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(54) Title: PROTEOLYSIS-TARGETING CHIMERA (PROTAC) COMPOUNDS AND USES THEREOF FIELD

(57) Abstract: The present disclosure relates generally to PROTAC (proteolysis-targeting chimera) compounds, pharmaceutical compositions comprising such compounds, and methods of treating various diseases and conditions with such compounds.

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PROTEOLYSIS-TARGETING CHIMERA (PROTAC) COMPOUNDS AND USES THEREOF

FIELD

[1] Provided herein are PROTAC (proteolysis-targeting chimera) compounds, pharmaceutical compositions comprising such compounds, and methods of treating various diseases and conditions with such compounds.

BACKGROUND

[2] Proteolysis-targeting chimera (PROTAC), through which target protein is recruited to E3 ligase for ubiquitination and then degraded via the proteasome pathway, utilizes the functional characteristics of the ubiquitin proteasome pathway to degrade protein substrate specifically. As a compound, PROTAC does not have immunogenicity; it is simple in structure, can be easily synthesized, and can easily and flexibly travel within the bodies and enter cells.

[3] Although many PROTAC molecules have been developed by drug developers, there remains a need for more specific and effective PROTAC molecules.

BRIEF SUMMARY

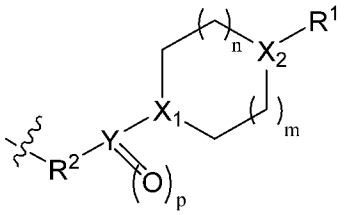
[4] In one aspect, provided herein is a bifunctional compound of formula (I):

PTM-L-ULM (I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

the PTM is a moiety that binds a target protein;

the ULM is an E3 ubiquitin ligase CDC20 (Cell Division Cycle 20) binding moiety of formula (A):



(A)

wherein

R^1 is C_1-C_6 alkyl, C_{6-10} aryl or 5- to 6-membered heteroaryl, each of which is optionally substituted with C_1-C_6 alkyl, halogen, -OH, oxo, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), -NO_2, or -CN;

R^2 is a bond, C_1-C_6 alkylene, C_{3-8} cycloalkylene, 3- to 10- membered heterocyclylene, C_{6-10} arylene, or 5- to 10- membered heteroarylene;

X_1 and X_2 are independently N or CH;

Y is C or S;

m and n are independently 0 1, or 2; and

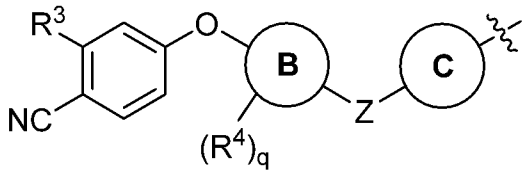
p is 0, 1 or 2;

and

L is a bond or a chemical linker covalently connecting the PTM and the ULM.

[5] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the ULM target is an E3 ubiquitin ligase CDC20 (Cell Division Cycle 20), that is Anaphase Promoting Complex (APC).

[6] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the PTM is of formula (B):

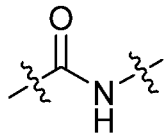
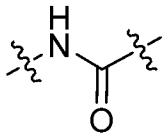


(B)

wherein

Ring B is C_3-C_8 cycloalkyl;

Ring C is C_{6-10} aryl or 5- to 10- membered heteroaryl;

Z is  or  ;

R^3 is halogen, or methoxy;

R^4 is C_1-C_6 alkyl; and

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

[7] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L is *—A^{L1}-A^{L2}-A^{L3}-A^{L4}—**, wherein

* represents the point of attachment to the PTM,

** represents the point of attachment to the ULM,

A^{L1} and A^{L4} are each independently a bond, -(C=O)-, -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, or C_{3-8} cycloalkylene;

wherein the -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, and C_{3-8} cycloalkylene of A^{L1} and A^{L4}

are each independently and optionally substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen; and

A^{L2} and A^{L3} are each independently a bond, $-(CH_2)_r-$, $-(OCH_2CH_2)_s-$, $-(CH_2CH_2O)_s-$, $-(NHCH_2CH_2)_s-$, $-(CH_2CH_2NH)_s-$, wherein r and s are each an integer between 0 and 10;

wherein the $-(CH_2)_r-$, $-(OCH_2CH_2)_s-$, $-(CH_2CH_2O)_s-$, $-(NHCH_2CH_2)_s-$, and $-(CH_2CH_2NH)_s-$ of A^{L2} and A^{L3} are each independently and optionally substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen.

[8] In another aspect, provided herein is a bifunctional compound selected from the compounds in Table 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[9] In another aspect, provided herein is a pharmaceutical composition comprising at least one bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient.

[10] In another aspect, provided herein is a method of treating a disease or disorder in an individual in need thereo, comprising administering to the individual a therapeutically effective amount of a bifunctional compound according to formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a therapeutically effective amount of a pharmaceutical composition containing a bifunctional compound according to formula (I).

DETAILED DESCRIPTION

Definitions

[11] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The terminology used in the description is for describing particular embodiments only and is not intended to be limiting of the invention.

[12] For use herein, unless clearly indicated otherwise, use of the terms "a", "an" and the like refers to one or more.

[13] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X".

[14] When a range of values is given (e.g., C_{1-6} alkyl), each value within the range as well as all intervening ranges are included. For example, "C_{1-6} alkyl" includes C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{2-6}, C_{3-6}, C_{4-6}, C_{5-6}, C_{1-5}, C_{2-5}, C_{3-5}, C_{4-5}, C_{1-4}, C_{2-4}, C_{3-4}, C_{1-3}, C_{2-3}, and C_{1-2} alkyl.

[15] "Alkyl" as used herein refers to and includes, unless otherwise stated, a saturated linear (*i.e.*, unbranched) or branched univalent hydrocarbon chain or combination thereof, having the number of carbon atoms designated (*i.e.*, C_{1-10} means one to ten carbon atoms). Particular alkyl groups are those having 1 to

20 carbon atoms (a "C_{1-20} alkyl"), having 1 to 10 carbon atoms (a "C_{1-10} alkyl"), having 6 to 10 carbon atoms (a "C_{6-10} alkyl"), having 1 to 6 carbon atoms (a "C_{1-6} alkyl"), having 2 to 6 carbon atoms (a "C_{2-6} alkyl"), or having 1 to 4 carbon atoms (a "C_{1-4} alkyl"). Examples of alkyl groups include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, and the like.

[16] "Alkylene" as used herein refers to the same residues as alkyl, but having bivalency. Particular alkylene groups are those having 1 to 20 carbon atoms (a "C_{1-20} alkylene"), having 1 to 10 carbon atoms (a "C_{1-10} alkylene"), having 6 to 10 carbon atoms (a "C_{6-10} alkylene"), having 1 to 6 carbon atoms (a "C_{1-6} alkylene"), 1 to 5 carbon atoms (a "C_{1-5} alkylene"), 1 to 4 carbon atoms (a "C_{1-4} alkylene") or 1 to 3 carbon atoms (a "C_{1-3} alkylene"). Examples of alkylene include, but are not limited to, groups such as methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), isopropylene ($-CH_2CH(CH_3)-$), butylene ($-CH_2(CH_2)_2CH_2-$), isobutylene ($-CH_2CH(CH_3)CH_2-$), pentylene ($-CH_2(CH_2)_3CH_2-$), hexylene ($-CH_2(CH_2)_4CH_2-$), heptylene ($-CH_2(CH_2)_5CH_2-$), octylene ($-CH_2(CH_2)_6CH_2-$), and the like.

[17] "Cycloalkyl" as used herein refers to and includes, unless otherwise stated, cyclic univalent nonaromatic hydrocarbon structures, which may be fully saturated, mono- or polyunsaturated, but which are non-aromatic, having the number of carbon atoms designated (*i.e.,* C_{3-10} means three to ten carbon atoms). Cycloalkyl can consist of one ring, such as cyclohexyl, or multiple rings, such as adamantyl. A cycloalkyl comprising more than one ring may be fused, spiro or bridged, or combinations thereof. Particular cycloalkyl groups are those having from 3 to 12 annular carbon atoms. A preferred cycloalkyl is a cyclic hydrocarbon having from 3 to 8 annular carbon atoms (a "C_{3-8} cycloalkyl"), having 3 to 6 carbon atoms (a "C_{3-6} cycloalkyl"), or having from 3 to 4 annular carbon atoms (a "C_{3-4} cycloalkyl"). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like. A cycloalkyl group may be fused with aryl, heteroaryl, or heterocyclyl. In one variation, a cycloalkyl group having more than one ring where at least one ring is aryl, heteroaryl, or heterocyclyl is connected to the parent structure at an atom in the nonaromatic hydrocarbon cyclic group.

[18] "Cycloalkylene" as used herein refers to the same residues as cycloalkyl, but having bivalency. Cycloalkylene can consist of one ring or multiple rings which may be fused, spiro or bridged, or combinations thereof. Particular cycloalkylene groups are those having from 3 to 12 annular carbon atoms. A preferred cycloalkylene is a cyclic hydrocarbon having from 3 to 8 annular carbon atoms (a "C_{3-8} cycloalkylene"), having 3 to 6 carbon atoms (a "C_{3-6} cycloalkylene"), or having from 3 to 4 annular carbon atoms (a "C_{3-4} cycloalkylene"). Examples of cycloalkylene include, but are not limited to, cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene, norbornylene, and the like. A cycloalkylene may attach to the remaining structures via the same ring carbon atom or different ring carbon atoms. When

a cycloalkylene attaches to the remaining structures via two different ring carbon atoms, the connecting bonds may be cis- or trans- to each other.

[19] "Aryl" or "Ar" as used herein refers to an unsaturated aromatic carbocyclic group having a single ring (*e.g.,* phenyl) or multiple condensed rings (*e.g.,* naphthyl or anthryl) which condensed rings may or may not be aromatic. Particular aryl groups are those having from 6 to 14 annular carbon atoms (a "C_{6-14} aryl"). An aryl group may be fused with heteroaryl, cycloalkyl, or heterocyclyl. In one variation, an aryl group having more than one ring where at least one ring is heteroaryl, cycloalkyl, or heterocyclyl is connected to the parent structure at an atom in the aromatic carbocyclic group.

[20] "Arylene" as used herein refers to the same residues as aryl, but having bivalency. Particular arylene groups are those having from 6 to 14 annular carbon atoms (a "C_{6-14} arylene").

[21] "Heteroaryl" as used herein refers to an unsaturated aromatic cyclic group having from 1 to 14 annular carbon atoms and at least one annular heteroatom, including but not limited to heteroatoms such as nitrogen, oxygen, and sulfur. A heteroaryl group may have a single ring (*e.g.*, pyridyl, furyl) or multiple condensed rings (*e.g.*, indolizinyl, benzothienyl) which condensed rings may or may not be aromatic. Particular heteroaryl groups are 5 to 14-membered rings having 1 to 12 annular carbon atoms and 1 to 6 annular heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 10-membered rings having 1 to 8 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 5, 6 or 7-membered rings having 1 to 5 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen, and sulfur. In one variation, particular heteroaryl groups are monocyclic aromatic 5-, 6- or 7-membered rings having from 1 to 6 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. In another variation, particular heteroaryl groups are polycyclic aromatic rings having from 1 to 12 annular carbon atoms and 1 to 6 annular heteroatoms independently selected from nitrogen, oxygen, and sulfur. A heteroaryl group may be fused with aryl, cycloalkyl, or heterocyclyl. In one variation, a heteroaryl group having more than one ring where at least one ring is aryl, cycloalkyl, or heterocyclyl is connected to the parent structure at an atom in the aromatic cyclic group having at least one annular heteroatom. A heteroaryl group may be connected to the parent structure at a ring carbon atom or a ring heteroatom.

[22] "Heteroarylene" as used herein refers to the same residues as heteroaryl, but having bivalency.

[23] "Heterocycle", "heterocyclic", or "heterocyclyl" as used herein refers to a saturated or an unsaturated non-aromatic cyclic group having a single ring or multiple condensed rings, and having from 1 to 14 annular carbon atoms and from 1 to 6 annular heteroatoms, such as nitrogen, sulfur or oxygen, and the like. In certain embodiments, the nitrogen and/or sulfur atom(s) of the heterocyclic group are optionally oxidized to provide for N-oxide, -S(O)-, or $-SO_2-$ moieties. A heterocycle comprising more than one ring may be fused, bridged or spiro, or any combination thereof, but excludes heteroaryl. The heterocyclyl group

may be optionally substituted independently with one or more substituents described herein. Particular heterocyclyl groups are 3 to 14-membered rings having 1 to 13 annular carbon atoms and 1 to 6 annular heteroatoms independently selected from nitrogen, oxygen and sulfur, 3 to 12-membered rings having 1 to 11 annular carbon atoms and 1 to 6 annular heteroatoms independently selected from nitrogen, oxygen and sulfur, 3 to 10-membered rings having 1 to 9 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur, 3 to 8-membered rings having 1 to 7 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur, or 3 to 6-membered rings having 1 to 5 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. In one variation, heterocyclyl includes monocyclic 3-, 4-, 5-, 6- or 7-membered rings having from 1 to 2, 1 to 3, 1 to 4, 1 to 5, or 1 to 6 annular carbon atoms and 1 to 2, 1 to 3, or 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. In another variation, heterocyclyl includes polycyclic non-aromatic rings having from 1 to 12 annular carbon atoms and 1 to 6 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. A heterocyclyl group may be fused with aryl, cycloalkyl, or heteroaryl. In one variation, a heterocyclyl group having more than one ring where at least one ring is aryl, cycloalkyl, or heteroaryl is connected to the parent structure at an atom in the non-aromatic cyclic group having at least one heteroatom.

[24] "Heterocyclylene" as used herein refers to the same residues as heterocyclyl, but having bivalency.

[25] "Halo" or "halogen" refers to elements of the Group 17 series having atomic number 9 to 85. Preferred halo groups include the radicals of fluorine, chlorine, bromine and iodine. A haloalkyl is an alkyl group that is substituted with one or more halogens. Where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached, *e.g.*, dihaloaryl, dihaloalkyl, trihaloaryl etc. refer to aryl and alkyl substituted with two ("di") or three ("tri") halo groups, which may be but are not necessarily the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl.

[26] "Optionally substituted" unless otherwise specified means that a group may be unsubstituted or substituted with one or more (*e.g.*, 1, 2, 3, 4 or 5) of the substituents listed for that group in which the substituents may be the same or different. In one embodiment, an optionally substituted group has one substituent. In another embodiment, an optionally substituted group has two substituents. In another embodiment, an optionally substituted group has three substituents. In another embodiment, an optionally substituted group has four substituents. In some embodiments, an optionally substituted group has 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, or 2 to 5 substituents. In one embodiment, an optionally substituted group is unsubstituted.

[27] "Oxo" as used herein refers to a =O moiety.

[28] Furthermore, some compounds may sometimes exist in tautomeric forms. It will be understood that although structures are shown, or named, in a particular form, the invention also includes the tautomer thereof. Also, some compounds may sometimes exist in atropoisomeric forms. It will be understood that although structures are shown in a particular form, the invention also includes the corresponding atropoisomeric forms thereof.

[29] The compounds of the invention and disclosure may contain one or more chiral centers and therefore, such compounds (and intermediates thereof) can exist as racemic mixtures; pure stereoisomers (i.e., enantiomers or diastereomers); stereoisomer-enriched mixtures and the like. Chiral compounds shown or named herein without a defined stereochemistry at a chiral center are intended to include any or all possible stereoisomer variations at the undefined stereocenter unless otherwise indicated. The depiction or naming of a particular stereoisomer means the indicated stereocenter has the designated stereochemistry with the understanding that minor amounts of other stereoisomers may also be present unless otherwise indicated, provided that the utility of the depicted or named compound is not eliminated by the presence of another stereoisomer.

[30] If the compound described herein is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the compound is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds (see, e.g., Berge et al., Pharmaceutical Salts, *J. Pharmaceutical Sciences*, January 1977, 66(1), 1-19). Those skilled in the art will recognize various synthetic methodologies that may be used to prepare pharmaceutically acceptable addition salts.

[31] The term "Ubiquitin Ligase" refers to a family of proteins that facilitate the transfer of ubiquitin to a specific substrate protein, targeting the substrate protein for degradation.

[32] Unless clearly indicated otherwise, "an individual" as used herein intends a mammal, including but not limited to a primate, human, bovine, horse, feline, canine, or rodent. In one variation, the individual is a human.

[33] As used herein, "treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. For purposes of this disclosure, beneficial or desired results include, but are not limited to, one or more of the following: decreasing one more symptoms resulting from the disease, diminishing the extent of the disease, stabilizing the disease (*e.g.*, preventing or delaying the worsening of the disease), preventing or delaying the spread of the disease, delaying the occurrence or recurrence of the disease, delay or slowing the progression of the disease, ameliorating the disease state, providing a remission (whether partial or total) of the disease, decreasing the dose of one or more other medications required to treat the disease, enhancing effect of another medication, delaying the progression of the disease, increasing

the quality of life, and/or prolonging survival. The methods of the present disclosure contemplate any one or more of these aspects of treatment.

[34] As used herein, the term "effective amount" intends such amount of a compound described herein which should be effective in a given therapeutic form. As is understood in the art, an effective amount may be in one or more doses, *i.e.*, a single dose or multiple doses may be required to achieve the desired treatment endpoint. An effective amount may be considered in the context of administering one or more therapeutic agents (*e.g.*, a compound, or pharmaceutically acceptable salt thereof), and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved. Suitable doses of any of the co-administered compounds may optionally be lowered due to the combined action (*e.g.*, additive or synergistic effects) of the compounds.

[35] A "therapeutically effective amount" refers to an amount sufficient to produce a desired therapeutic outcome.

[36] As used herein, "unit dosage form" refers to physically discrete units, suitable as unit dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Unit dosage forms may contain a single or a combination therapy.

[37] As used herein, by "pharmaceutically acceptable" or "pharmacologically acceptable" is meant a material that is not biologically or otherwise undesirable, *e.g.*, the material may be incorporated into a pharmaceutical composition administered to a patient without causing any significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. Pharmaceutically acceptable carriers or excipients have preferably met the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration.

[38] "Pharmaceutically acceptable salts" are those salts which retain at least some of the biological activity of the free (non-salt) compound and which can be administered as drugs or pharmaceuticals to an individual. Such salts, for example, include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, oxalic acid, propionic acid, succinic acid, maleic acid, tartaric acid and the like; (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. Pharmaceutically acceptable salts can be prepared *in situ* in the manufacturing process, or by separately reacting a purified compound of the present disclosure in its free

acid or base form with a suitable organic or inorganic base or acid, respectively, and isolating the salt thus formed during subsequent purification.

[39] The term "excipient" as used herein means an inert or inactive substance that may be used in the production of a drug or pharmaceutical, such as a tablet containing a compound of the present disclosure as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Binders include, *e.g.*, carbomers, povidone, xanthan gum, etc.; coatings include, *e.g.*, cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, enteric coatings, etc.; compression/encapsulation aids include, *e.g.*, calcium carbonate, dextrose, fructose dc (dc = "directly compressible"), honey dc, lactose (anhydrate or monohydrate; optionally in combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc.; disintegrants include, *e.g.*, croscarmellose sodium, gellan gum, sodium starch glycolate, etc.; creams or lotions include, *e.g.*, maltodextrin, carrageenans, etc.; lubricants include, *e.g.*, magnesium stearate, stearic acid, sodium stearyl fumarate, etc.; materials for chewable tablets include, *e.g.*, dextrose, fructose dc, lactose (monohydrate, optionally in combination with aspartame or cellulose), etc.; suspending/gelling agents include, *e.g.*, carrageenan, sodium starch glycolate, xanthan gum, etc.; sweeteners include, *e.g.*, aspartame, dextrose, fructose dc, sorbitol, sucrose dc, etc.; and wet granulation agents include, *e.g.*, calcium carbonate, maltodextrin, microcrystalline cellulose, etc.

Compounds

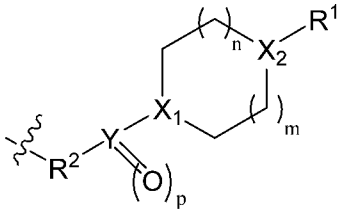
[40] In one aspect, provided is a compound of formula (I):

PTM-L-ULM (I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

the PTM is a moiety that binds a target protein;

the ULM is an E3 ubiquitin ligase CDC20 (Cell Division Cycle 20) binding moiety of formula (A):



(A)

wherein

R^1 is C_1-C_6 alkyl, C_{6-10} aryl or 5- to 6-membered heteroaryl, each of which is optionally substituted with C_1-C_6 alkyl, halogen, -OH, oxo, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), -NO_2, or -CN;

R^2 is a bond, C_1-C_6 alkylene, C_{3-8} cycloalkylene, 3- to 10- membered heterocyclylene, C_{6-10} arylene, or 5- to 10- membered heteroarylene;

X_1 and X_2 are independently N or CH;

Y is C or S;

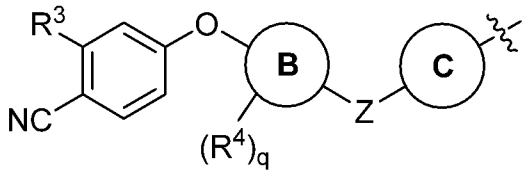
m and n are independently 0 1, or 2; and

p is 0, 1 or 2;

and

L is a bond or a chemical linker covalently connecting the PTM and the ULM.

[41] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the PTM is of formula (B):

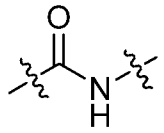
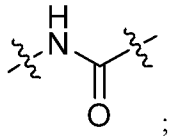


(B)

wherein

Ring B is C_3-C_8 cycloalkyl;

Ring C is C_{6-10} aryl or 5- to 10- membered heteroaryl;

Z is  or  ;

R^3 is halogen, or methoxy;

R^4 is C_1-C_6 alkyl; and

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

[42] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L is *—A^{L1}-A^{L2}-A^{L3}-A^{L4}—**, wherein

* represents the point of attachment to the PTM,

** represents the point of attachment to the ULM,

A^{L1} and A^{L4} are each independently a bond, -(C=O)-, -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, or C_{3-8} cycloalkylene;

wherein the -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, and C_{3-8} cycloalkylene of A^{L1} and A^{L4}

are each independently and optionally substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen; and

A^{L2} and A^{L3} are each independently a bond, $-(CH_2)_r-$, $-(OCH_2CH_2)_s-$, $-(CH_2CH_2O)_s-$, $-(NHCH_2CH_2)_s-$, $-(CH_2CH_2NH)_s-$, wherein r and s are each an integer between 0 and 10;

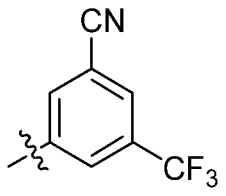
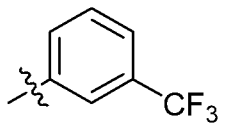
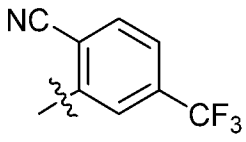
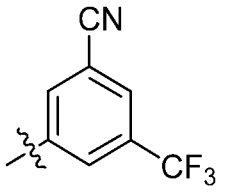
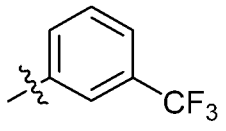
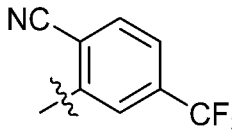
wherein the $-(CH_2)_r-$, $-(OCH_2CH_2)_s-$, $-(CH_2CH_2O)_s-$, $-(NHCH_2CH_2)_s-$, and $-(CH_2CH_2NH)_s-$ of A^{L2} and A^{L3} are each independently and optionally substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen.

[43] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the ULM is an E3 ubiquitin ligase CDC20 (Cell Division Cycle 20) binding moiety of formula (A), wherein R^1 is C_1-C_6 alkyl, C_{6-10} aryl or 5- to 6-membered heteroaryl, each of which is optionally substituted with C_1-C_6 alkyl, halogen, -OH, oxo, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), $-NO_2$, or -CN. In some embodiments, R^1 is C_1-C_6 alkyl, C_{6-10} aryl or 5- to 6-membered heteroaryl, each of which is optionally substituted with with fluoro, chloro, -OH, -COOH, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, $-NO_2$, or -CN. In some embodiments, R^1 is C_1-C_6 alkyl, C_{6-10} aryl or 5- to 6-membered heteroaryl, each of which is optionally substituted with with -CN or $-CF_3$.

