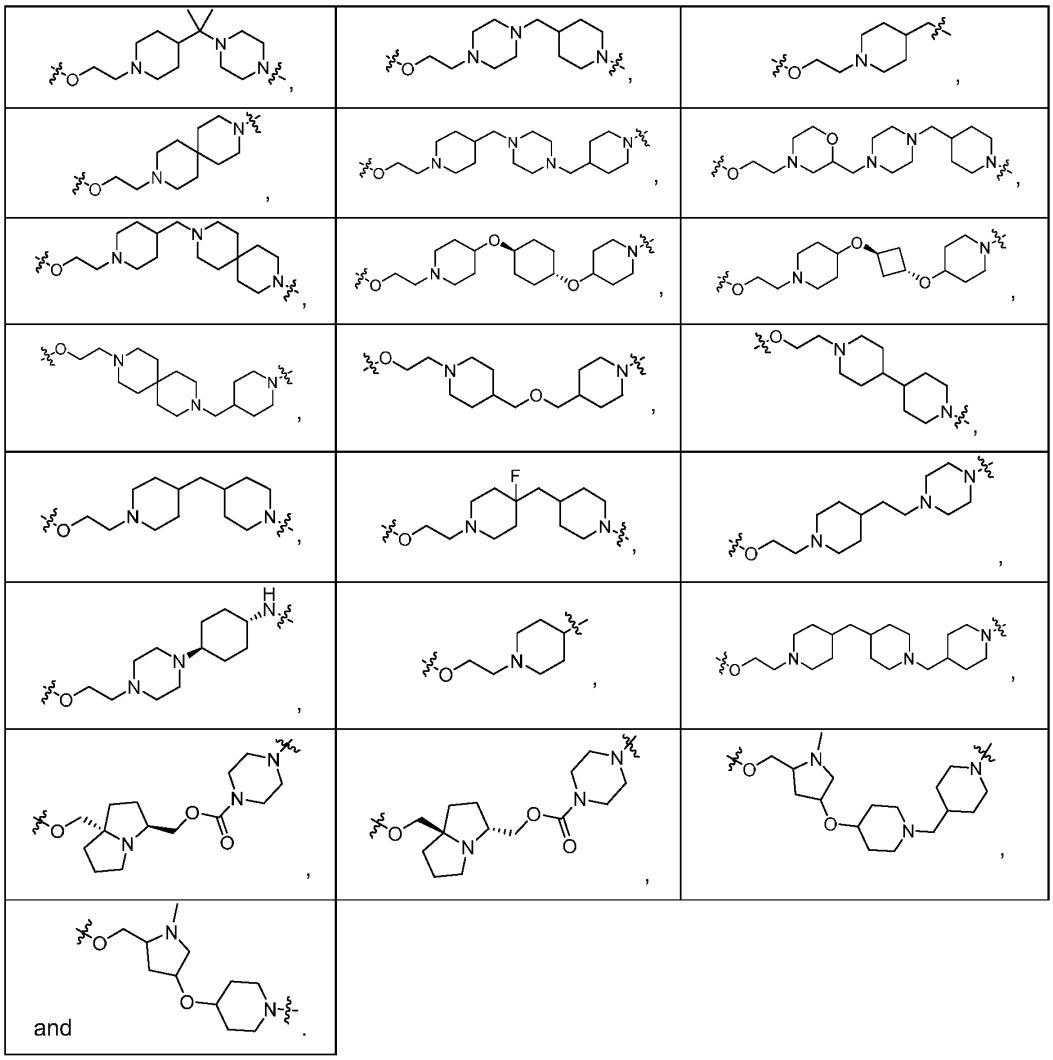
91. The compound of any one of claims 1–13, 15–72, 79, and 90, wherein n is 4, and each L forms the following linker: (C_{1-6} alkoxy)-(5-membered heterocycloalkyl)-(O)-(6-membered heterocycloalkyl), wherein 5 membered heterocycloalkyl is optionally substituted with C_{1-6} alkyl.