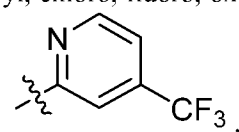
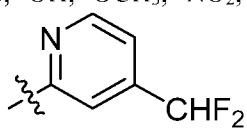
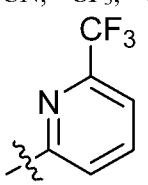
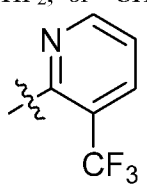
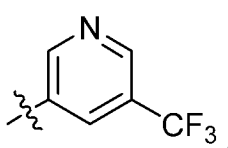
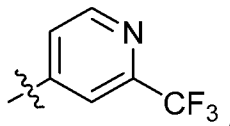
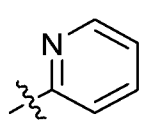
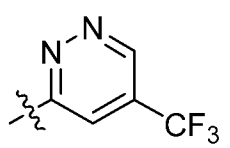
[44] In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with halogen, -OH, -COOH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), $-NO_2$, or -CN. In some embodiments, R^1 is unsubstituted C_1-C_6 alkyl. In some embodiments, R^1 is unsubstituted methyl, ethyl, or propyl. In some embodiments, R^1 is unsubstituted methyl.

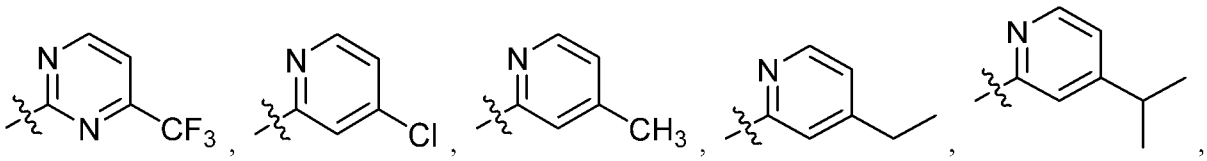
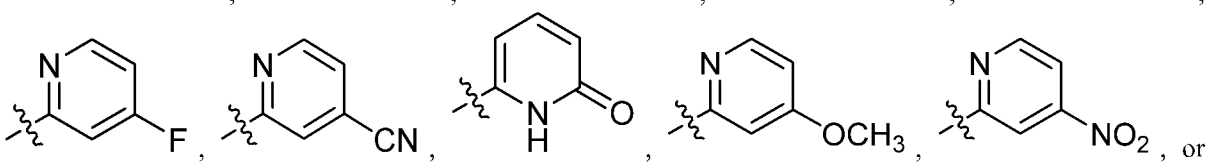
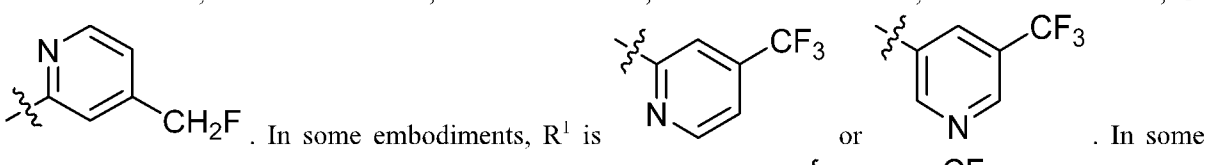
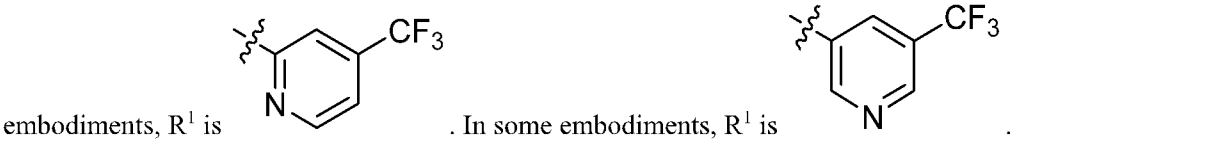
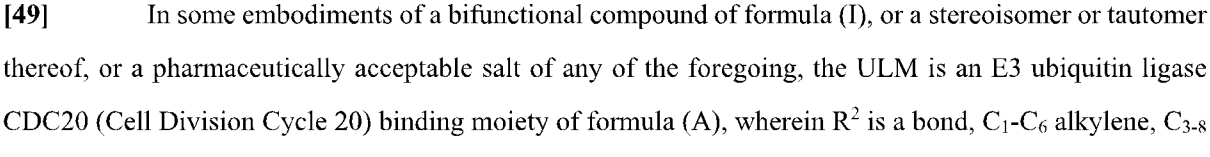
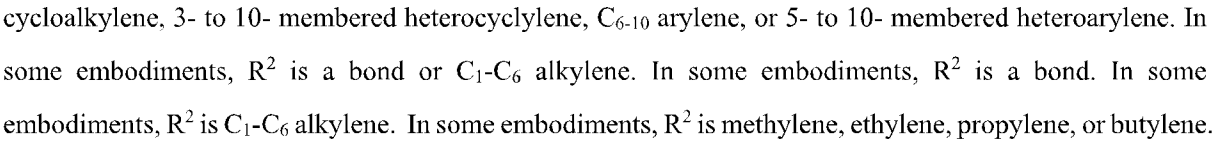
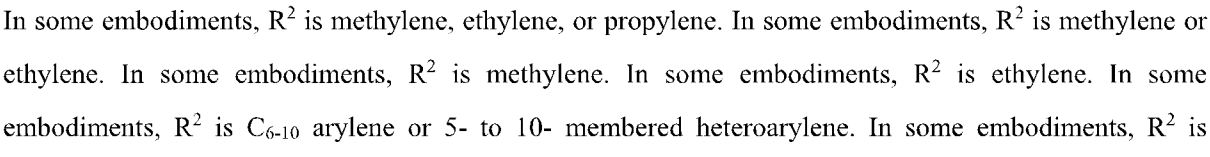
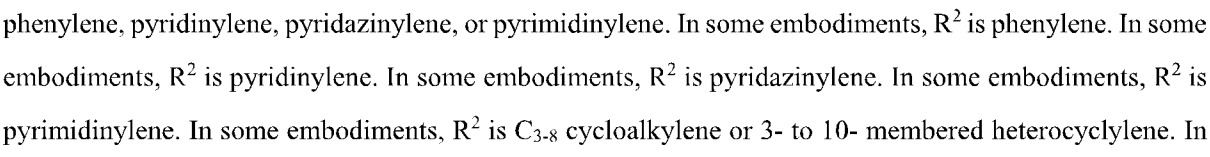
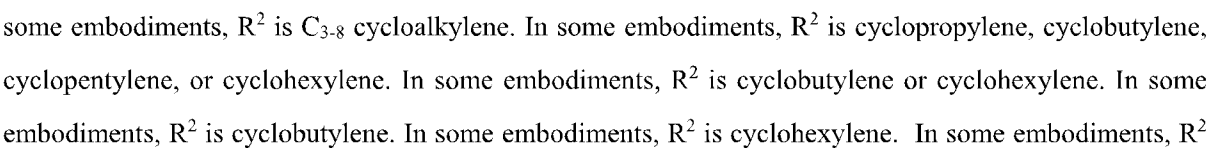
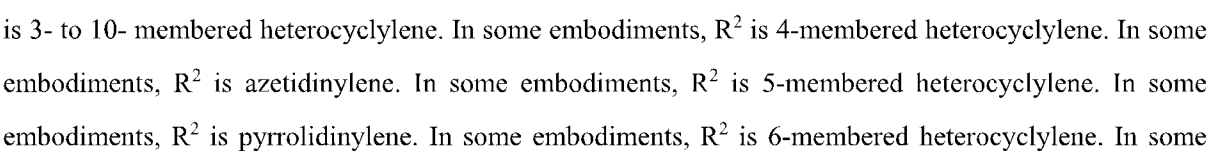
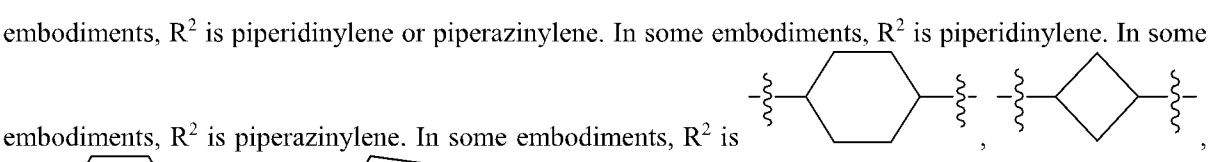
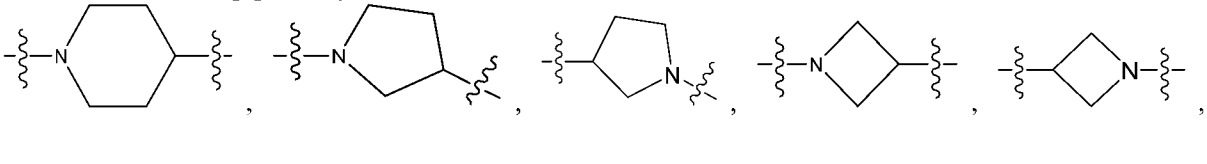
[45] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the ULM is an E3 ubiquitin ligase CDC20 (Cell Division Cycle 20) binding moiety of formula (A), wherein R^1 is C_{6-10} aryl or 5- to 6-membered heteroaryl, each of which is optionally substituted with C_1-C_6 alkyl, halogen, -OH, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), $-NO_2$, or -CN.

[46] In some embodiments, R^1 is C_{6-10} aryl optionally substituted with C_1-C_6 alkyl, halogen, -OH, oxo, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), $-NO_2$, or -CN. In some embodiments, R^1 is naphthalene optionally substituted with C_1-C_6 alkyl, halogen, -OH, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), $-NO_2$, or -CN. In some embodiments, R^1 is phenyl optionally substituted with C_1-C_6 alkyl, halogen, -OH, oxo, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), $-NO_2$, or -CN. In some embodiments, R^1 is phenyl optionally substituted with -CN or C_1-C_6 haloalkyl. In some embodiments, R^1 is phenyl substituted with -CN and C_1-C_6 haloalkyl. In some embodiments, R^1 is phenyl substituted with -CN and $-CF_3$. In some embodiments, R^1 is phenyl substituted with -CN. In some

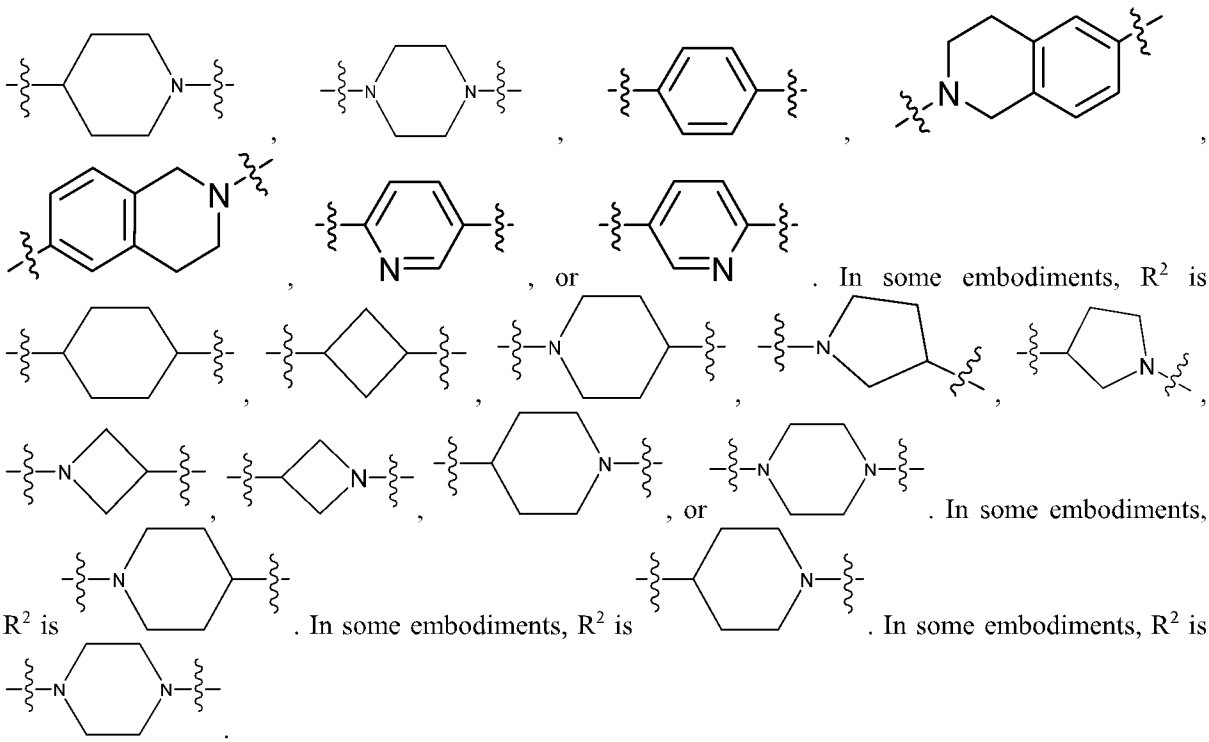
embodiments, R^1 is , , or . In some embodiments, R^1 is . In some embodiments, R^1 is . In some embodiments, R^1 is .

[47] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the ULM is an E3 ubiquitin ligase CDC20 (Cell Division Cycle 20) binding moiety of formula (A), wherein R^1 is 5- to 6-membered heteroaryl optionally substituted with C_1-C_6 alkyl, halogen, -OH, oxo, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), -NO_2, or -CN. In some embodiments, R^1 is 5- to 6-membered heteroaryl optionally substituted with C_1-C_6 alkyl or C_1-C_6 haloalkyl. In some embodiments, R^1 is 5- to 6-membered heteroaryl optionally substituted with -CH_3 or -CF_3.

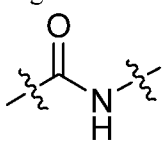
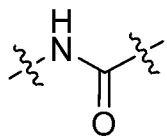
[48] In some embodiments, R^1 is 5-membered heteroaryl optionally substituted with C_1-C_6 alkyl, halogen, -OH, oxo, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), -NO_2, or -CN. In some embodiments, R^1 is 6-membered heteroaryl optionally substituted with C_1-C_6 alkyl, halogen, -OH, oxo, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), -NO_2, or -CN. In some embodiments, R^1 is pyridinyl, pyridazinyl, or pyrimidinyl, each of which is optionally substituted with C_1-C_6 alkyl, halogen, -OH, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), -NO_2, or -CN. In some embodiments, R^1 is unsubstituted pyridyl. In some embodiments, R^1 is pyridinyl, pyridazinyl, or pyrimidinyl, each of which is optionally substituted with methyl, ethyl, propyl, chloro, fluoro, oxo, -OH,-OCH_3, -NO_2, -CN, -CF_3, -CHF_2, or -CH_2F. In some embodiments, R^1 is pyridinyl substituted with -CH_3 or -CF_3. In some embodiments, R^1 is pyridinyl optionally substituted with methyl, ethyl, propyl, chloro, fluoro, oxo, -OH, -OCH_3, -NO_2, -CN, -CF_3, -CHF_2, or -CH_2F. In some embodiments, R^1 is , , , , , , , ,

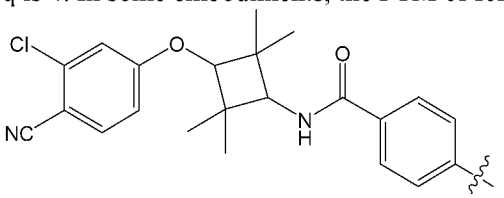
[49] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the ULM is an E3 ubiquitin ligase CDC20 (Cell Division Cycle 20) binding moiety of formula (A), wherein R^2 is a bond, C_1-C_6 alkylene, C_{3-8} cycloalkylene, 3- to 10- membered heterocyclylene, C_{6-10} arylene, or 5- to 10- membered heteroarylene. In some embodiments, R^2 is a bond or C_1-C_6 alkylene. In some embodiments, R^2 is a bond. In some embodiments, R^2 is C_1-C_6 alkylene. In some embodiments, R^2 is methylene, ethylene, propylene, or butylene. In some embodiments, R^2 is methylene, ethylene, or propylene. In some embodiments, R^2 is methylene or ethylene. In some embodiments, R^2 is methylene. In some embodiments, R^2 is ethylene. In some embodiments, R^2 is C_{6-10} arylene or 5- to 10- membered heteroarylene. In some embodiments, R^2 is phenylene, pyridinylene, pyridazinylene, or pyrimidinylene. In some embodiments, R^2 is phenylene. In some embodiments, R^2 is pyridinylene. In some embodiments, R^2 is pyridazinylene. In some embodiments, R^2 is pyrimidinylene. In some embodiments, R^2 is C_{3-8} cycloalkylene or 3- to 10- membered heterocyclylene. In some embodiments, R^2 is C_{3-8} cycloalkylene. In some embodiments, R^2 is cyclopropylene, cyclobutylene, cyclopentylene, or cyclohexylene. In some embodiments, R^2 is cyclobutylene or cyclohexylene. In some embodiments, R^2 is cyclobutylene. In some embodiments, R^2 is cyclohexylene. In some embodiments, R^2 is 3- to 10- membered heterocyclylene. In some embodiments, R^2 is 4-membered heterocyclylene. In some embodiments, R^2 is azetidinylene. In some embodiments, R^2 is 5-membered heterocyclylene. In some embodiments, R^2 is pyrrolidinylene. In some embodiments, R^2 is 6-membered heterocyclylene. In some embodiments, R^2 is piperidinylene or piperazinylene. In some embodiments, R^2 is piperidinylene. In some embodiments, R^2 is piperazinylene. In some embodiments, R^2 is



[50] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the ULM is an E3 ubiquitin ligase CDC20 (Cell Division Cycle 20) binding moiety of formula (A). In some embodiments, X_1 and X_2 are independently N or CH. In some embodiments, X_1 is N and X_2 is CH. In some embodiments, X_1 is CH and X_2 is N. In some embodiments, X_1 and X_2 are both CH. In some embodiments, X_1 and X_2 are both N. In some embodiments, Y is C. In some embodiments, Y is S. In some embodiments, ma and n are each 1. In some embodiments, n is 1 and m is 2. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2.

[51] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the PTM is of formula (B). In some embodiments of formula (B), Ring B is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, Ring B is cyclopropyl. In some embodiments, Ring B is cyclobutyl. In some embodiments, Ring B is cyclopentyl. In some embodiments, Ring B is cyclohexyl. In some embodiments, Ring C is phenyl. In some embodiments, Ring C is 5- to 10-membered heteroaryl. In some embodiments, Ring C is 5- to 6-membered heteroaryl. In some embodiments, Ring C is 5-membered heteroaryl. In some embodiments, Ring C is pyrazolyl. In some embodiments, Ring C is 6-membered heteroaryl. In some embodiments, Ring C is pyridazinyl. In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, R^3 is chloro. In some embodiments, R^3 is fluoro. In some embodiments, R^3 is bromo. In some

embodiments, R^3 is methoxy. In some embodiments, each R^4 is methyl. In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2. In some embodiments, q is 3. In some embodiments, q is 4. In some embodiments, the PTM of formula (B) is selected from the group consisting of: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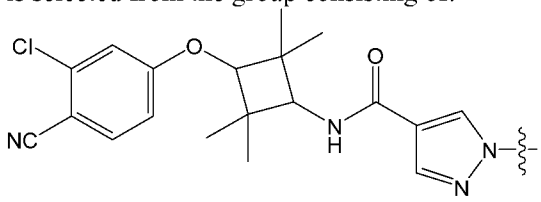
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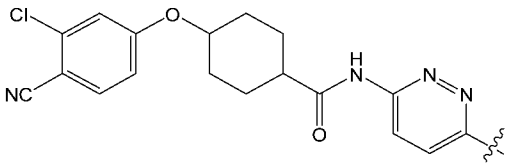
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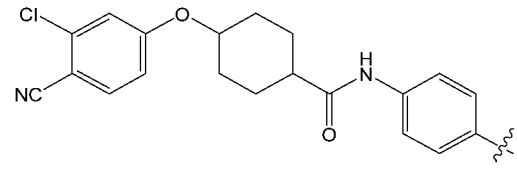
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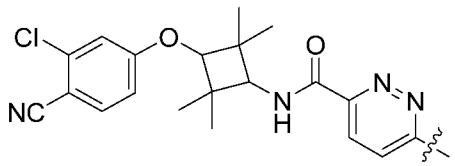
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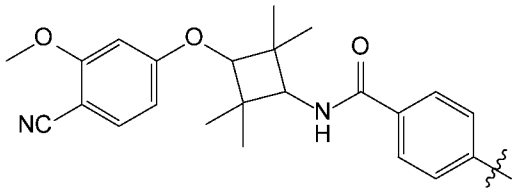
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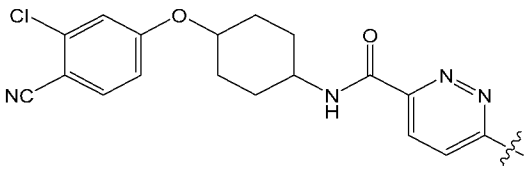
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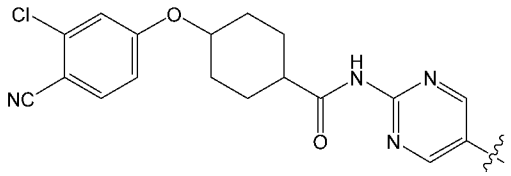
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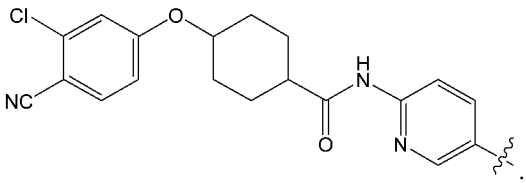
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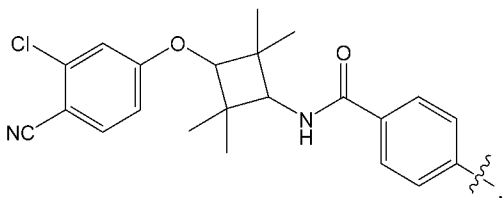
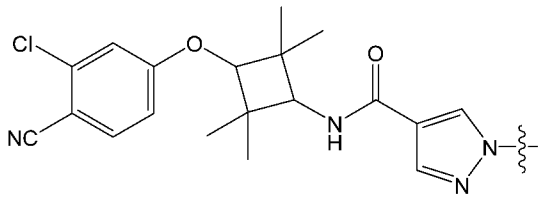
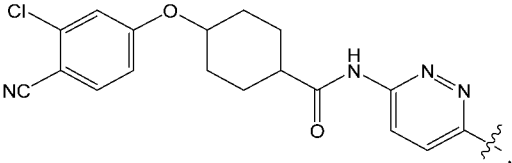
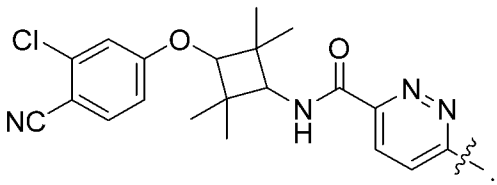
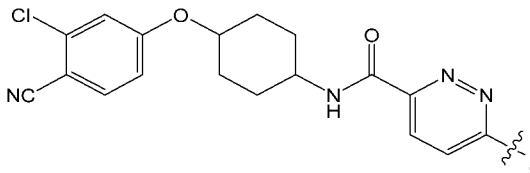
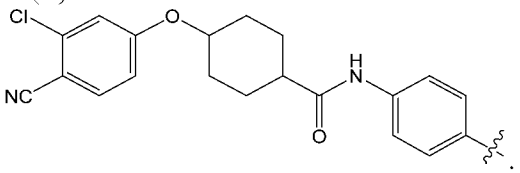
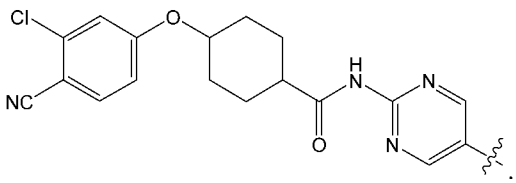
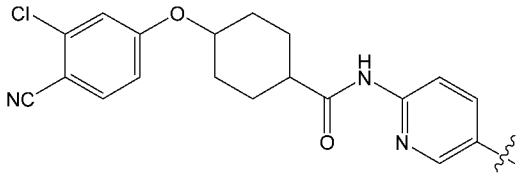
In some embodiments, the PTM of formula (B) is .

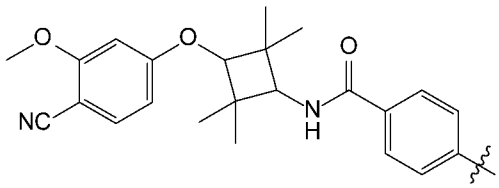
In some embodiments, the PTM of formula (B) is . In some embodiments, the PTM of formula (B) is .

In some embodiments, the PTM of formula (B) is .

In some embodiments, the PTM of formula (B) is . In some embodiments, the PTM of formula (B) is .

In some embodiments, the PTM of formula (B) is .

In some embodiments, the PTM of formula (B) is .

In some embodiments, the PTM of formula (B) is .

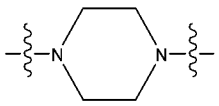
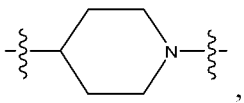
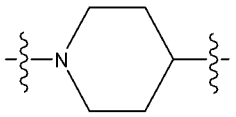
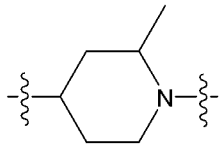
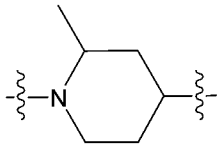
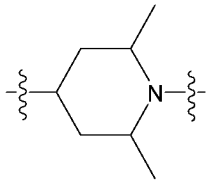
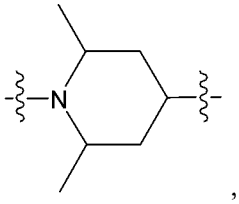
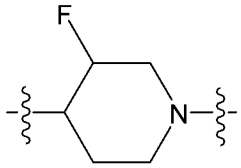
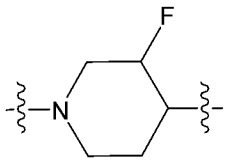
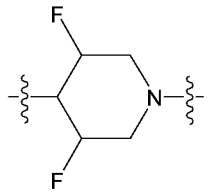
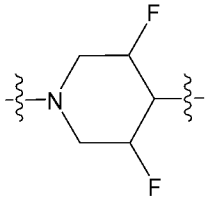
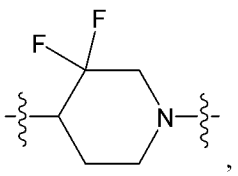
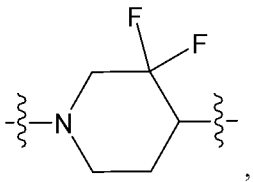
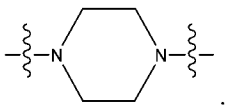
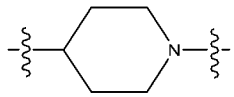
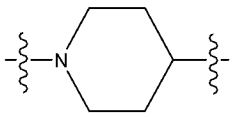
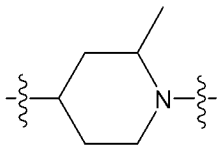
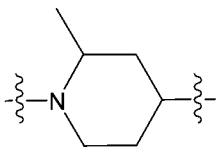
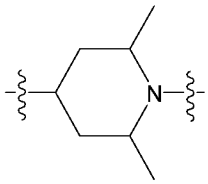
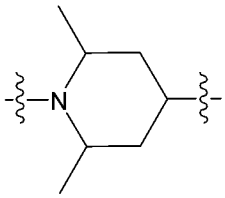
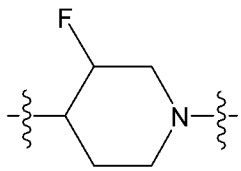
[52] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L is *—A^{L1}-A^{L2}-A^{L3}-A^{L4}—**, wherein * represents the point of attachment to the PTM, and ** represents the point of attachment to the ULM. In some embodiments, A^{L1} and A^{L4} are each independently a bond, -(C=O)-, -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene-, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10-membered heterocyclylene, -C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, or C_{3-8} cycloalkylene. In some embodiments, A^{L1} and A^{L4} are each independently a bond, -(C=O)-, -(C=O)NH-, -(C=O)NH-CH_2-, -(C=O)NH-CH_2CH_2-, -(C=O)NH-$CH_2CH_2CH_2$-, -CH_2-NH(C=O)-, -CH_2CH_2-NH(C=O)-, -$CH_2CH_2CH_2$-NH(C=O)-, -NH(C=O)-, -NH-CH_2-, -NH-CH_2CH_2-, -NH-$CH_2CH_2CH_2$-, -CH_2-NH-, -CH_2CH_2-NH-, -$CH_2CH_2CH_2$-NH-, azetidinylene, pyrrolidinylene, piperidinylene, piperazinylene, cyclopropylene-CH_2-, cyclobutylene-CH_2-, cyclopentylene-CH_2-, cyclohexylene-CH_2-, -CH_2-cyclopropylene-, -CH_2-cyclobutylene-, -CH_2-cyclopentylene-, -CH_2-cyclohexylene-, azetidinylene-CH_2-, pyrrolidinylene-CH_2-, piperidinylene-CH_2-, piperazinylene-CH_2-, -CH_2-azetidinylene,

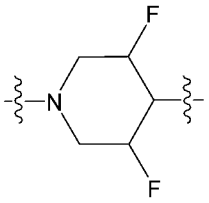
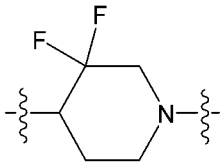
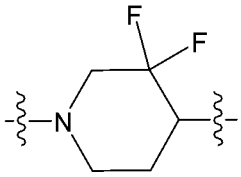
-CH_2-pyrrolidinylene, -CH_2-piperidinylene, -CH_2-piperazinylene, cyclobutylene, cyclopentylene, or cyclohexylene. In some embodiments, A^{L1} and A^{L4} are each independently a bond, -(C=O)NH-, -NH(C=O)-,

-(C=O)NH-CH_2-, -CH_2-NH(C=O)-, -(C=O)NH-CH_2CH_2-, -CH_2CH_2-NH(C=O)-, -(C=O)NH-$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2$-NH(C=O)-, piperazinylene-CH_2-, -CH_2-piperazinylene, piperazinylene, piperidinylene, azetidinylene, pyrrolidinylene, -NH-CH_2-, or -CH_2-NH-.

[53] In some embodiments, the -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, and C_{3-8} cycloalkylene of A^{L1} and A^{L4} are each independently and optionally substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen. In some embodiments, the -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, and C_{3-8} cycloalkylene of A^{L1} and A^{L4} are each independently substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen. In some embodiments, the -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, and C_{3-8} cycloalkylene of A^{L1} and A^{L4} are each independently substituted with 1-5 independently selected substituents selected from methyl and fluoro. In some embodiments, the -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, and C_{3-8} cycloalkylene of A^{L1} and A^{L4} are each independently substituted with 1-5 selected methyl substitutents. In some embodiments, the -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, and C_{3-8} cycloalkylene of A^{L1} and A^{L4} are each independently substituted with 1-5 fluoro substituents.

[54] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L is *—A^{L1}-A^{L2}-A^{L3}-A^{L4}—**, wherein * represents the point of attachment to the PTM, and ** represents the point of attachment to the ULM. In some embodiments, A^{L1} is a bond. In some embodiments, A^{L1} is -(C=O)NH-. In some embodiments, A^{L1} is -NH(C=O)-. In some embodiments, A^{L1} is -(C=O)NH-CH_2-. In some embodiments, A^{L1} is -CH_2-NH(C=O)-. In some embodiments, A^{L1} is -(C=O)NH-CH_2CH_2-. In some embodiments, A^{L1} is -CH_2CH_2-NH(C=O)-. In some embodiments, A^{L1} is -(C=O)NH-$CH_2CH_2CH_2$-. In some embodiments, A^{L1} is -$CH_2CH_2CH_2$-

NH(C=O)-. In some embodiments, A^{L1} is piperazinylene-CH_2-. In some embodiments, A^{L1} is -CH_2-piperazinylene. In some embodiments, A^{L1} is piperazinylene. In some embodiments, A^{L1} is piperidinylene. In some embodiments, A^{L1} is azetidinylene. In some embodiments, A^{L1} is pyrrolidinylene. In some embodiments, A^{L1} is -NH-CH_2-. In some embodiments, A^{L1} is -CH_2-NH-. In some embodiments, A^{L1} is , , , , , , , , , , , , , -NH(C=O)-, or -(C=O)NH-. In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is


. In some embodiments, A^{L1} is 
. In some embodiments, A^{L1} is 
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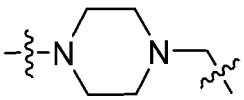
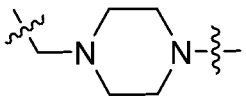
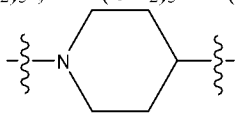
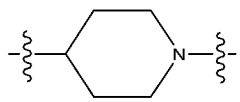
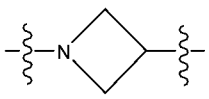
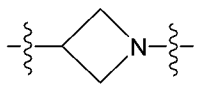
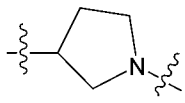
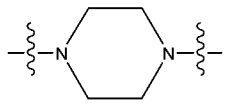
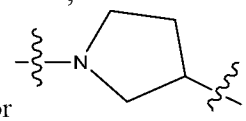
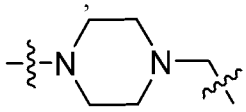
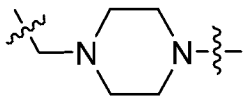
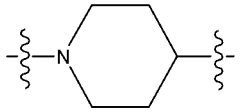
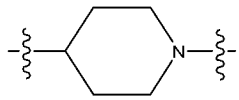
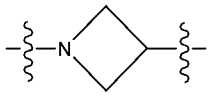
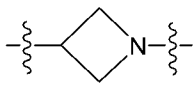
[55] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L is *—A^{L1}-A^{L2}-A^{L3}-A^{L4}—**, wherein * represents the point of attachment to the PTM, and ** represents the point of attachment to the ULM. In some embodiments, A^{L4} is a bond. In some embodiments, A^{L4} is -(C=O)NH-. In some embodiments, A^{L4} is -NH(C=O)-. In some embodiments, A^{L4} is -(C=O)NH-CH_2-. In some embodiments, A^{L4} is -CH_2-NH(C=O)-. In some embodiments, A^{L4} is -(C=O)NH-CH_2CH_2-. In some embodiments, A^{L4} is -CH_2CH_2-NH(C=O)-. In some embodiments, A^{L4} is -(C=O)NH-$CH_2CH_2CH_2$-. In some embodiments, A^{L4} is -$CH_2CH_2CH_2$-NH(C=O)-. In some embodiments, A^{L4} is piperazinylene-CH_2-. In some embodiments, A^{L4} is -CH_2-piperazinylene. In some embodiments, A^{L4} is piperazinylene. In some embodiments, A^{L4} is piperidinylene. In some embodiments, A^{L4} is azetidinylene. In some embodiments, A^{L4} is pyrrolidinylene. In some embodiments, A^{L4} is -NH-CH_2-. In some embodiments, A^{L4} is -NH-$CH_2CH_2CH_2$-. In some embodiments, A^{L4} is -CH_2-NH-. In some embodiments, A^{L4} is -$CH_2CH_2CH_2$-NH-. In some embodiments, A^{L4} is -(C=O)NHCH_2-, -CH_2-NH(C=O)-, -(C=O)NH$(CH_2)_3$-, -$(CH_2)_3$-NH(C=O)-, -NH$(CH_2)_3$-, -$(CH_2)_3$-NH-, 
, 
, 
, 
, 
, 
, 
, 
, or 
. In some embodiments, A^{L4} is 
. In some embodiments, A^{L4} is 
. In some embodiments, A^{L4} is 
. In some embodiments, A^{L4} is 
. In some embodiments, A^{L4} is 
. In some embodiments, A^{L4} is 
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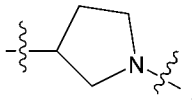
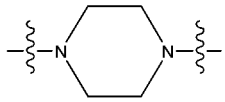
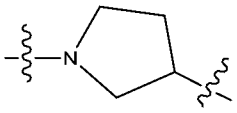
embodiments, A^{L4} is . In some embodiments, A^{L4} is . In some embodiments, A^{L4} is .

[56] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L is *—A^{L1}-A^{L2}-A^{L3}-A^{L4}—**, wherein * represents the point of attachment to the PTM, and ** represents the point of attachment to the ULM. In some embodiments, the -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, and C_{3-8} cycloalkylene of A^{L1} and A^{L4} are each independently and optionally substituted with 1-5 independently selected substituents selected from:

a) C_1-C_6 alkyl and halogen;

b) methyl and halogen;

c) methyl and fluoro;

d) C_1-C_6 alkyl and fluoro;

e) methyl; or

f) fluoro.

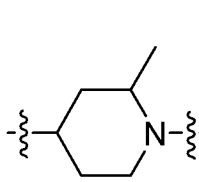
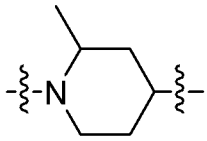
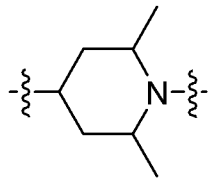
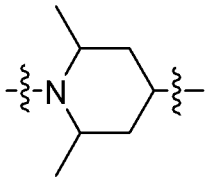
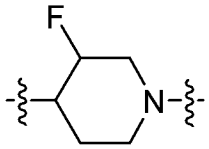
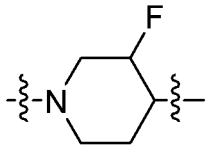
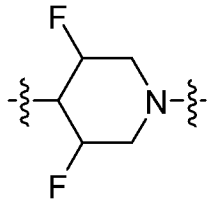
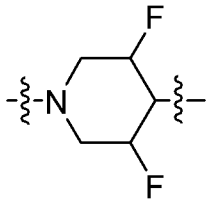
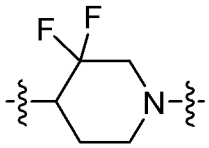
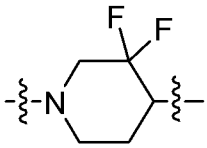
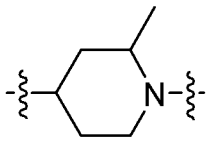
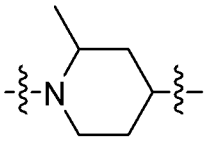
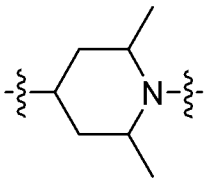
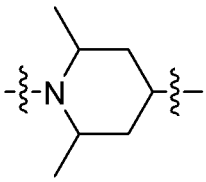
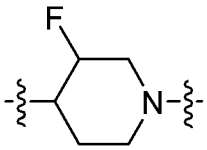
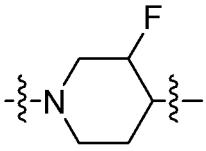
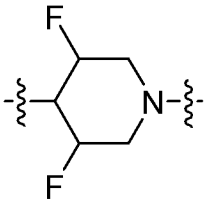
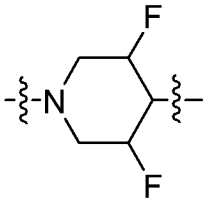
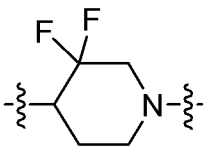
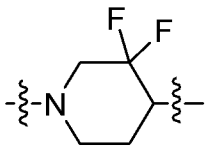
[57] In some embodiments, the -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, and C_{3-8} cycloalkylene of A^{L1} are unsubstituted. In other embodiments, the -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, and C_{3-8} cycloalkylene of A^{L1} are substituted with:

a) 1 methyl substituent;

b) 2 methyl substituents;

c) 1 fluoro substituent; or

d) 2 fluoro substituents.

[58] In some embodiments, A^{L1} is , , , , , , , , , or . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is . In some embodiments, A^{L1} is .

[59] In some embodiments, the -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, and C_{3-8} cycloalkylene of A^{L4} are unsubstituted. In other embodiments, the -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered

heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, and C_{3-8} cycloalkylene of A^{L4} are substituted with:

a) 1 methyl substituent;

b) 2 methyl substituents;

c) 1 fluoro substituent; or

d) 2 fluoro substituents.

[60] In some embodiments of a bifunctional compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L is *—A^{L1}-A^{L2}-A^{L3}-A^{L4}—**, wherein * represents the point of attachment to the PTM, and ** represents the point of attachment to the ULM. In some embodiments, A^{L2} and A^{L3} are each independently a bond, -$(CH_2)_r$-, -$(OCH_2CH_2)_s$-, -$(CH_2CH_2O)_s$-, -$(NHCH_2CH_2)_s$-, -$(CH_2CH_2NH)_s$-, wherein r and s are each an integer between 0 and 10. In some embodiments, A^{L2} is a bond. In some embodiments, A^{L2} is -$(CH_2)_r$-. In some embodiments, A^{L2} is -$(OCH_2CH_2)_s$-. In some embodiments, A^{L2} is -$(CH_2CH_2O)_s$-. In some embodiments, A^{L2} is -$(NHCH_2CH_2)_s$-. In some embodiments, A^{L2} is -$(CH_2CH_2NH)_s$-. In some embodiments, A^{L3} is a bond. In some embodiments, A^{L3} is -$(CH_2)_r$-. In some embodiments, A^{L3} is -$(OCH_2CH_2)_s$-. In some embodiments, A^{L3} is -$(CH_2CH_2O)_s$-. In some embodiments, A^{L3} is -$(NHCH_2CH_2)_s$-. In some embodiments, A^{L3} is -$(CH_2CH_2NH)_s$-. In some embodiments, A^{L2} is a bond and A^{L3} is a bond. In some embodiments, A^{L2} is a bond and A^{L3} is -$(CH_2)_r$-. In some embodiments, A^{L2} is a bond and A^{L3} is -$(OCH_2CH_2)_s$-. In some embodiments, A^{L2} is a bond and A^{L3} is -$(CH_2CH_2O)_s$-. In some embodiments, A^{L2} is -$(CH_2)_r$- and A^{L3} is a bond. In some embodiments, A^{L2} is -$(CH_2)_r$- and A^{L3} is -$(CH_2)_r$-. In some embodiments, A^{L2} is -$(NHCH_2CH_2)_s$- and A^{L3} is -$(CH_2)_r$-. In some embodiments, A^{L2} is -$(CH_2CH_2NH)_s$- and A^{L3} is -$(CH_2)_r$-. In some embodiments, A^{L2} is -$(CH_2)_r$- and A^{L3} is -$(OCH_2CH_2)_s$-. In some embodiments, A^{L2} is -$(CH_2)_r$- and A^{L3} is -$(CH_2CH_2O)_s$-. In some embodiments, A^{L2} is -$(OCH_2CH_2)_s$- and A^{L3} is a bond. In some embodiments, A^{L2} is -$(OCH_2CH_2)_s$- and A^{L3} is -$(CH_2)_r$-. In some embodiments, A^{L2} is -$(OCH_2CH_2)_s$- and A^{L3} is -$(OCH_2CH_2)_s$-. In some embodiments, A^{L2} is -$(OCH_2CH_2)_s$- and A^{L3} is -$(CH_2CH_2O)_s$-. In some embodiments, A^{L2} is -$(CH_2CH_2O)_s$- and A^{L3} is a bond. In some embodiments, A^{L2} is -$(CH_2CH_2O)_s$- and A^{L3} is -$(CH_2)_r$-. In some embodiments, A^{L2} is -$(CH_2CH_2O)_s$- and A^{L3} is -$(OCH_2CH_2)_s$-. In some embodiments, A^{L2} is -$(CH_2CH_2O)_s$- and A^{L3} is -$(CH_2CH_2O)_s$-. In some embodiments, A^{L2}-A^{L3} is a bond. In some embodiments, A^{L2}-A^{L3} is -$(CH_2)_r$-. In some embodiments, A^{L2}-A^{L3} is -$(CH_2CH_2O)_s$-$(CH_2)_r$- or -$(CH_2)_r$-$(CH_2CH_2O)_s$-. In some embodiments, A^{L2}-A^{L3} is -$(CH_2CH_2O)_s$-$(CH_2)_r$-. In some embodiments, A^{L2}-A^{L3} is -$(CH_2)_r$-$(CH_2CH_2O)_s$-.

[61] In some embodiments, r is 0. In some embodiments, r is 1. In some embodiments, r is 2. In some embodiments, r is 3. In some embodiments, r is 4. In some embodiments, r is 5. In some embodiments, r is 6. In some embodiments, r is 7. In some embodiments, r is 8. In some embodiments, r is 9. In some

embodiments, r is 10. In some embodiments, s is 0. In some embodiments, s is 1. In some embodiments, s is 2. In some embodiments, s is 3. In some embodiments, s is 4. In some embodiments, s is 5. In some embodiments, s is 6. In some embodiments, s is 7. In some embodiments, s is 8. In some embodiments, s is 9. In some embodiments, s is 10.

[62] In some embodiments, the $-(CH_2)_r-$, $-(OCH_2CH_2)_s-$, $-(CH_2CH_2O)_s-$, $-(NHCH_2CH_2)_s-$, and $-(CH_2CH_2NH)_s-$ of A^{L2} and A^{L3} are each independently and optionally substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen. In some embodiments, A^{L2} is substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen. In some embodiments, A^{L3} is substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen. In some embodiments, A^{L2} is substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen, and A^{L3} is unsubstituted. In some embodiments, A^{L3} is substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen, and A^{L2} is unsubstituted.

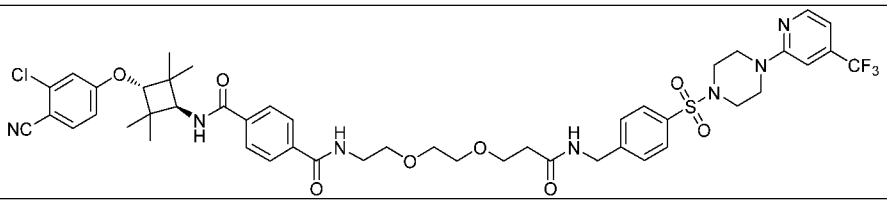
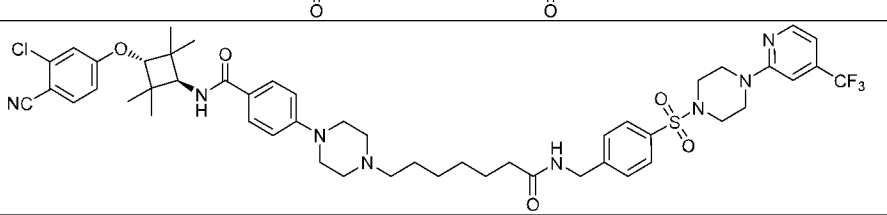
[63] In some embodiments, A^{L2} is substituted with 1-5 C_1-C_6 alkyl substituents. In some embodiments, A^{L2} is substituted with 1 C_1-C_6 alkyl substituent. In some embodiments, A^{L2} is substituted with 2 C_1-C_6 alkyl substituents. In some embodiments, A^{L2} is substituted with 3 C_1-C_6 alkyl substituents. In some embodiments, A^{L2} is substituted with 4 C_1-C_6 alkyl substituents. In some embodiments, A^{L2} is substituted with 5 C_1-C_6 alkyl substituents. In some embodiments, A^{L2} is substituted with 1 methyl substituent. In some embodiments, A^{L2} is substituted with 2 methyl substituents. In some embodiments, A^{L2} is substituted with 3 methyl substituents. In some embodiments, A^{L2} is substituted with 4 methyl substituents. In some embodiments, A^{L2} is substituted with 5 methyl substituents. In some embodiments, A^{L2} is substituted with 1-5 halogen substituents. In some embodiments, A^{L2} is substituted with 1 halogen substituent. In some embodiments, A^{L2} is substituted with 2 halogen substituents. In some embodiments, A^{L2} is substituted with 3 halogen substituents. In some embodiments, A^{L2} is substituted with 4 halogen substituents. In some embodiments, A^{L2} is substituted with 5 halogen substituents. In some embodiments, A^{L2} is substituted with 1 fluoro substituent. In some embodiments, A^{L2} is substituted with 2 fluoro substituents. In some embodiments, A^{L2} is substituted with 3 fluoro substituents. In some embodiments, A^{L2} is substituted with 4 fluoro substituents. In some embodiments, A^{L2} is substituted with 5 fluoro substituents. In some embodiments, A^{L2} is substituted with 1 chloro substituent. In some embodiments, A^{L2} is substituted with 2 chloro substituents. In some embodiments, A^{L2} is substituted with 3 chloro substituents. In some embodiments, A^{L2} is substituted with 4 chloro substituents. In some embodiments, A^{L2} is substituted with 5 chloro substituents.