92. The compound of any one of claims 1–13, 15–72, and 79–91, wherein each L forms the linker:

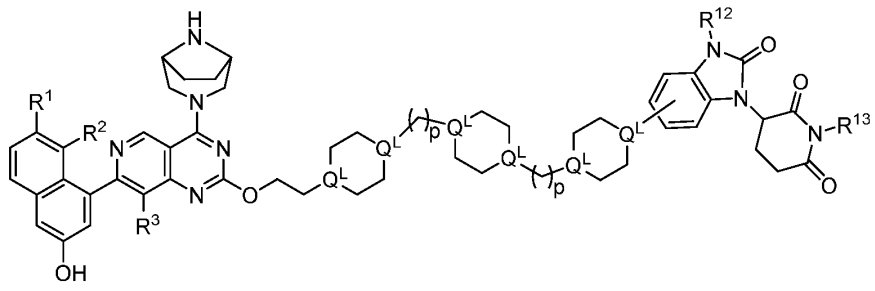


93. The compound of any one of claims 1–13, 15–72, 78, and 92, wherein $(L)_n$ is selected from:





94. A compound of Formula IVB:



(IVB)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 are each independently selected from H, halo, C_{1-6} alkyl, and C_{2-6} alkynyl;
R^3 is selected from H, halo, and CN;
each Q^L is independently CR^L or N;
each R^L is independently H, halo, or CN;
each p is 1, 2, 3, 4, 5, or 6; and
R^{12} and R^{13} are each independently selected from H, C_{1-6} alkyl, and C_{1-6} alkoxy.

95. The compound of any one of claims 1–94, wherein the compound is selected from a compound in Table 1, or a pharmaceutically acceptable salt thereof.

96. A pharmaceutical composition comprising a compound of any one of claims 1–95 and a pharmaceutically acceptable carrier.

97. A method of treating cancer in a subject comprising administering to the subject an effective amount of a compound according to any one of claims 1–95, or the pharmaceutical composition of claim 96.

98. The method of claim 97, wherein the cancer is selected from bladder cancer, bowel cancer, breast cancer, cervical cancer, colon cancer, colorectal cancer, endometrial cancer, esophageal cancer, head cancer, kidney cancer, liver cancer, lung cancer, neck cancer, ovary cancer, pancreatic cancer, prostate cancer, stomach cancer, uterine cancer, ovarian cancer, testicular cancer, thyroid cancer, pineal cell tumor, carcinoma, cytoma, ependymoma, ganglioglioma, ganglioneuroma, gliobastoma, glioma, leukemia, lymphoma, medulloblastoma, melanoma, meningioma, myeloma, nephroblastoma, neuroblastoma, neurofibroma, oligodendroglioma peripheral neuroepithelioma, sarcoma, and schwannoma.

99. The method of claim 98, wherein the carcinoma is teratocarcinoma.

100. The method of claim 98, wherein the cytoma is astrocytoma.

101. The method of claim 98, wherein the carcinoma is selected from squamous-cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinoma, and renal cell carcinoma.

102. The method of claim 98, wherein the leukemia is selected from precursor B-lymphoblastic leukemia, T-cell acute lymphoblastic Leukemia, adult T-cell leukemia, Philadelphia chromosome positive acute lymphoblastic leukemia, Philadelphia chromosome positive chronic myeloid leukemia, and acute lymphoblastic leukemia.

103. The method of claim 98, wherein the lymphoma is selected from Burkitt lymphoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, precursor T-lymphoblastic lymphoma, peripheral T-cell lymphoma, precursor lymphoblastic lymphoma, diffuse large B-cell lymphoma, and B-cell lymphoma.

104. The method of claim 98, wherein the nephroblastoma is Wilms' tumor.

105. The method of claim 98, wherein the sarcoma is selected from carcinosarcoma, Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcoma, synovial sarcoma, and meningeal sarcoma.

106. A method of degrading a target protein in a cell comprising contacting the cell with an effective amount of the compound according to any one of claims 1–95, or the pharmaceutical composition of claim 96, wherein the compound effectuates the degradation of the target protein.