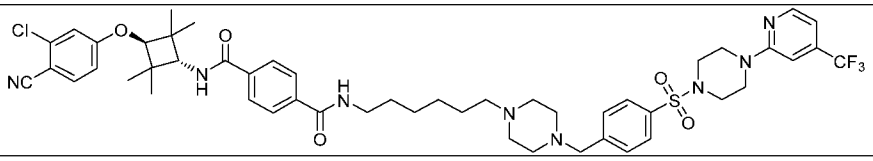
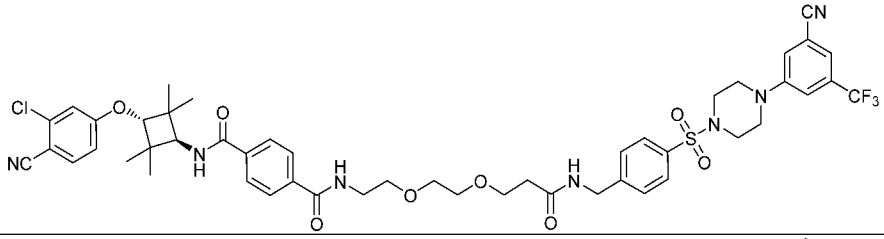
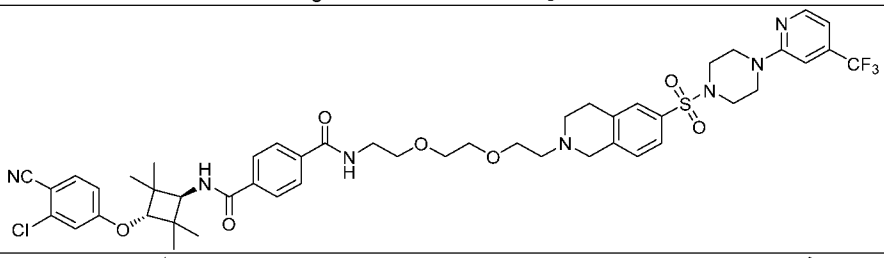
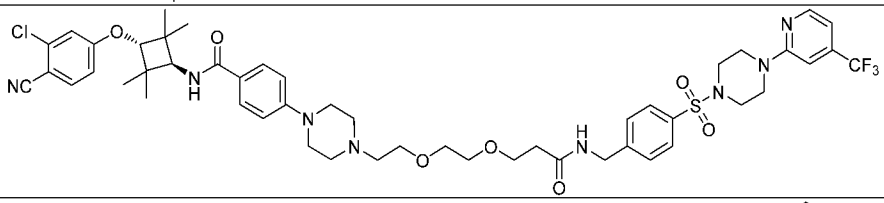
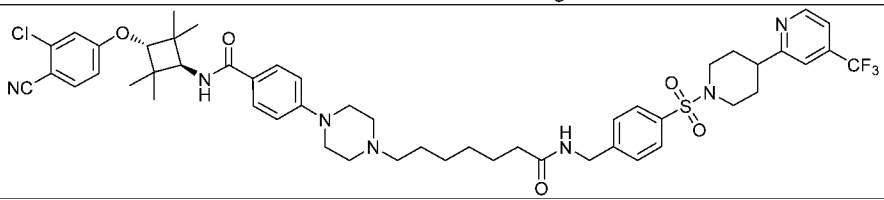
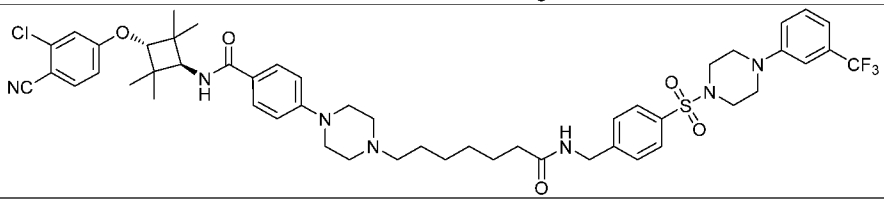
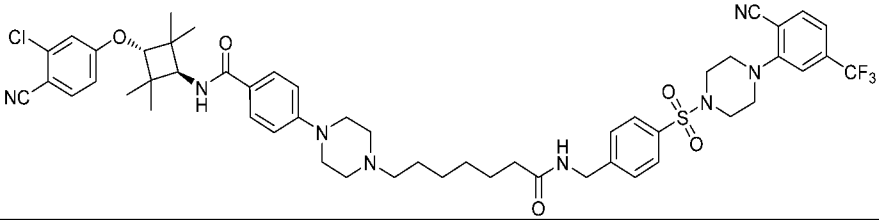
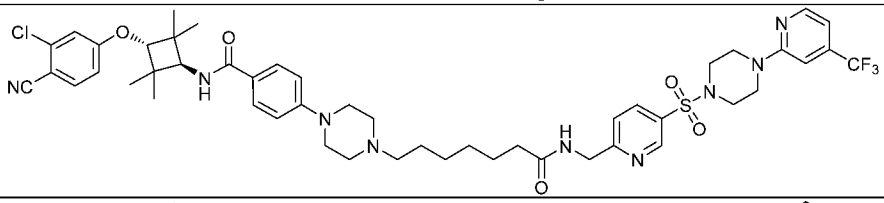
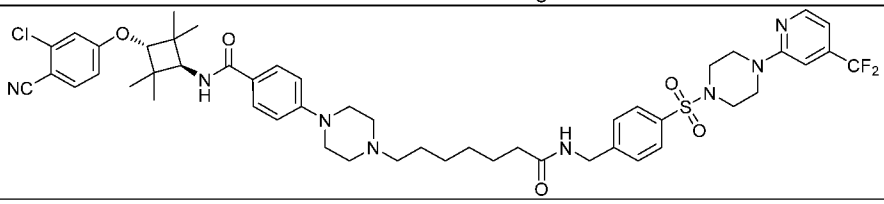
[64] In some embodiments, A^{L3} is substituted with 1-5 C_1-C_6 alkyl substituents. In some embodiments, A^{L3} is substituted with 1 C_1-C_6 alkyl substituent. In some embodiments, A^{L3} is substituted with 2 C_1-C_6 alkyl substituents. In some embodiments, A^{L3} is substituted with 3 C_1-C_6 alkyl substituents. In

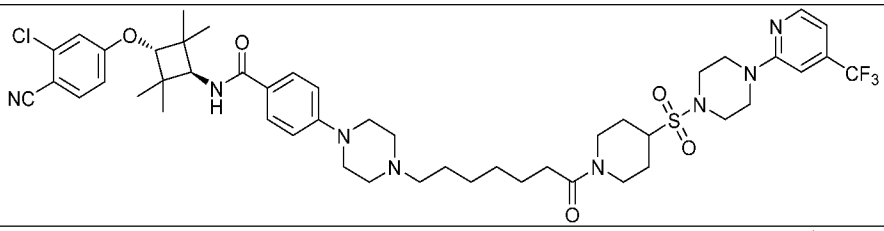
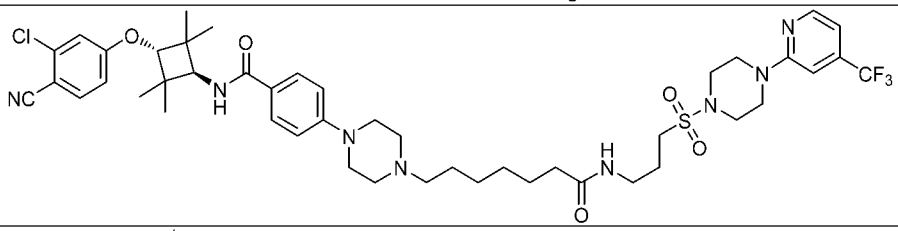
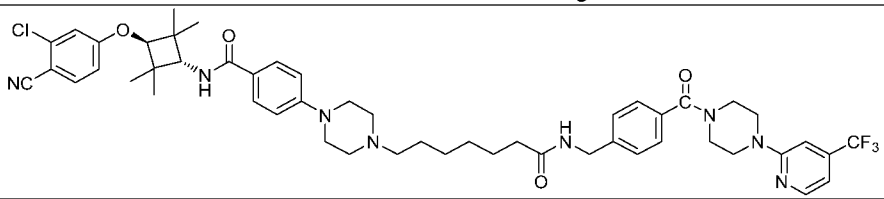
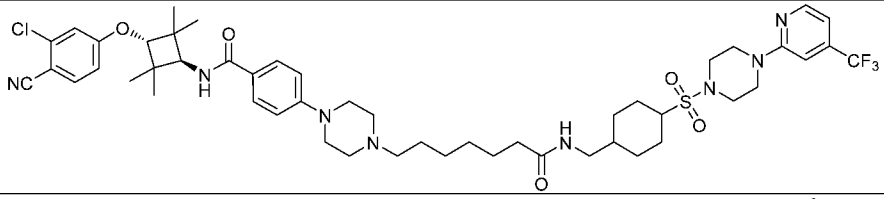
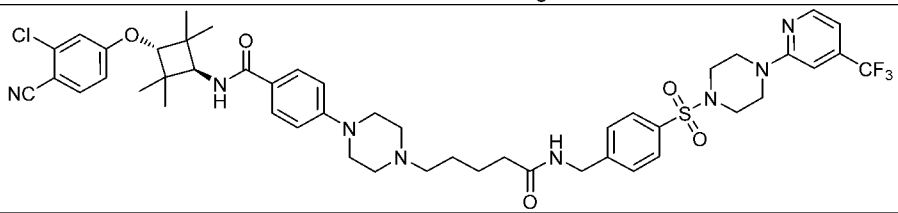
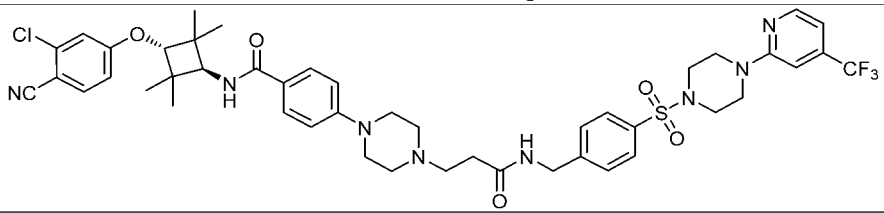
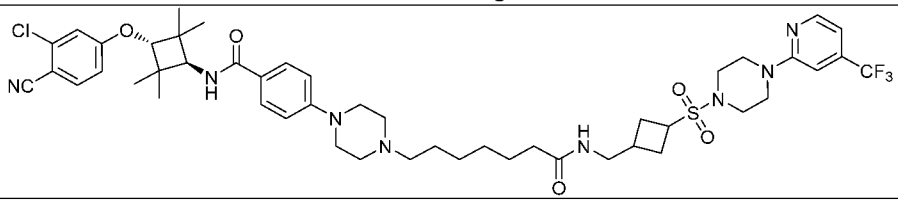
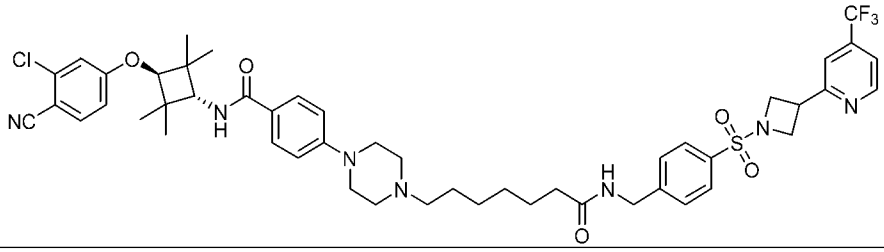
some embodiments, A^{L3} is substituted with 4 C_1-C_6 alkyl substituents. In some embodiments, A^{L3} is substituted with 5 C_1-C_6 alkyl substituents. In some embodiments, A^{L3} is substituted with 1 methyl substituent. In some embodiments, A^{L3} is substituted with 2 methyl substituents. In some embodiments, A^{L3} is substituted with 3 methyl substituents. In some embodiments, A^{L3} is substituted with 4 methyl substituents. In some embodiments, A^{L3} is substituted with 5 methyl substituents. In some embodiments, A^{L3} is substituted with 1-5 halogen substituents. In some embodiments, A^{L3} is substituted with 1 halogen substituent. In some embodiments, A^{L3} is substituted with 2 halogen substituents. In some embodiments, A^{L3} is substituted with 3 halogen substituents. In some embodiments, A^{L3} is substituted with 4 halogen substituents. In some embodiments, A^{L3} is substituted with 5 halogen substituents. In some embodiments, A^{L3} is substituted with 1 fluoro substituent. In some embodiments, A^{L3} is substituted with 2 fluoro substituents. In some embodiments, A^{L3} is substituted with 3 fluoro substituents. In some embodiments, A^{L3} is substituted with 4 fluoro substituents. In some embodiments, A^{L3} is substituted with 5 fluoro substituents. In some embodiments, A^{L3} is substituted with 1 chloro substituent. In some embodiments, A^{L3} is substituted with 2 chloro substituents. In some embodiments, A^{L3} is substituted with 3 chloro substituents. In some embodiments, A^{L3} is substituted with 4 chloro substituents. In some embodiments, A^{L3} is substituted with 5 chloro substituents.

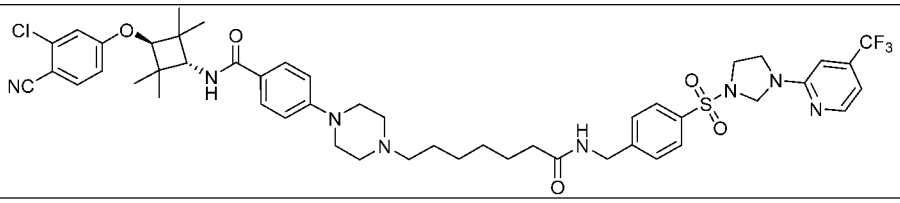
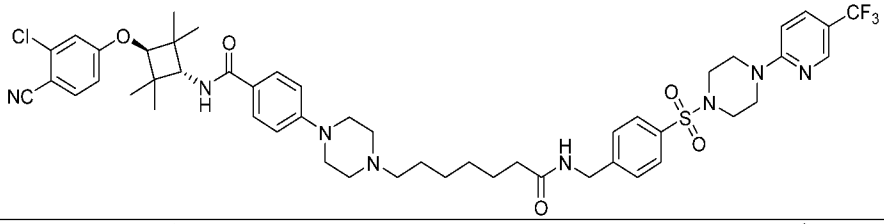
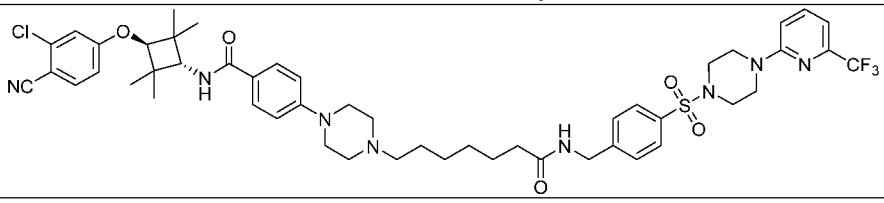
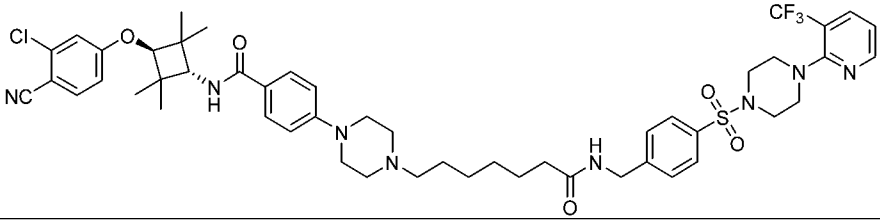
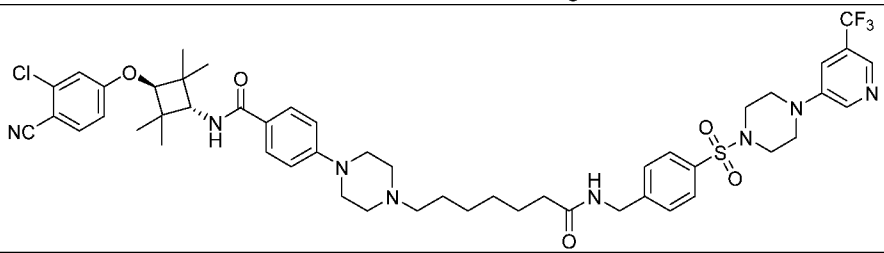
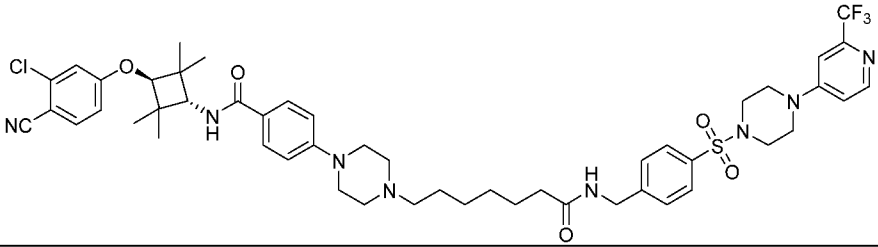
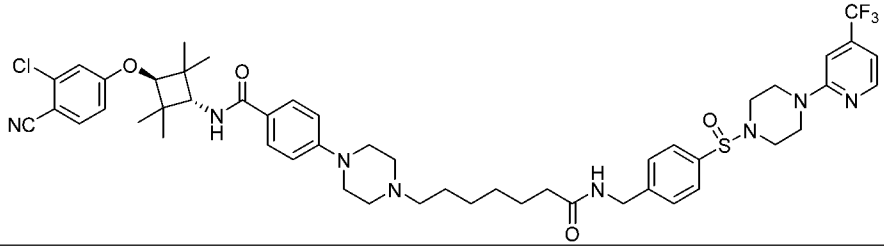
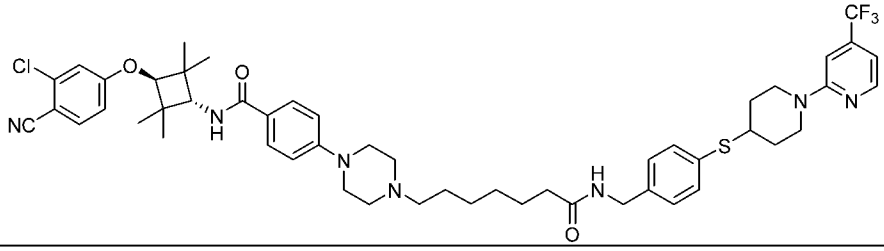
[65] In some embodiments, provided is a compound selected from compounds in Table 1, or a stereoisomer, tautomer, solvate, prodrug or salt thereof. In some embodiments, provided is a compound selected from compounds in Table 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing. Although certain compounds described in Table 1 are presented as specific stereoisomers and/or in a non-stereochemical form, it is understood that any or all stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of any of the compounds of Table 1 are herein described.

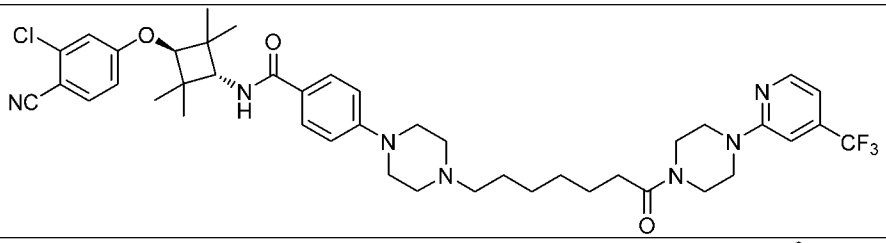
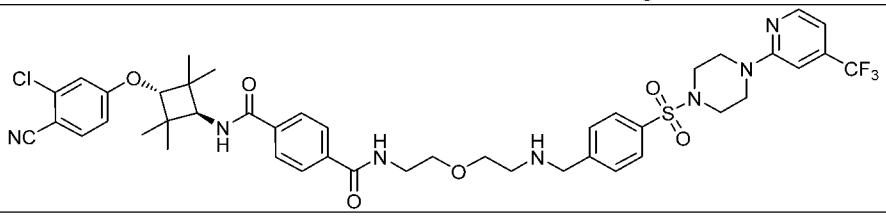
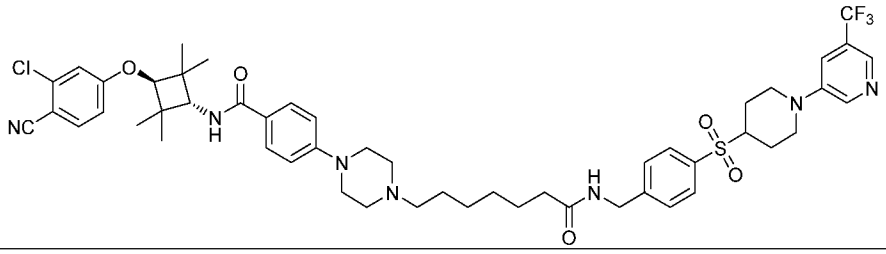
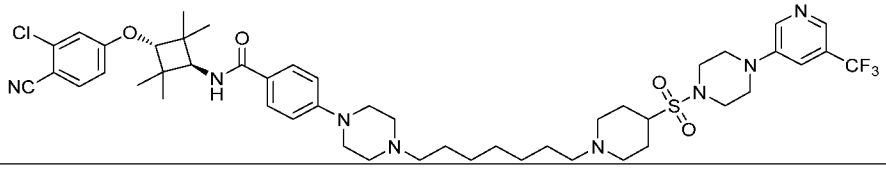
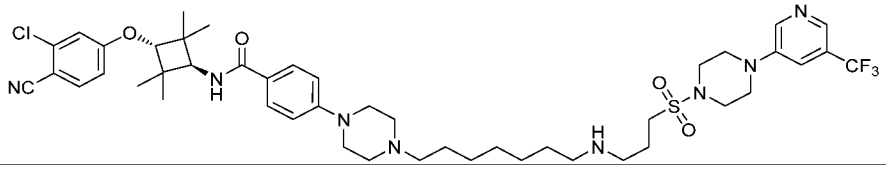
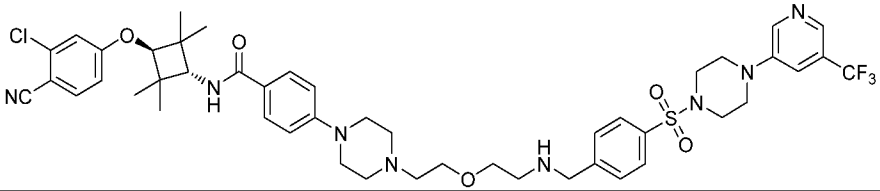
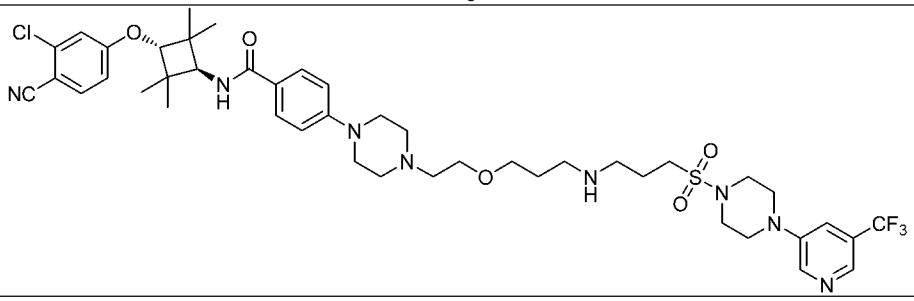
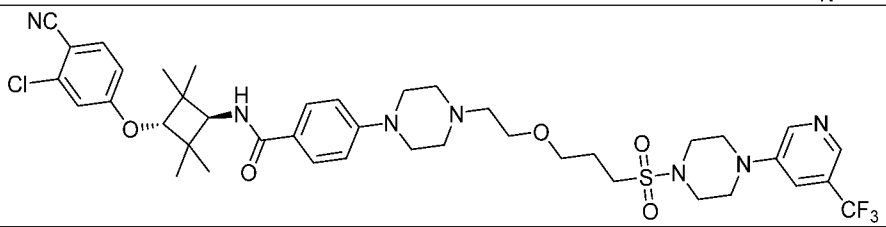
Table 1

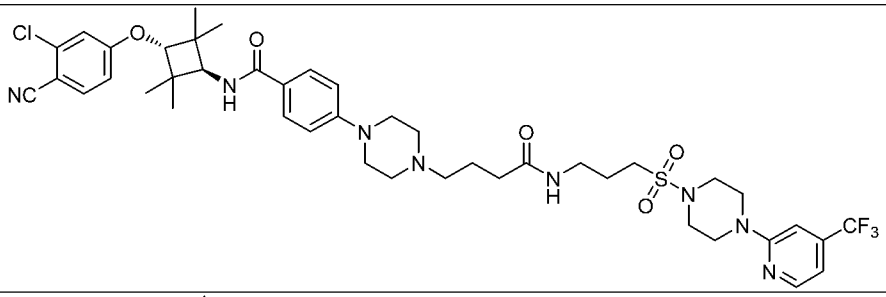
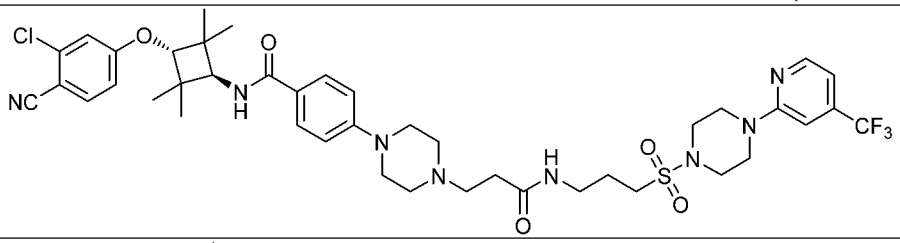
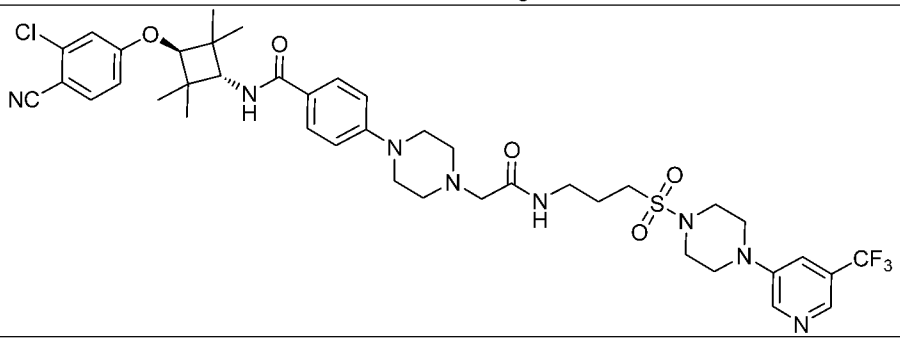
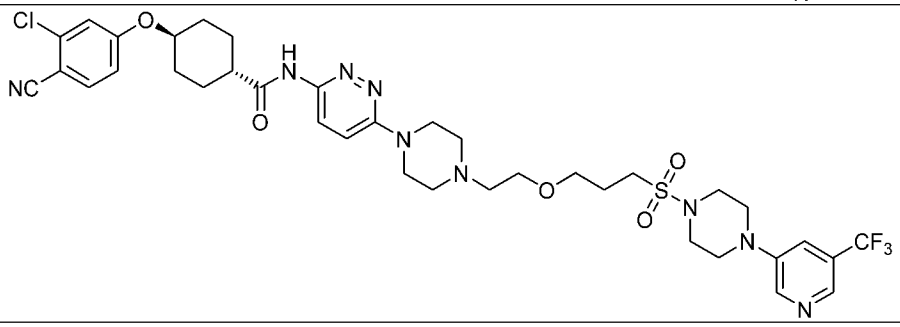
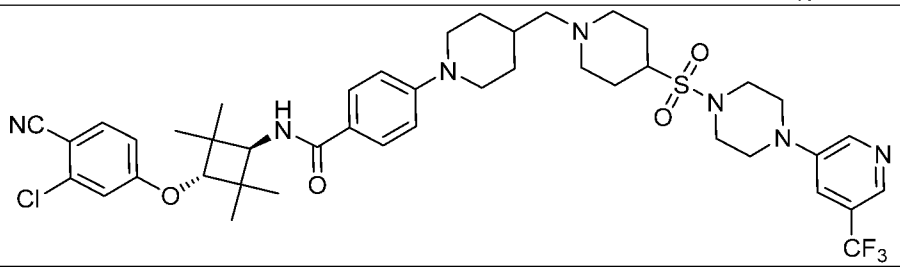
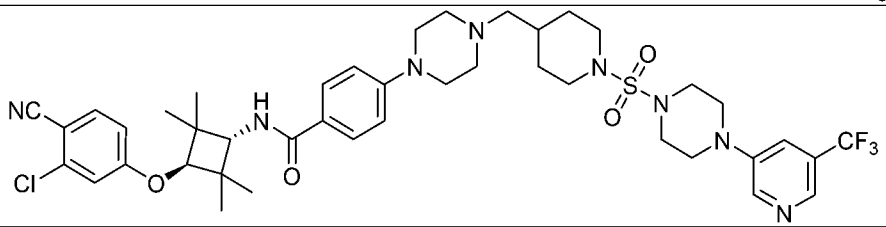
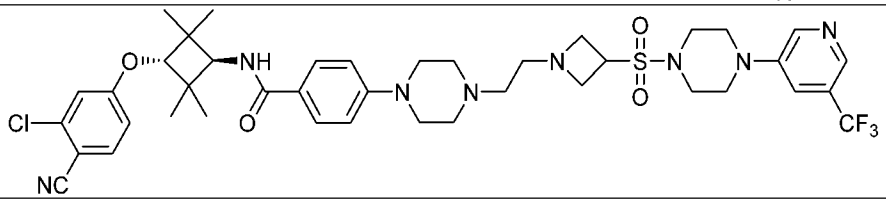
No.	Structure
1	
2	

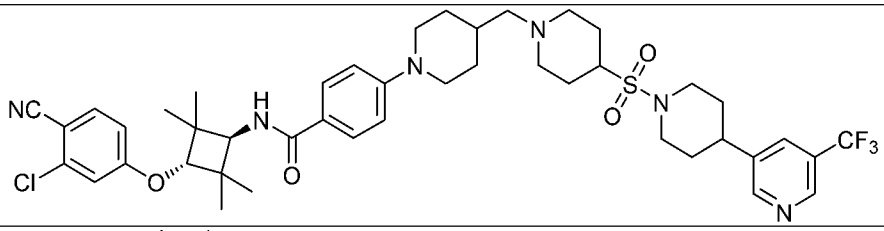
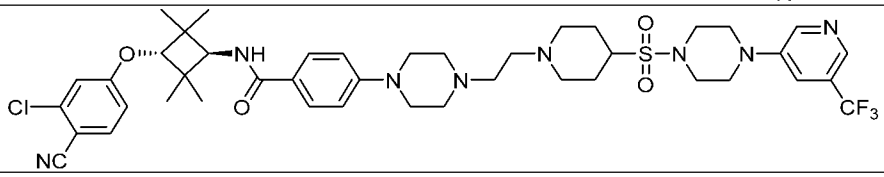
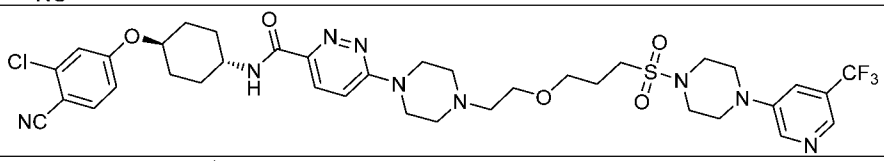
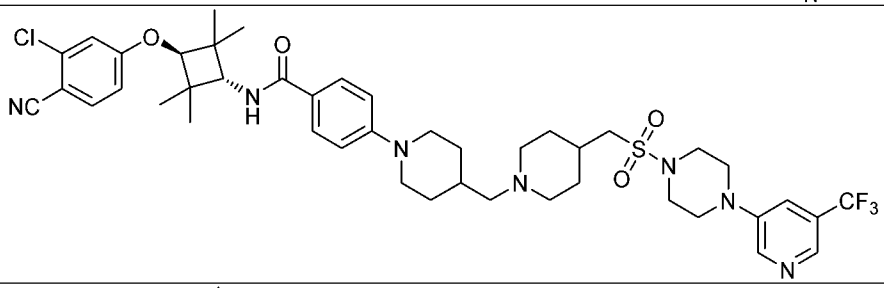
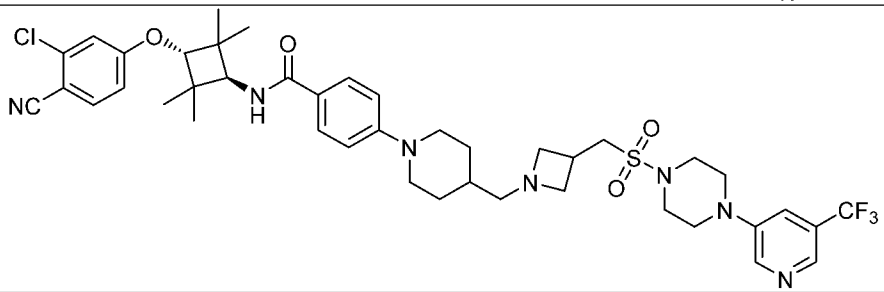
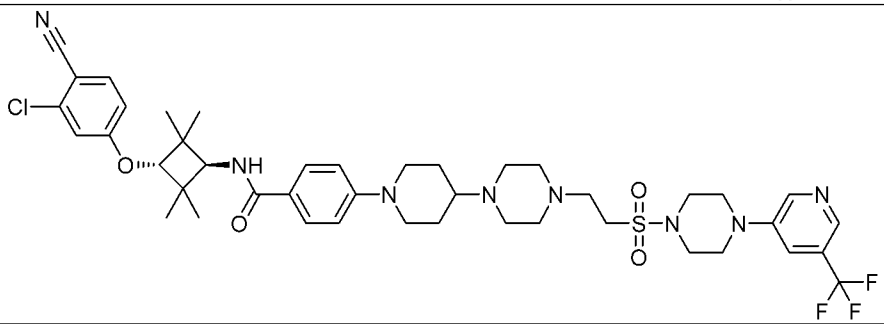
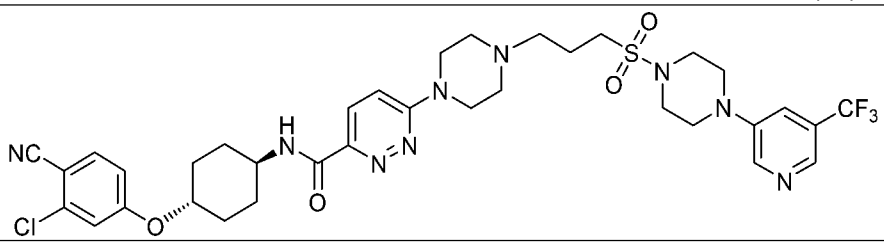
3	
4	
5	
6	
7	
8	
9	
10	
11	

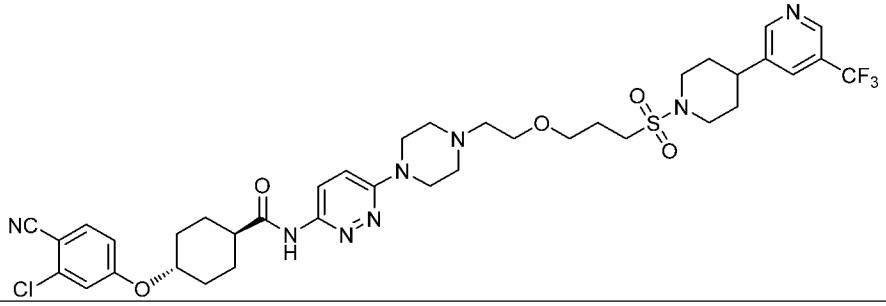
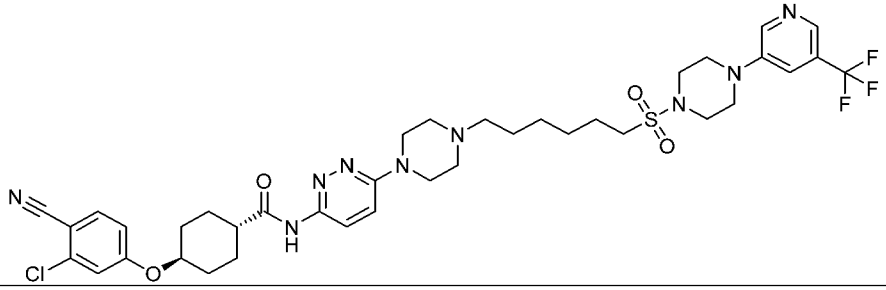
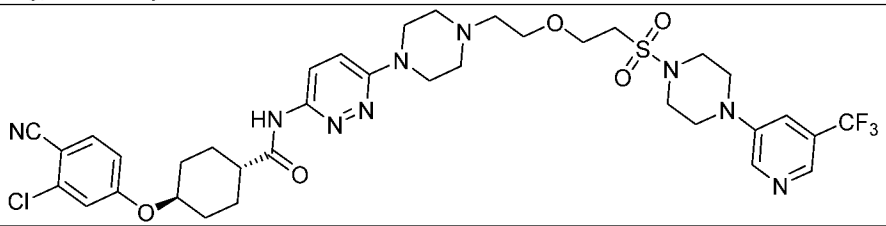
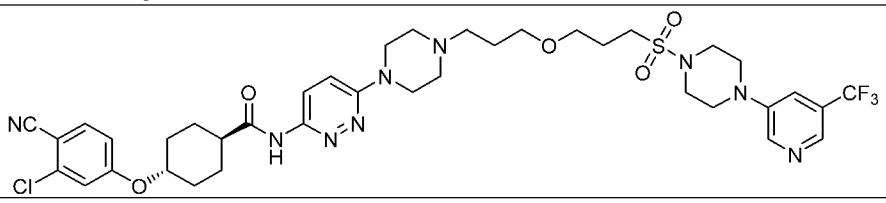
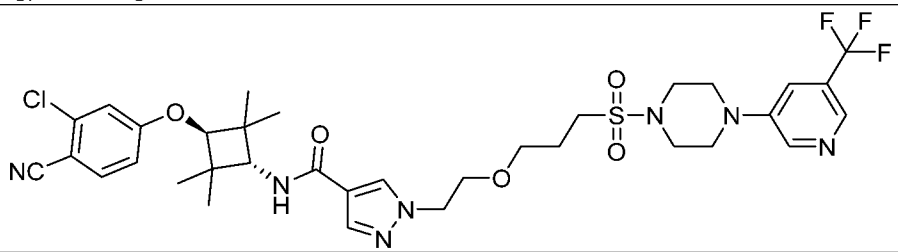
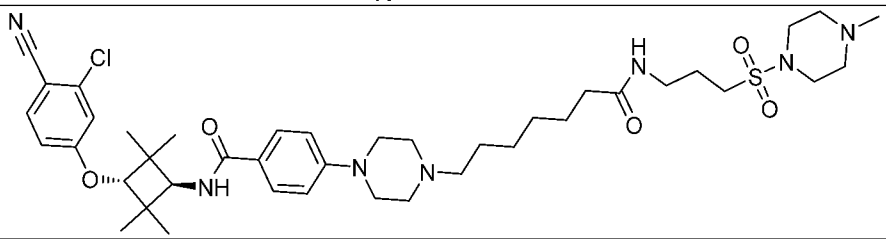
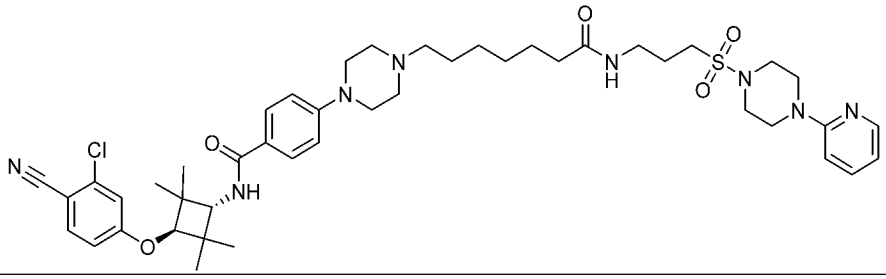
12	
13	
14	
15	
16	
17	
18	
19	

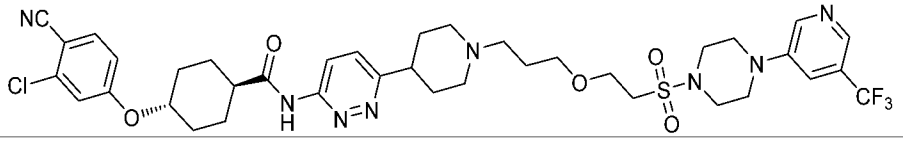
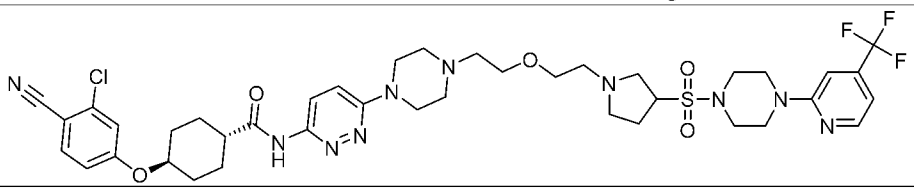
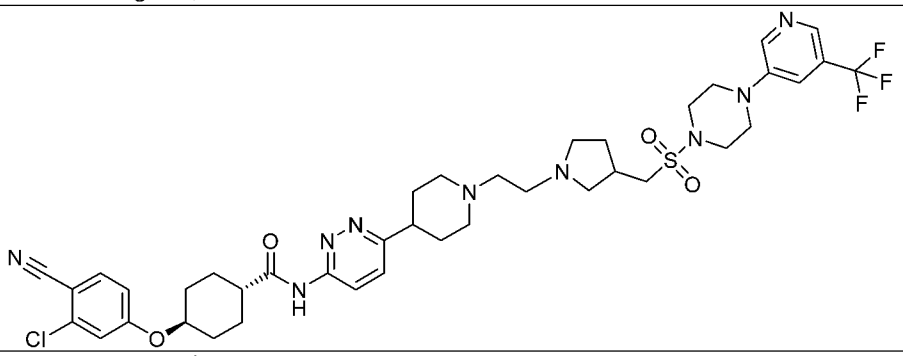
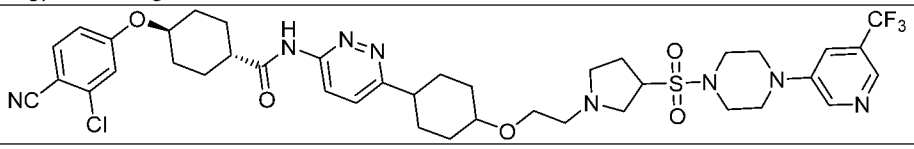
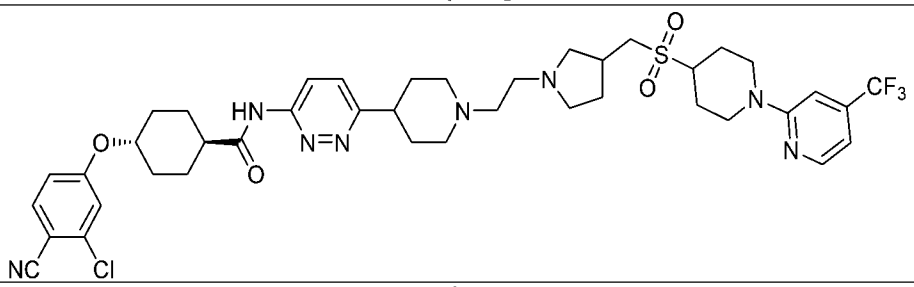
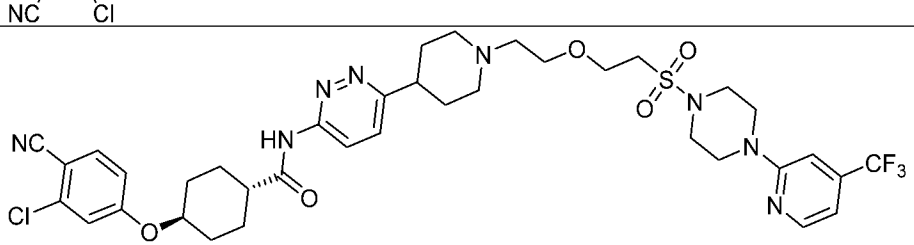
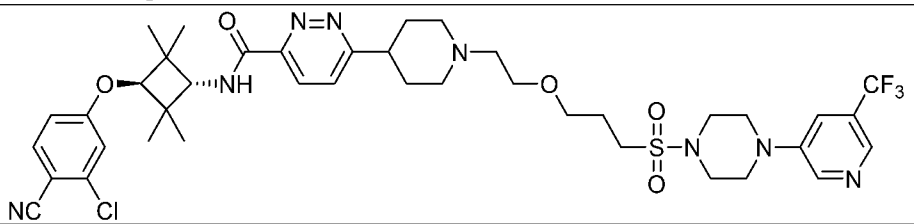
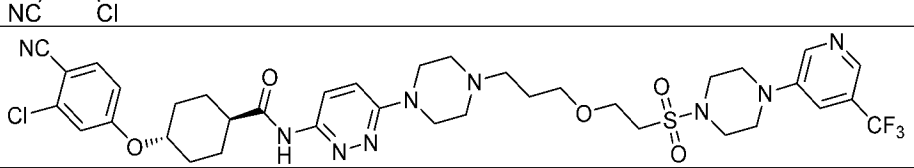
20	
21	
22	
23	
24	
25	
26	
27	

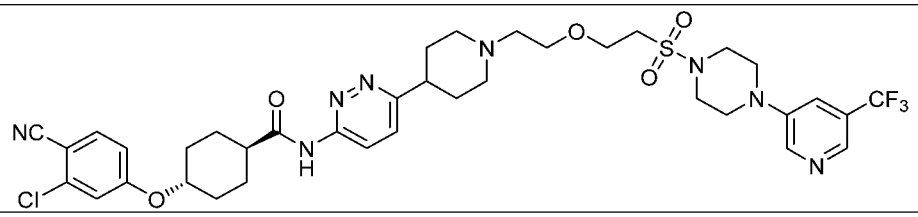
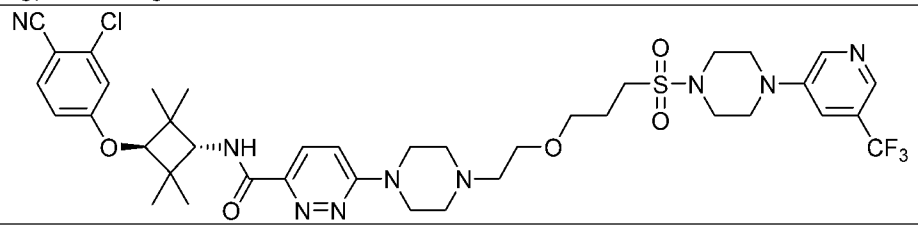
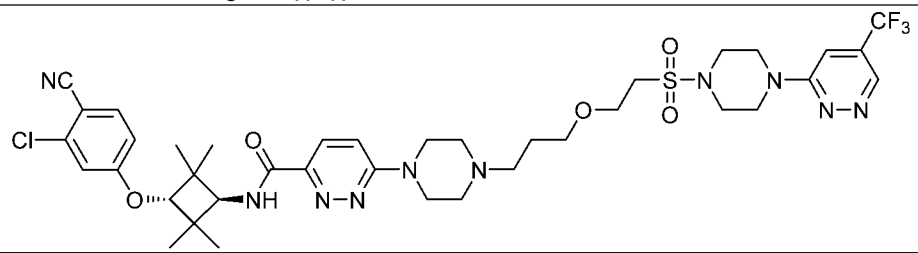
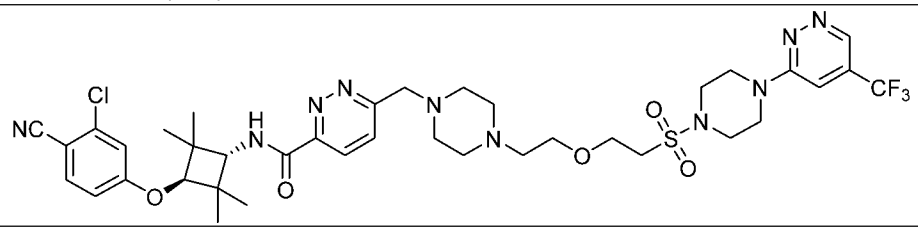
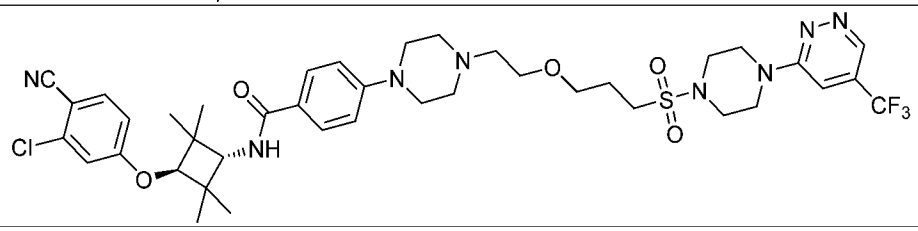
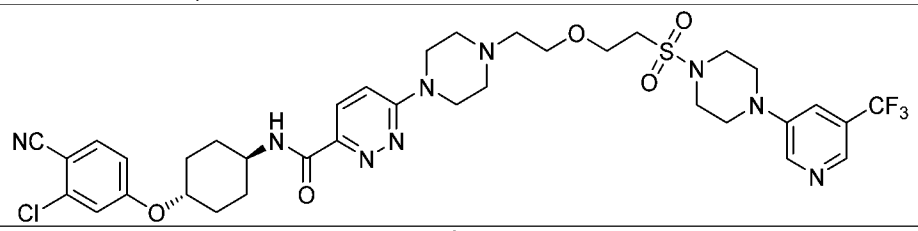
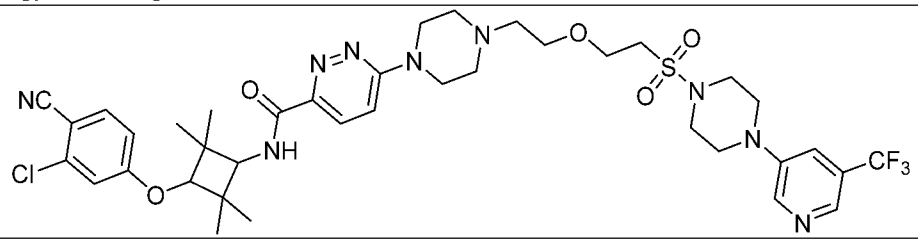
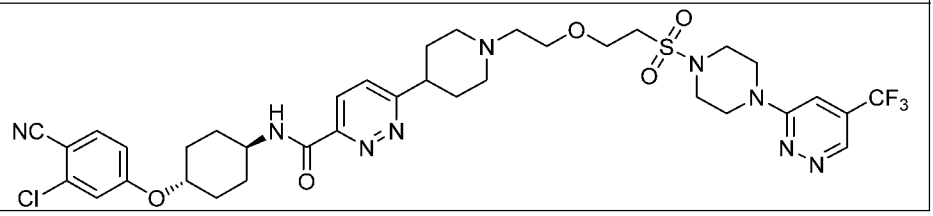
28	
29	
30	
31	
32	
33	
34	
35	

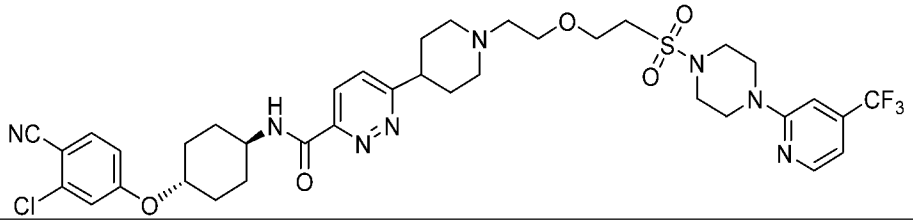
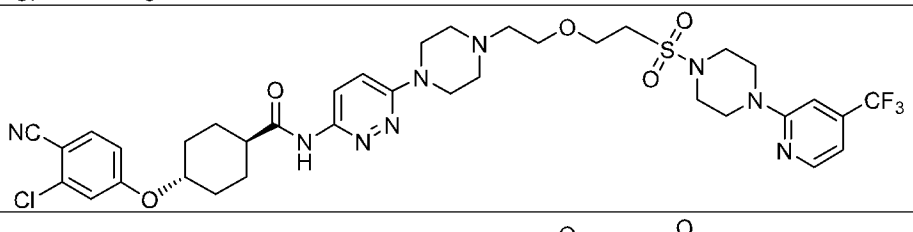
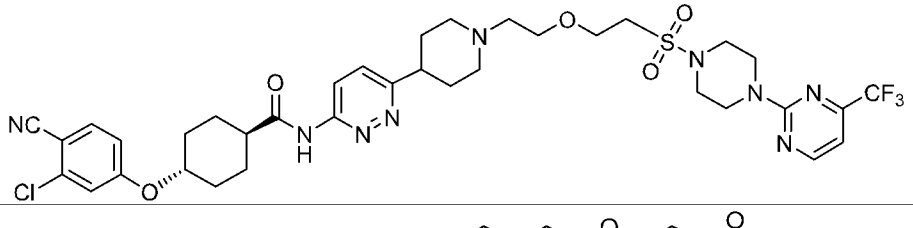
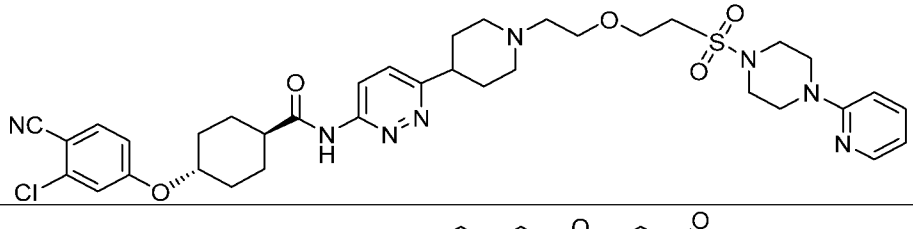
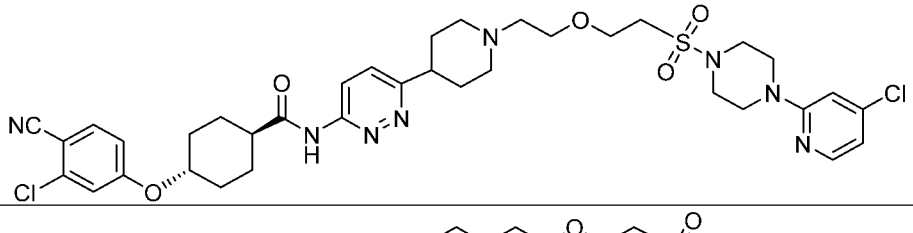
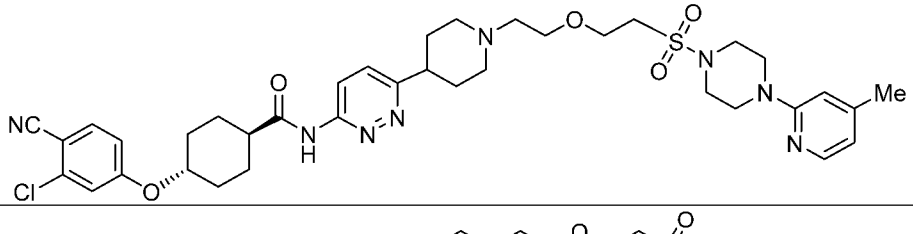
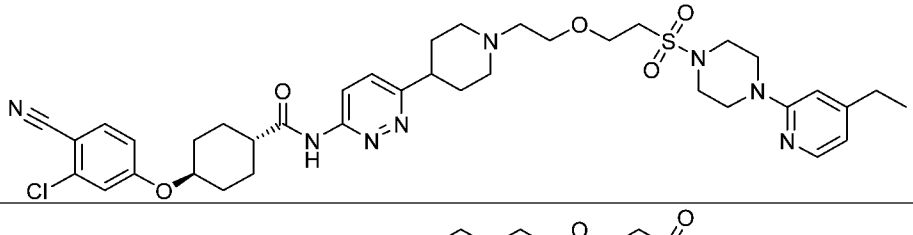
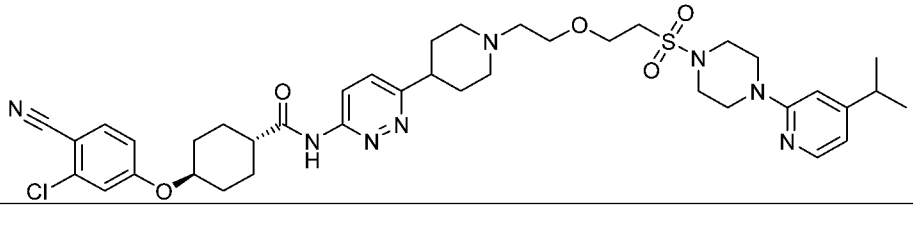
36	
37	
38	
39	
40	
41	
42	

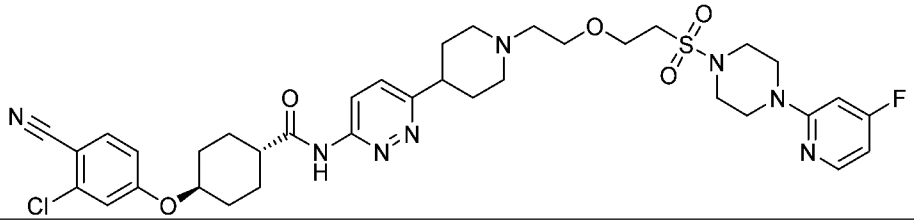
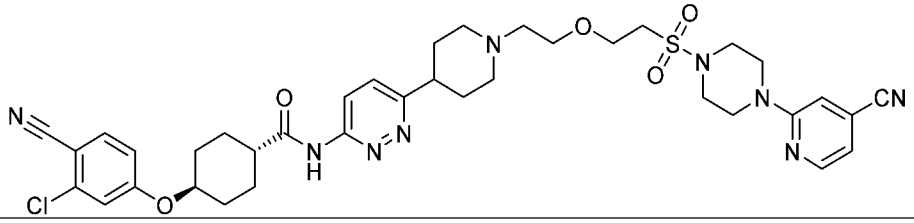
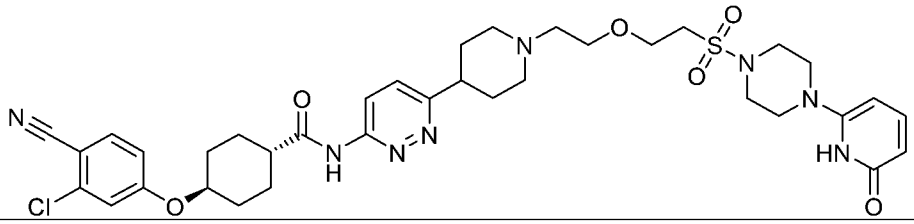
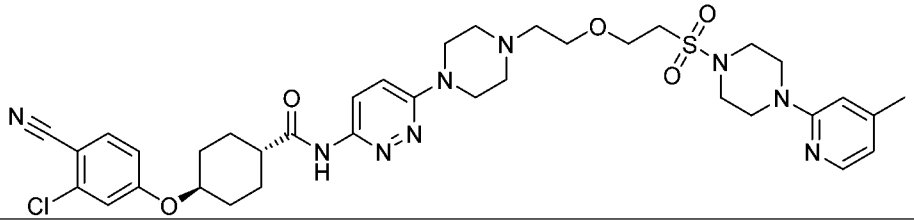
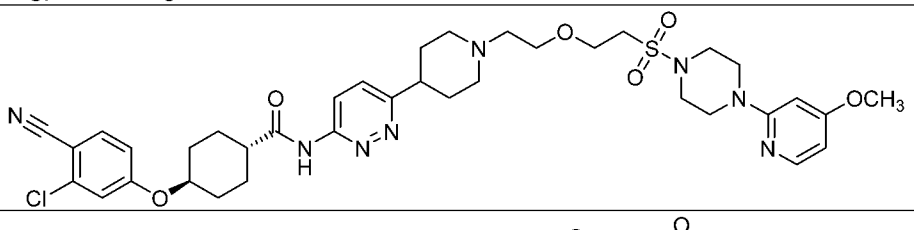
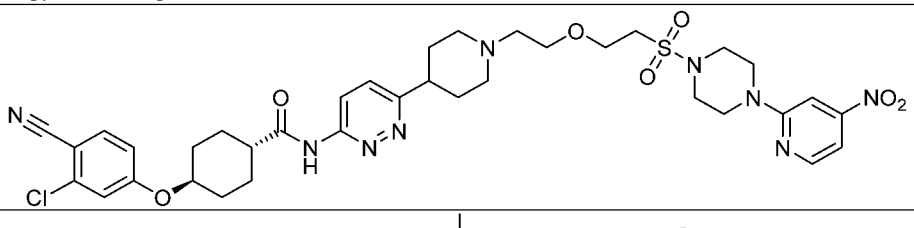
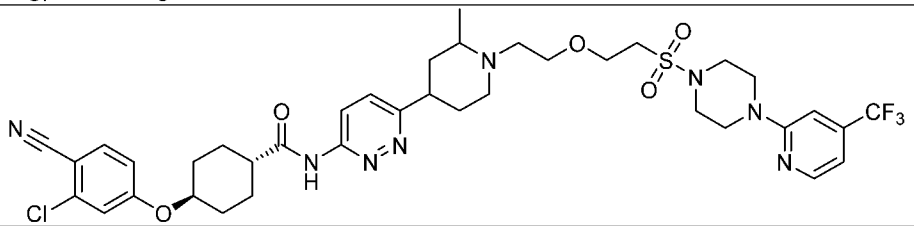
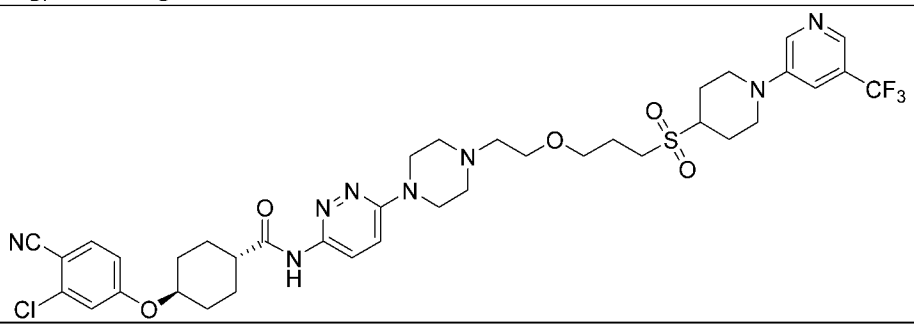
43	
44	
45	
46	
47	
48	
49	

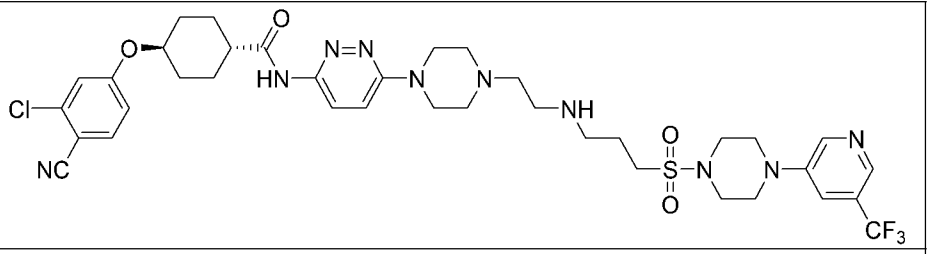
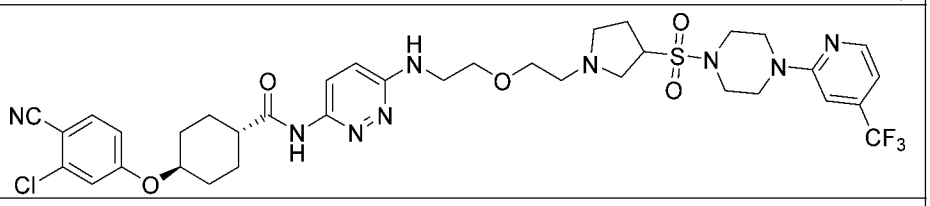
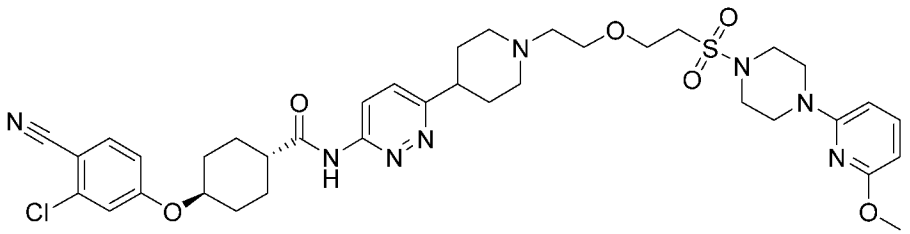
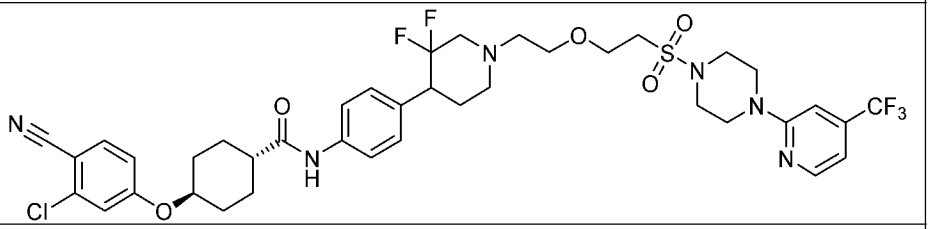
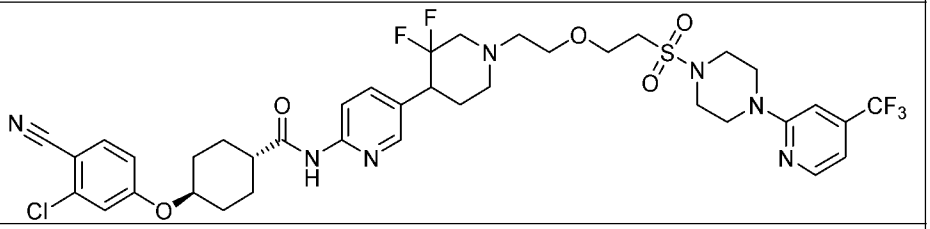
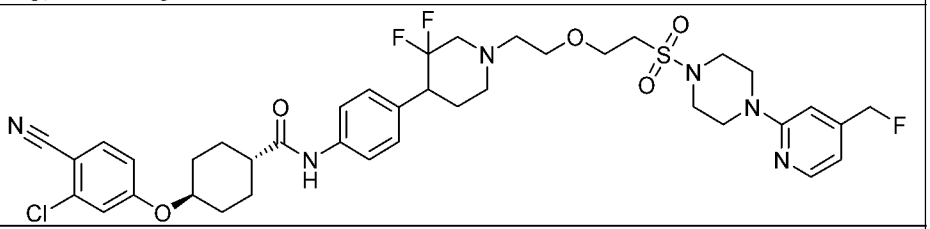
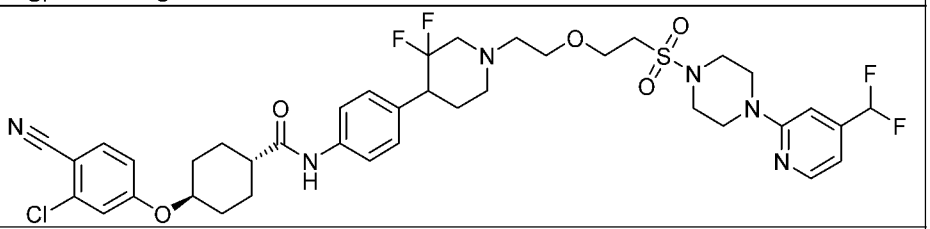
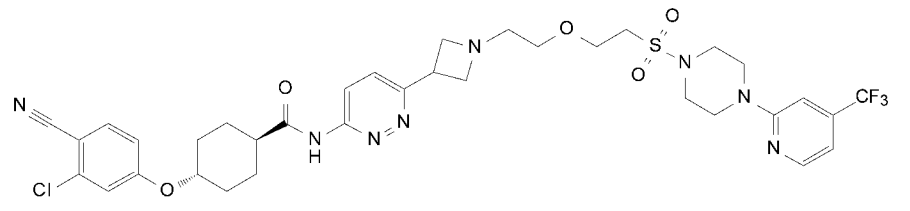
50	
51	
52	
53	
54	
55	
56	

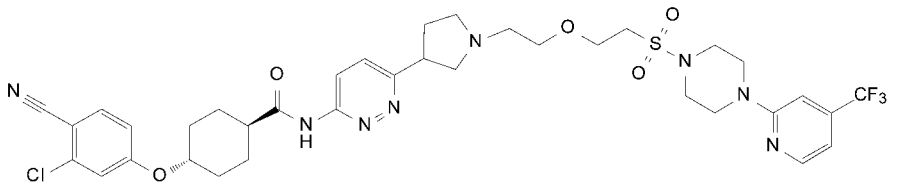
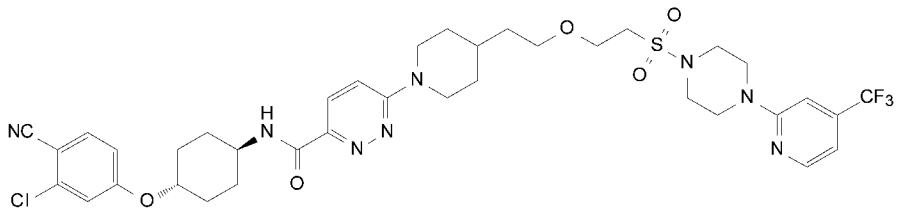
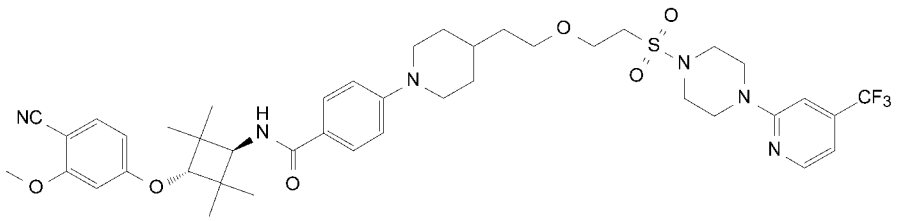
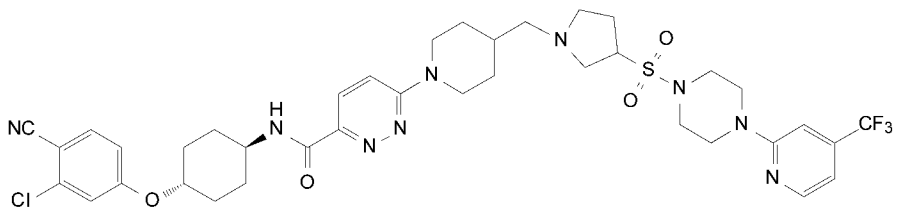
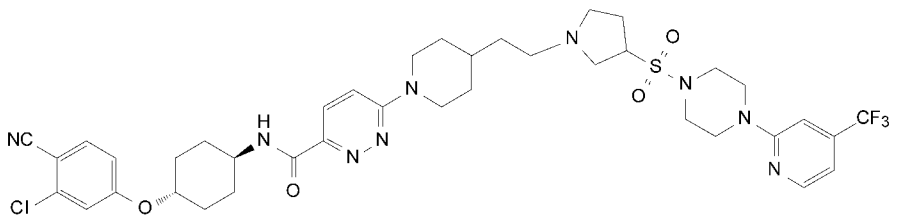
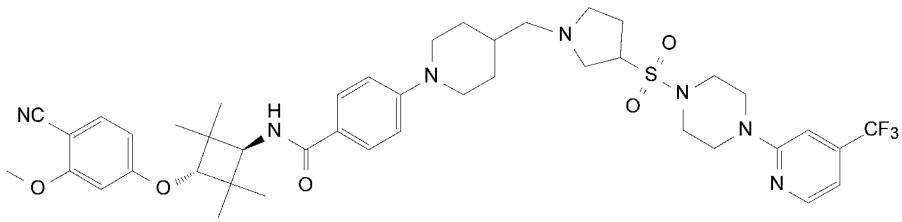
57	
58	
59	
60	
61	
62	
63	
64	

65	
66	
67	
68	
69	
70	
71	
72	

73	
74	
75	
76	
77	
78	
79	
80	

81	
82	
83	
84	
85	
86	
87	
88	

89	
90	
91	
92	
93	
94	
95	
96	

97	
98	
99	
100	
101	
102	

[66] In some embodiments, provided is a compound selected from the group consisting of: N^1-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-N^4-(2-(2-(3-oxo-3-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)propoxy)ethoxy)ethyl)terephthalamide;

N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide;

N^1-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-N^4-(6-(4-(4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)piperazin-1-yl)hexyl)terephthalamide;

N^1-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-N^4-(2-(2-(3-((4-((4-(3-cyano-5-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)amino)-3-oxopropoxy)ethoxy)ethyl)terephthalamide;

N^1-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-N^4-(2-(2-(2-(6-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethoxy)ethoxy)ethyl)terephthalamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(2-(3-oxo-3-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)propoxy)ethoxy)ethyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperidin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-((4-((4-(2-cyano-5-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)amino)-7-oxoheptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-(((5-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyridin-2-yl)methyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-(((4-((4-(4-(difluoro-λ3-methyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)methyl)amino)-7-oxoheptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-(4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-(4-(4-(trifluoromethyl)pyridin-2-yl)piperazine-1-carbonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-(((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)cyclohexyl)methyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(5-oxo-5-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)pentyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(3-oxo-3-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)propyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-(((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)cyclobutyl)methyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((3-(4-(trifluoromethyl)pyridin-2-yl)azetidin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((3-(4-(trifluoromethyl)pyridin-2-yl)imidazolidin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(2-(trifluoromethyl)pyridin-4-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfinyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)thio)benzyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-(4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)heptyl)piperazin-1-yl)benzamide;

N^1-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-N^4-(2-(2-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)ethoxy)ethyl)terephthalamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-isocyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-(4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-((3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl)amino)heptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(2-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)benzyl)amino)ethoxy)ethyl)piperazin-1-yl)benzamide;

2-chloro-4-(2,2,4,4-tetramethyl-3-((4-(4-(2-(3-((3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl)amino)propoxy)ethyl)piperazin-1-yl)benzyl)amino)cyclobutoxy)benzonitrile;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(4-oxo-4-((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propyl)amino)butyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(3-oxo-3-((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propyl)amino)propyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-oxo-2-((3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl)amino)ethyl)piperazin-1-yl)benzamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((1-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-4-yl)methyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)azetidin-1-yl)ethyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)ethyl)piperazin-1-yl)benzamide;

N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)pyridazine-3-carboxamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((4-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)piperidin-1-yl)methyl)piperidin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)azetidin-1-yl)methyl)piperidin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(4-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethyl)piperazin-1-yl)piperidin-1-yl)benzamide;

N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl)piperazin-1-yl)pyridazine-3-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(6-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)hexyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(3-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)propyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-1-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)-1H-pyrazole-4-carboxamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-((3-((4-methylpiperazin-1-yl)sulfonyl)propyl)amino)-7-oxoheptyl)piperazin-1-yl)benzamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((3-((4-(pyridin-2-yl)piperazin-1-yl)sulfonyl)propyl)amino)heptyl)piperazin-1-yl)benzamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(3-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)pyrrolidin-1-yl)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)cyclohexyl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(3-(((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)sulfonyl)methyl)pyrrolidin-1-yl)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(1-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)piperidin-4-yl)pyridazine-3-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(3-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)pyridazine-3-carboxamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(3-(2-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propyl)piperazin-1-yl)pyridazine-3-carboxamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-((4-(2-(2-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperazin-1-yl)methyl)pyridazine-3-carboxamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(3-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)benzamide;

N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(2-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperazin-1-yl)pyridazine-3-carboxamide;

N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(2-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperazin-1-yl)pyridazine-3-carboxamide;

N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(1-(2-(2-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazine-3-carboxamide;

N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazine-3-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-chloropyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-methylpyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-ethylpyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-isopropylpyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-fluoropyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-cyanopyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(6-oxo-1,6-dihydropyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(2-((4-(4-methylpyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-methoxypyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-nitropyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(2-methyl-1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(3-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-((3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl)amino)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-((2-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)ethyl)amino)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(6-methoxypyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(4-(3,3-difluoro-1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)phenyl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(5-(3,3-difluoro-1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridin-2-yl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(4-(3,3-difluoro-1-(2-(2-((4-(4-(fluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)phenyl)cyclohexane-1-carboxamide;

4-(3-chloro-4-cyanophenoxy)-N-(4-(1-(2-(2-((4-(4-(difluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)-3,3-difluoropiperidin-4-yl)phenyl)cyclohexane-1-carboxamide;

(1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)azetidin-3-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;
(1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)pyrrolidin-3-yl)pyridazin-3-yl)cyclohexane-1-carboxamide;
N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-1-yl)pyridazine-3-carboxamide;
N-((1r,3r)-3-(4-cyano-3-methoxyphenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-1-yl)benzamide;
N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)methyl)piperidin-1-yl)pyridazine-3-carboxamide;
N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(2-((R)-3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethyl)piperidin-1-yl)pyridazine-3-carboxamide, and
N-((1r,3r)-3-(4-cyano-3-methoxyphenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)methyl)piperidin-1-yl)benzamide, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing.

[67] Also provided are salts of compounds referred to herein, such as pharmaceutically acceptable salts. The present disclosure also includes any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of the compounds described. Thus, if a particular stereochemical form, such as a specific enantiomeric form or diastereomeric form, is depicted for a given compound, then it is understood that any or all stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of any of that same compound are herein described. Where tautomeric forms may be present for any of the compounds described herein, each and every tautomeric form is intended even though only one or some of the tautomeric forms may be explicitly depicted. The tautomeric forms specifically depicted may or may not be the predominant forms in solution or when used according to the methods described herein.

[68] The disclosure also intends isotopically-labeled and/or isotopically-enriched forms of compounds described herein. The compounds herein may contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. In some embodiments, the compound is isotopically-labeled, such as an isotopically-labeled compound of the formula (I) or variations thereof described herein, where a fraction of one or more atoms are replaced by an isotope of the same element. Exemplary isotopes that can be incorporated into compounds described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C ^{13}N, ^{15}O, ^{17}O, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl. Certain isotope labeled compounds (e.g. ^{3}H and ^{14}C) are useful in compound or substrate tissue distribution studies. Incorporation of heavier isotopes such as deuterium (^{2}H) can afford certain therapeutic

advantages resulting from greater metabolic stability, for example, increased in vivo half-life, or reduced dosage requirements and, hence may be preferred in some instances. Isotopically-labeled compounds described herein can generally be prepared by standard methods and techniques known to those skilled in the art or by procedures similar to those described in the accompanying Examples substituting appropriate isotopically-labeled reagents in place of the corresponding non-labeled reagent. In some embodiments, one or more hydrogen atoms are replaced by deuterium.

[69] The disclosure also includes any or all metabolites of any of the compounds described. The metabolites may include any chemical species generated by a biotransformation of any of the compounds described, such as intermediates and products of metabolism of the compound, such as would be generated *in vivo* following administration to a human.

[70] Solvates and/or polymorphs of a compound provided herein or a salt thereof are also contemplated. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and/or solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate

[71] A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound as detailed herein or a salt thereof are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a salt thereof is in substantially pure form. Unless otherwise stated, "substantially pure" intends a composition that contains no more than 35% impurity, wherein the impurity denotes a compound other than the compound comprising the majority of the composition or a salt thereof. In some embodiments, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains no more than 25%, 20%, 15%, 10%, or 5% impurity. In some embodiments, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 3%, 2%, 1% or 0.5% impurity.

[72] Articles of manufacture comprising a compound described herein, or a salt or solvate thereof, in a suitable container are provided. The container may be a vial, jar, ampoule, preloaded syringe, i.v. bag, and the like.

[73] In some embodiments, the compounds detailed herein are orally bioavailable. However, the compounds may also be formulated for parenteral (*e.g.*, intravenous) administration.

[74] One or several compounds described herein can be used in the preparation of a medicament by combining the compound or compounds as an active ingredient with a pharmacologically acceptable carrier, which are known in the art. Depending on the therapeutic form of the medication, the carrier may be in various forms. In one variation, the manufacture of a medicament is for use in any of the methods disclosed herein, *e.g.*, for the treatment of cancer.

Pharmaceutical Compositions and Formulations

[75] Pharmaceutical compositions of any of the compounds detailed herein are embraced by this disclosure. Thus, the present disclosure includes pharmaceutical compositions comprising a compound as detailed herein, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient. In one aspect, the pharmaceutically acceptable salt is an acid addition salt, such as a salt formed with an inorganic or organic acid. Pharmaceutical compositions may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration or a form suitable for administration by inhalation.

[76] A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound as detailed herein or a salt thereof are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a salt thereof is in substantially pure form.

[77] In one variation, the compounds herein are synthetic compounds prepared for administration to an individual. In another variation, compositions are provided containing a compound in substantially pure form. In another variation, the present disclosure embraces pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier. In another variation, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and methods of administering the compounds are suitable for any compound or form thereof detailed herein.

[78] A compound detailed herein, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, may be formulated for any available delivery route, including an oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal or rectal), parenteral (*e.g.*, intramuscular, subcutaneous or intravenous), topical or transdermal delivery form. A compound or salt thereof may be formulated with suitable carriers to provide delivery forms that include, but are not limited to, tablets, caplets, capsules (such as hard gelatin capsules or soft elastic gelatin capsules), cachets, troches, lozenges, gums, dispersions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, solutions, patches, aerosols (*e.g.*, nasal spray or inhalers), gels, suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions or water-in-oil liquid emulsions), solutions and elixirs.

[79] A compound detailed herein, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, can be used in the preparation of a formulation, such as a pharmaceutical formulation, by combining the compound or compounds, or a salt thereof, as an active ingredient with a pharmaceutically acceptable carrier. Depending on the therapeutic form of the system (*e.g.*, transdermal patch vs. oral tablet), the carrier may be in various forms. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants. Formulations comprising the compound may also contain other substances which have valuable therapeutic properties. Pharmaceutical formulations may be prepared by known pharmaceutical methods. Suitable formulations can be found, *e.g.*, in *Remington's Pharmaceutical Sciences,* Mack Publishing Company, Philadelphia, PA, 20th ed. (2000), which is incorporated herein by reference.

[80] A compound detailed herein, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, may be administered to individuals in a form of generally accepted oral compositions, such as tablets, coated tablets, and gel capsules in a hard or in soft shell, emulsions or suspensions. Examples of carriers, which may be used for the preparation of such compositions, are lactose, corn starch or its derivatives, talc, stearate or its salts, *etc.* Acceptable carriers for gel capsules with soft shell are, for instance, plant oils, wax, fats, semisolid and liquid poly-ols, and so on. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants.

[81] Any of the compounds described herein can be formulated in a tablet in any dosage form described, for example, a compound as described herein or a salt thereof can be formulated as a 10 mg tablet.

[82] Compositions comprising a compound provided herein are also described. In one variation, the composition comprises a compound, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient. In another variation, a composition of substantially pure compound is provided. In some embodiments, the composition is for use as a human or veterinary medicament. In some embodiments, the composition is for use in a method described herein. In some embodiments, the composition is for use in the treatment of a disease or disorder described herein.

Methods of Use

[83] Compounds and compositions detailed herein, such as a pharmaceutical composition containing a compound of any formula provided herein, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient, may be used in methods of administration and treatment as provided herein. The compounds and compositions may also be used in

in vitro methods, such as *in vitro* methods of administering a compound or composition to cells for screening purposes and/or for conducting quality control assays.

[84] Provided herein is a method of treating a disease or disorder in an individual in need thereof comprising administering a compound describes herein or any embodiment, variation, or aspect thereof, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound, pharmaceutically acceptable salt thereof, or composition is administered to the individual according to a dosage and/or method of administration described herein.

[85] In another aspect, the disclosure provides methods of modulating protein ubiquitination and degradation in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a PROTAC compound as described herein or a composition comprising an effective amount of the same to a subject, wherein the compound or composition comprising the same is effective in modulating protein ubquitination and degradation of the protein in the subject. In certain embodiments, the protein is androgen receptor (AR).

[86] In certain embodiments, the description provides a method for regulating protein activity of the androgen receptor in a patient in need comprising administering to said patient an amount of a compound as described herein to a patient.

[87] In still additional embodiments, the description provides a method of treating a disease state or condition in a patient wherein dysregulated protein activity is responsible for said disease state or condition, said method comprising administering to said patient an effective amount of a compound as described herein to said patient in order to regulate said protein activity in said patient. In certain embodiments, the protein is AR.

[88] The terms "treat", "treating", and "treatment", etc., as used herein, refer to any action providing a benefit to a patient for which the present compounds may be administered, including the treatment of any disease state or condition which is modulated through the protein to which the present compounds bind. Disease states or conditions, including cancer, which may be treated using compounds according to the present disclosure are set forth hereinabove.

[89] In another aspect, the disclosure provides methods of modulating AR protein ubiquitination and degradation in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a compound as described herein or a composition comprising an effective amount of a compound as described herein to a subject, wherein the compound or composition comprising the same is effective in modulating AR protein ubquitination and degradation of the protein in the subject.

[90] In another aspect, the disclosure provides methods of treating or ameliorating a symptom of a disease related to AR activity in a subject, e.g., a cell, a tissue, mammal, or human patient, the method

comprising administering an effective amount of a compound as described herein or a composition comprising an effective amount of the same to a subject in need thereof, wherein the compound or composition comprising the same is effective in treating or ameliorating a symptom of a disease related to AR activity in the subject.

[91] In certain embodiments, the disease or disorder is asthma, multiple sclerosis, cancer, prostate cancer, Kenney's disease, ciliopathies, cleft palate, diabetes, heart disease, hypertension, inflammatory bowel disease, mental retardation, mood disorder, obesity, refractive error, infertility, Angelman syndrome, Canavan disease, Coeliac disease, Charcot-Marie-Tooth disease, Cystic fibrosis, Duchenne muscular dystrophy, Haemochromatosis, Haemophilia, Klinefelter's syndrome, Neurofibromatosis, Phenylketonuria, Polycystic kidney disease, (PKD1) or 4 (PKD2) Prader-Willi syndrome, Sickle-cell disease, Tay-Sachs disease, Turner syndrome. In certain embodiments, the cancer is squamous-cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogliomas, ependymomas, gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor or teratocarcinomas. In certain embodiments, the disease to be treated is cancer, e.g., prostate cancer, or Kennedy's Disease. In a preferred embodiment, the subject is a human.

[92] In another aspect, the disclosure provides methods of treating or ameliorating a symptom of a disease related to AR activity in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a compound as described herein or a composition comprising an effective amount of the same and an effective or synergistic amount of another bioactive agent to a subject in need thereof, wherein the composition comprising the same is effective in treating or ameliorating a symptom of a disease related to AR activity in the subject. In certain embodiments, the disease to be treated is cancer, e.g., prostate cancer, or Kennedy's Disease. In a preferred embodiment, the subject is a human. In certain additional embodiments, the additional bioactive agent is an anti-cancer agent.

[93] In alternative aspects, the present disclosure relates to a method for treating a disease state by degrading a protein or polypeptide through which a disease state or condition is modulated comprising

administering to said patient or subject an effective amount of at least one compound as described hereinabove, optionally in combination with an additional bioactive agent. The method according to the present disclosure may be used to treat a large number of disease states or conditions including cancer, by virtue of the administration of effective amounts of at least one compound described herein.

[94] In another aspect, the disclosure provides methods for identifying the effects of the degradation of proteins of interest in a biological system using compounds according to the present disclosure.

Combinations

[95] In certain aspects, compounds or compositions described herein are administered to an individual for treatment of a disease in combination with one or more additional pharmaceutical agents that can treat the disease. For example, in some embodiments, an effective amount of the compound is administered to an individual for the treatment of cancer in combination with one or more additional anticancer agents.

[96] Disease states of conditions which may be treated using compounds or compositions according to the present description include, but not limited to, for example, cancer (e.g., prostate cancer), and Kennedy's disease. In certain embodiments, the therapeutic or pharmaceutical compositions comprise an effective amount of an additional biologically or bioactive active agent, e.g., an agent effective for the treatment of cancer, that is co-administered.

[97] The terms "coadministration", "combination therapy", "administered in combination with", or "coadministered in combination with" shall mean that at least two compounds or compositions are administered to the patient at the same time, such that effective amounts or concentrations of each of the two or more compounds may be found in the patient at a given point in time. Although compounds according to the present disclosure may be co-administered to a patient at the same time, the term embraces both administration of two or more agents at the same time or at different times, provided that effective concentrations of all coadministered compounds or compositions are found in the subject at a given time. In certain preferred aspects of the present disclosure, one or more of the present compounds described above, are coadministered in combination with at least one additional bioactive agent, especially including an anticancer agent. In particularly preferred aspects of the disclosure, the co-administration of compounds results in synergistic therapeutic, including anticancer therapy.

[98] In another aspect, the description provides a composition comprising an effective amount of two or more of the PROTAC compounds as described herein, and a pharmaceutically acceptable carrier. In certain embodiments, the composition further comprises an effective or synergistic amount of another bioactive agent that is not a PROTAC compound.

[99] Pharmaceutical compositions comprising combinations of an effective amount of at least one bifunctional compound according to the present disclosure, and one or more of the compounds otherwise

described herein, all in effective amounts, in combination with a pharmaceutically effective amount of a carrier, additive or excipient, represents a further aspect of the present disclosure.

[100] The term "bioactive agent" is used to describe an agent, other than the PROTAC compounds described herein, which is used in combination with the present compounds as an agent with biological activity to assist in effecting an intended therapy, inhibition and/or prevention/prophylaxis for which the present compounds are used. Preferred bioactive agents for use herein include those agents which have pharmacological activity similar to that for which the present compounds are used or administered and include for example, anti-cancer agents.

[101] The term "additional anti-cancer agent" is used to describe an anti-cancer agent, which may be combined with PROTAC compounds according to the present description to treat cancer. These agents include, for example, everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, an androgen receptor inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhbitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601, ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001, IPdR1 KRX-0402, lucanthone, LY317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311, romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, liposomal doxorubicin, 5′-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib; PD0325901, AZD-6244, capecitabine, L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrazole, exemestane, letrozole, DES (diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11, CHIR-258); 3-[5-(methylsulfonylpiperadinemethyl)-indolylj-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D-Ser(Bu t) 6, Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro-Azgly-NH2 acetate [C59H84N18Oi4-(C2H4O2)x where x=1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-214662, tipifarnib;

amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951, aminoglutethimide, amsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, adriamycin, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gleevec, gemcitabine, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deooxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291, squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxyfene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox, gefitinib, bortezimib, paclitaxel, cremophor-free paclitaxel, docetaxel, epithilone B, BMS-247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA-923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR-3339, ZK186619, topotecan, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zolendronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11, dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritgumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonist, palonosetron, aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa, darbepoetin alfa and mixtures thereof.

Dosing and Method of Administration

[102] The dose of a compound described herein, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, administered to an individual (such as a human) may vary with the particular compound or salt thereof, the method of administration, and the particular disease, such as type and stage of cancer, being

treated. In some embodiments, the amount of the compound, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, is a therapeutically effective amount.

[103] The effective amount of the compound may in one aspect be a dose of between about 0.01 and about 100 mg/kg. Effective amounts or doses of the compounds of the present disclosure may be ascertained by routine methods, such as modeling, dose escalation, or clinical trials, taking into account routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease to be treated, the subject's health status, condition, and weight. An exemplary dose is in the range of about from about 0.7 mg to 7 g daily, or about 7 mg to 350 mg daily, or about 350 mg to 1.75 g daily, or about 1.75 to 7 g daily.

[104] Any of the methods provided herein may in one aspect comprise administering to an individual a pharmaceutical composition that contains an effective amount of a compound provided herein, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, and a pharmaceutically acceptable excipient.

[105] A compound or composition provided herein may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer, which in some variations may be for the duration of the individual's life. In one variation, the compound is administered on a daily or intermittent schedule. The compound can be administered to an individual continuously (for example, at least once daily) over a period of time. The dosing frequency can also be less than once daily, *e.g.*, about a once weekly dosing. The dosing frequency can be more than once daily, *e.g.*, twice or three times daily. The dosing frequency can also be intermittent, including a 'drug holiday' (*e.g.*, once daily dosing for 7 days followed by no doses for 7 days, repeated for any 14 day time period, such as about 2 months, about 4 months, about 6 months or more). Any of the dosing frequencies can employ any of the compounds described herein together with any of the dosages described herein.

Articles of Manufacture and Kits

[106] The present disclosure further provides articles of manufacture comprising a compound described herein or a salt thereof, a composition described herein, or one or more unit dosages described herein in suitable packaging. In certain embodiments, the article of manufacture is for use in any of the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

[107] The present disclosure further provides kits for carrying out the methods of the present disclosure, which comprises one or more compounds described herein or a composition comprising a compound described herein. The kits may employ any of the compounds disclosed herein. In one variation, the kit employs a compound described herein or a stereoisomer, tautomer, solvate, prodrug or salt thereof.

The kits may be used for any one or more of the uses described herein, and, accordingly, may contain instructions for the treatment of any disease or described herein, for example for the treatment of cancer.

[108] Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit.

[109] The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein and/or an additional pharmaceutically active compound useful for a disease detailed herein to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (*e.g.*, hospital pharmacies and compounding pharmacies).

[110] The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods of the present disclosure. The instructions included with the kit generally include information as to the components and their administration to an individual.

[111] Certain representative embodiments are provided below.

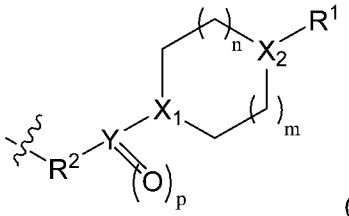
Embodiment 1. A bifunctional compound of formula (I):

PTM-L-ULM (I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

the PTM is a moiety that binds a target protein;

the ULM is an E3 ubiquitin ligase CDC20 (Cell Division Cycle 20) binding moiety of formula (A):



(A)

wherein

R^1 is C_1-C_6 alkyl, C_{6-10} aryl or 5- to 6-membered heteroaryl, each of which is optionally substituted with C_1-C_6 alkyl, halogen, -OH, oxo, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), -NO_2, or -CN;

R^2 is a bond, C_1-C_6 alkylene, C_{3-8} cycloalkylene, 3- to 10- membered heterocyclylene, C_{6-10} arylene, or 5- to 10- membered heteroarylene;

X_1 and X_2 are independently N or CH;

Y is C or S;

m and n are independently 0 1, or 2; and

p is 0, 1 or 2;

and

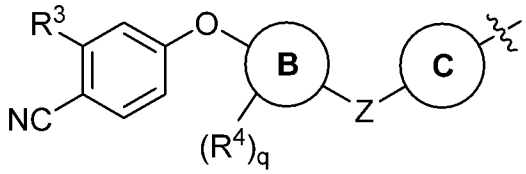
L is a bond or a chemical linker covalently connecting the PTM and the ULM.

Embodiment 2. The bifunctional compound of embodiment 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the ULM target is an E3 ubiquitin ligase CDC20 (Cell Division Cycle 20) that is Anaphase Promoting Complex (APC).

Embodiment 3. The bifunctional compound of embodiment 1 or 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the target protein is selected from the group consisting of AR, ER, Hsp90, MDM2, BET, HDAC, AAK, ABL, AKT, AURKA, AURKB, BCKSK, BLK, BMP2K, BMPR1A, BTK, BUB1, CAMKK1, CDK, CHEK1, CIT, CLK1, COQ8, CSK, CSNK1, DAPK1, DDR2, EEF2K, EIF2AK, EPHA, EPHB, ERN1, FER, FGFR, FLT1, FYN, GAK, GSK3, HASPIN, HIPK1, IRAK, ITK, Kras, LATS1, LCK, LIMK, LRRK2, LYN, MAPK, MARK, MAST3, MELK, MINK1, MKNK2, NEK, NLK, NUAK1, PAK4, PDIK1L, PDK, PIK3CG, PIM2, PKMYT1, PKN3, PLK, PRAG1, PRKAA, PRKCI, PKT, RIOK2, RIPK, RPS6KA, RPS6KB, RPS6KC, SBK1, SGK3, SIK, SNRK, SRC, STK, TAOK, TBCK, TBK1, TEC, TESK2, TGFBR1, TNK, TRIB3, TRPM7, TTK, TYK2, UHMK1, ULK, WEE1, YES1, ABCF1, ACHE, ASH1L, BCL2, BRD4, CD147, CYP1B1, GCN5, HDAC, HMACR, H-PGDS, Hsp90, IDO1, IKZF, LYPLA2, MCL1, PARP, PCAF, PDE, Plek2, SLC99A1, SMARCA, STAT3, Tau, TGF-β1, WDR5, AR, AR-V7, ATOX1, CCS, CREPT, EED, ER, EZH2, MLL, MYC, NAMPT, NSD, PRMT5, SHP2, Smad3, SMARCA2, SUZ12, and β-catenin.

Embodiment 4. The bifunctional compound of any one of embodiments 1-3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the target protein is androgen receptor (AR).

Embodiment 5. The bifunctional compound of any one of embodiments 1-4, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the PTM is of formula (B):

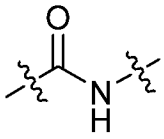
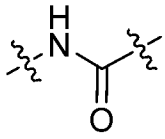


(B)

wherein

Ring B is C_3-C_8 cycloalkyl;

Ring C is C_{6-10} aryl or 5- to 10- membered heteroaryl;

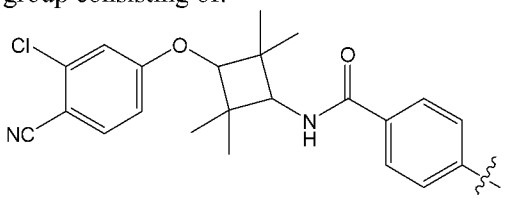
Z is  or  ;

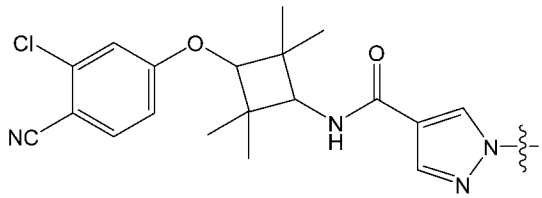
R^3 is halogen, or methoxy;

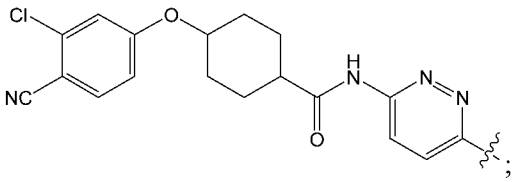
R^4 is C_1-C_6 alkyl; and

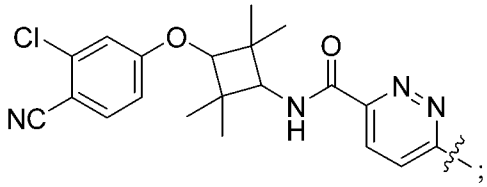
q is 0, 1, 2, 3, or 4.

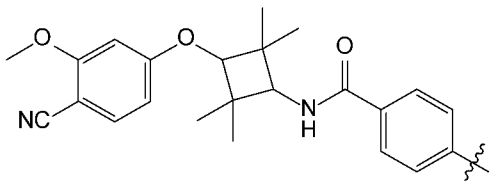
Embodiment 6. The bifunctional compound of any one of embodiments 1-5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the PTM is selected from the group consisting of:

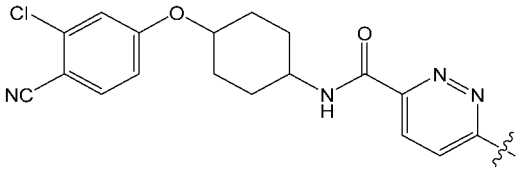
 ;

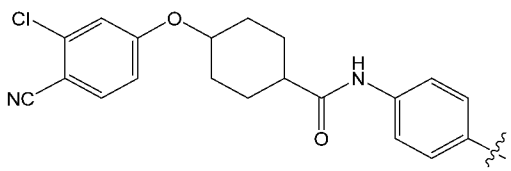
 ;

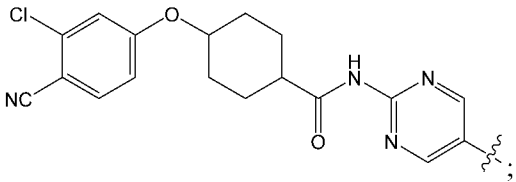
 ;

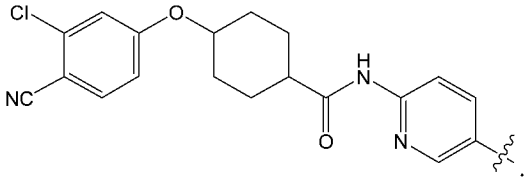
 ;

 ;

 ;

 ;

 ; and

 .

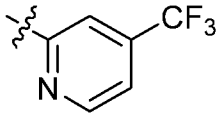
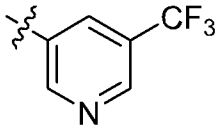
Embodiment 7. The bifunctional compound of any one of embodiments 1-6, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is C_{6-10} aryl or 5- to 6-membered heteroaryl, each of which is optionally substituted with C_1-C_6 alkyl, halogen, -OH, oxo, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), $-NO_2$, or -CN.

Embodiment 8. The bifunctional compound of any one of embodiments 1-7, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is 5- to 6-membered heteroaryl optionally substituted with C_1-C_6 alkyl, halogen, -OH, oxo, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), $-NO_2$, or -CN.

Embodiment 9. The bifunctional compound of any one of embodiments 1-8, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is optionally substituted with fluoro, chloro, -OH, -COOH, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, $-NO_2$, or -CN.

Embodiment 10. The bifunctional compound of any one of embodiments 1-9, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is 5- to 6-membered heteroaryl optionally substituted with -CH3, or $-CF_3$.

Embodiment 11. The bifunctional compound of any one of embodiments 1-10, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is pyridinyl substituted with CH3, or CF_3.

Embodiment 12. The bifunctional compound of any one of embodiments 1-11, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is  or .

Embodiment 13. The bifunctional compound of any one of embodiments 1-12, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a bond or C_1-C_6 alkylene.

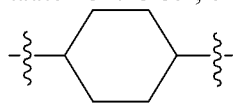
Embodiment 14. The bifunctional compound of any one of embodiments 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a bond.

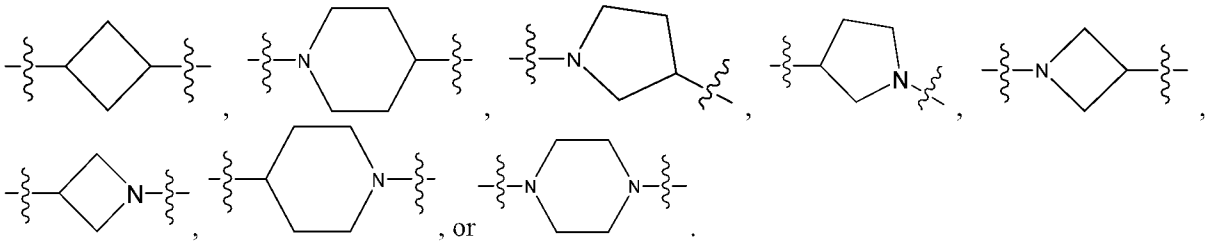
Embodiment 15. The bifunctional compound of any one of embodiments 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_1-C_6 alkylene.

Embodiment 16. The bifunctional compound of any one of embodiments 1-12, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is $C_{6\text{-}10}$ arylene or 5- to 10- membered heteroarylene.

Embodiment 17. The bifunctional compound of embodiment 16, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is phenylene, pyridinyl, pyridazinyl, or pyrimidinyl.

Embodiment 18. The bifunctional compound of any one of embodiments 1-12, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is $C_{3\text{-}8}$ cycloalkylene or 3- to 10- membered heterocyclylene.

Embodiment 19. The bifunctional compound of embodiment 18, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is, ,



Embodiment 20. The bifunctional compound of any one of embodiments 1-19, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X_1 and X_2 are each N.

Embodiment 21. The bifunctional compound of any one of embodiments 1-20, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y is S.

Embodiment 22. The bifunctional compound of any one of embodiments 1-21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein m and n are each 1.

Embodiment 23. The bifunctional compound of any one of embodiments 1-22, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein p is 2.

Embodiment 24. The bifunctional compound of any one of embodiments 1-23, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is *—A^{L1}-A^{L2}-A^{L3}-A^{L4}—**, wherein

* represents the point of attachment to the PTM,

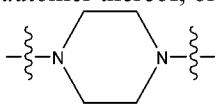
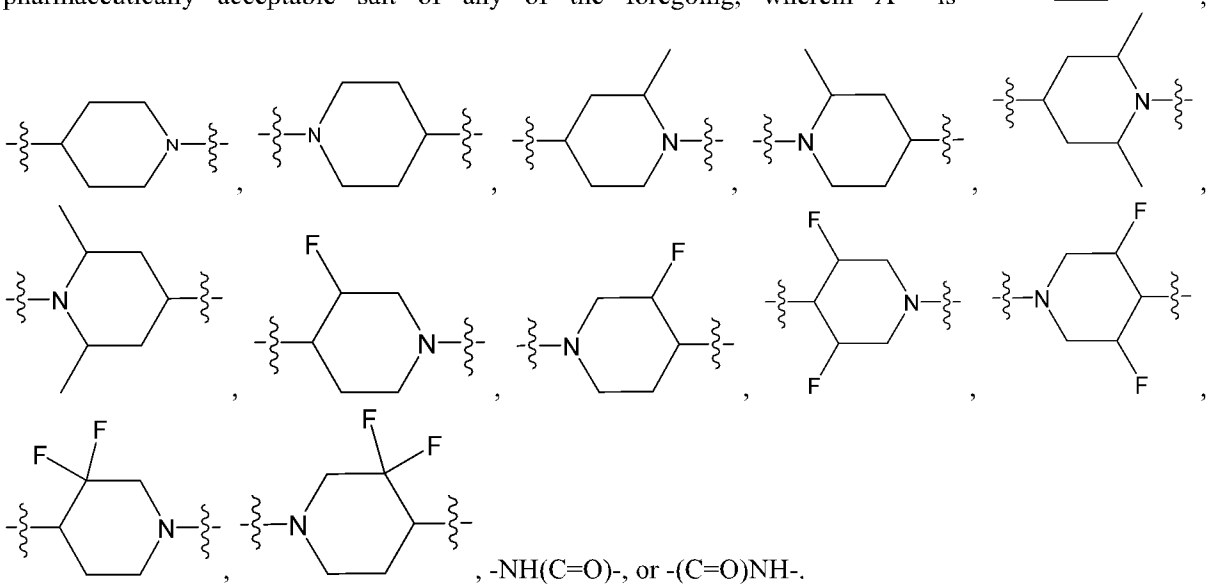
** represents the point of attachment to the ULM,

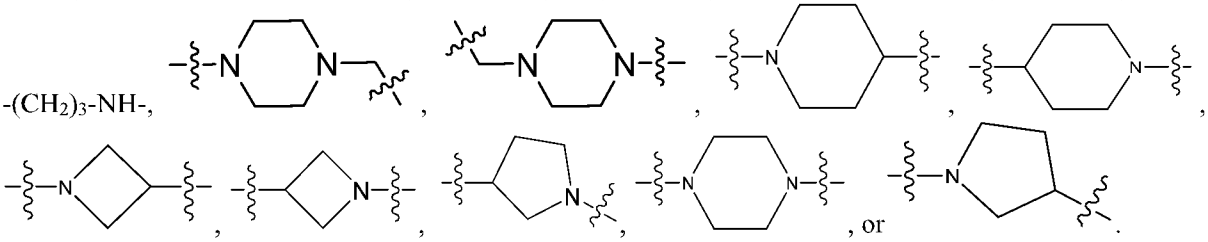
A^{L1} and A^{L4} are each independently a bond, -(C=O)-, -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, or C_{3-8} cycloalkylene;

wherein the -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, and C_{3-8} cycloalkylene of A^{L1} and A^{L4} are each independently and optionally substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen; and

A^{L2} and A^{L3} are each independently a bond, -$(CH_2)_r$-, -$(OCH_2CH_2)_s$-, -$(CH_2CH_2O)_s$-, -$(NHCH_2CH_2)_s$-, -$(CH_2CH_2NH)_s$-, wherein r and s are each an integer between 0 and 10;

wherein the -$(CH_2)_r$-, -$(OCH_2CH_2)_s$-, -$(CH_2CH_2O)_s$-, -$(NHCH_2CH_2)_s$-, and -$(CH_2CH_2NH)_s$- of A^{L2} and A^{L3} are each independently and optionally substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen.

Embodiment 25. The bifunctional compound of embodiment 24, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein A^{L1} is , , -NH(C=O)-, or -(C=O)NH-.

Embodiment 26. The bifunctional compound of embodiment 24 or 25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein A^{L4} is -(C=O)NHCH$_2$-, -CH$_2$-NH(C=O)-, -(C=O)NH(CH$_2$)$_3$-, -(CH$_2$)$_3$-NH(C=O)-, -NH(CH$_2$)$_3$-, -(CH$_2$)$_3$-NH-, , or .

Embodiment 27. The bifunctional compound of any one of embodiments 24-26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein A^{L2}-A^{L3} is a bond.

Embodiment 28. The bifunctional compound of any one of embodiments 24-26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein A^{L2}-A^{L3} is -(CH$_2$)$_r$-.

Embodiment 29. The bifunctional compound of any one of embodiments 24-26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein A^{L2}-A^{L3} is -(CH$_2$CH$_2$O)$_s$-(CH$_2$)$_r$- or -(CH$_2$)$_r$-(CH$_2$CH$_2$O)$_s$-.

Embodiment 30. A bifunctional compound selected from the compounds in Table 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

Embodiment 31. A pharmaceutical composition comprising at least one bifunctional compound according to any one of embodiments 1-30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient.

Embodiment 32. A method of treating a disease or disorder in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a bifunctional compound according to any one of embodiments 1-30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a therapeutically effective amount of a pharmaceutical composition of embodiment 31.

Embodiment 33. The method of embodiment 32, wherein disease or disorder is cancer.

Embodiment 34. The method of embodiment 32 or 33, wherein the compound, the stereoisomer or tautomer thereof, the pharmaceutically acceptable salt, or the pharmaceutical composition is administered in combination with a therapeutically effective amount of one or more additional bioactive agents.

Embodiment 35. The method of embodiment 34, wherein the additional bioactive agent is an anti-cancer agent.

Embodiment 36. The method of embodiment 35, wherein the additional bioactive agent is selected from the group consisting of a taxane, a Cox-2 inhibitor, a platinum-based antineoplastic drug, an anthracycline, a pyrimidine analog, a topoisomerase inhibitor, an mTOR inhibitor, an immune-check point inhibitor, and an agent that is used in immune oncology.

Embodiment 37. The method of any one of embodiments 33-36, further comprising administering radiation.

Embodiment 38. The method any one of embodiments 33-37, wherein the cancer is selected from the group consisting of pancreatic cancer, breast cancer, kidney cancer, bladder cancer, prostate cancer, testicular cancer, urothelial cancer, endometrial cancer, ovarian cancer, cervical cancer, renal cancer, esophageal cancer, gastrointestinal stromal tumor (GIST), multiple myeloma, cancer of secretory cells, thyroid cancer, gastrointestinal carcinoma, chronic myeloid leukemia, hepatocellular carcinoma, colon cancer, melanoma, malignant glioma, glioblastoma, glioblastoma multiforme, astrocytoma, dysplastic gangliocytoma of the cerebellum, Ewing's sarcoma, rhabdomyosarcoma, ependymoma, medulloblastoma, ductal adenocarcinoma, adenosquamous carcinoma, nephroblastoma, acinar cell carcinoma, lung cancer, non-Hodgkin's lymphoma, Burkitt's lymphoma, chronic lymphocytic leukemia, monoclonal gammopathy of undetermined significance (MGUS), plasmocytoma, lymphoplasmacytic lymphoma, and acute lymphoblastic leukemia.

General Synthetic Methods

[112] The compounds of the present disclosure may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter (such as the schemes provided in the Examples below). In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae herein.

[113] Where it is desired to obtain a particular enantiomer of a compound, this may be accomplished from a corresponding mixture of enantiomers using any suitable conventional procedure for separating or resolving enantiomers. Thus, for example, diastereomeric derivatives may be produced by reaction of a

mixture of enantiomers, *e.g.,* a racemate, and an appropriate chiral compound. The diastereomers may then be separated by any convenient means, for example by crystallization and the desired enantiomer recovered. In another resolution process, a racemate may be separated using chiral High-Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described.

[114] Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular isomer of a compound or to otherwise purify a product of a reaction.

[115] Solvates and/or polymorphs of a compound provided herein or a salt thereof are also contemplated. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and/or solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

[116] Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular isomer of a compound or to otherwise purify a product of a reaction.

EXAMPLES

[117] It is understood that the present disclosure has been made only by way of example, and that numerous changes in the combination and arrangement of parts can be resorted to by those skilled in the art without departing from the spirit and scope of the invention, as defined by the claims.

[118] The chemical reactions in the Examples described can be readily adapted to prepare a number of other compounds disclosed herein, and alternative methods for preparing the compounds of this disclosure are deemed to be within the scope of this disclosure. For example, the synthesis of non-exemplified compounds according to the present disclosure can be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, or by making routine modifications of reaction conditions, reagents, and starting materials. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the present disclosure. The following examples are intended to illustrate, but not limit, this disclosure.

[119] The following abbreviations may be used herein:

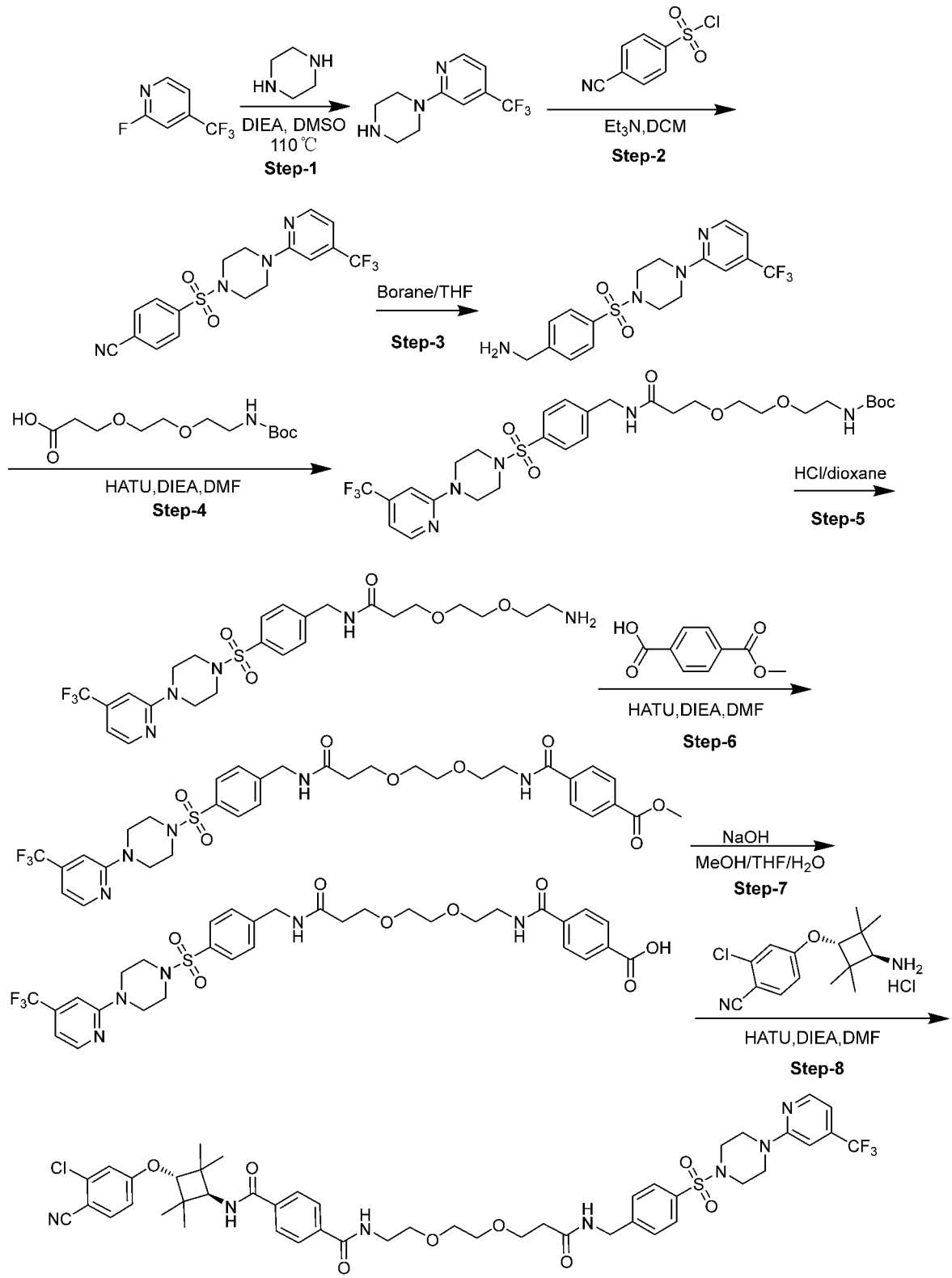
~	about
+ve or pos. ion	positive ion
Δ	heat
Ac	Acetyl
ACN	Acetonitrile
Ac_2O	acetic anhydride
aq	aqueous
AcOH	acetic acid
ATP	adenosine triphosphate
Bn	benzyl
Boc	tert-butyloxycarbonyl
BSA	bovine serum albumin
Bz	benzoyl
Calcd or Calc'd	calculated
Conc.	concentrated
d	day(s) or doublet (NMR)
DCE	dichloroethane
DCM	dichloromethane
dd	Dublet of doublets (NMR)
DEA	diethylamine
DIEA or DIPEA	diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
EA	Ethyl acetate
eq	equivalent
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethyl alcohol
FA	formic acid
FRET	fluorescence resonance energy transfer

g	gram(s)
h	hour(s)
HEPES	2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid
Hex	hexanes
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
Hz	Hertz
IPA or iPrOH	isopropyl alcohol
J	Coupling constant (NMR) in Hz
KOAc	potassium acetate
LCMS, LC-MS or LC/MS	liquid chromatography mass spectrometry
LDA	lithium diisopropylamide
LHMDS or LiHMDS	lithium hexamethyldisilazide
m	Multiplet (NMR)
M	molar (mol L^{-1})
Me	methyl
MeCN	acetonitrile
MeI	iodomethane
MeOH	methyl alcohol
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
M	mole(s)
MS	mass spectrometry
MsCl	methanesulfonyl chloride
MTBE or MtBE	methyl tert-butyl ether
m/z	mass-to-charge ratio
NaHMDS	sodium hexamethyldisilazide
NaOH	sodium hydroxide
NaOtBu	sodium tert-butoxide
nBuLi	n-butyl lithium
NCS	N-chloro succinimide
nm	Nanometer (wavelength)
NMR	nuclear magnetic resonance

P1	Product one; faster eluting isomer
P2	Product two; slower eluting isomer
PCC	Pyridinium chlorochromate, CAS Number: 26299-14-9
PE	Petroleum ether, CAS Number: 101316-46-5
PBS	phosphate buffered saline
PMB	*para*-methoxybenzyl, 4-methoxybenzyl
Pr	propyl
prep-TLC	preparative thin layer chromatography
ppm	parts per million
p-tol	para-toluoyl
rac	racemic
RP-HPLC or RPHPLC	reversed phase high performance liquid chromatography
RT or rt or r.t.	room temperature
s	singlet (NMR)
sat. or sat'd or satd	saturated
Selectfluor™	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SFC	Supercritical fluid chromatography
t	triplet (NMR)
TBS	tert-Butyldimethylsilyl
TBSCl	tert-Butyldimethylsilyl chloride
TEA	triethylamine
tert or t	tertiary
TFA	triflouroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl or trimethylsilane
tBuOH	tert-butyl alcohol
v/v	volume per volume

Example S1

Synthesis of N^1-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-N^4-(2-(2-(3-oxo-3-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)propoxy)ethoxy)ethyl)terephthalamide (Compound 1)



[120] **Step 1:** To a solution of 2-fluoro-4-(trifluoromethyl)pyridine (569.6 mg, 3.450 mmol) in DMSO (3.5 mL) were added piperazine (356.6 mg, 4.140 mmol) and DIEA (891.7 mg, 6.900 mmol) and the reaction was stirred at 110 °C for 4 h. The reaction was diluted with DCM and H_2O. The organic layer was separated, washed with H_2O and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (725.5 mg, 90.95%). ESI-MS:231.9$[M+H]^+$.

[121] **Step 2:** To a stirred solution of 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (368.7 mg 1.595 mmol) in DCM (5.0 mL) were added 4-cyanobenzenesulfonyl chloride (321.6 mg, 1.595 mmol) and Et_3N (322.8 mg, 3.190 mmol) and the reaction was stirred at room temperature for 3 h. The reaction was diluted with DCM and H_2O. The organic layer was separated, washed with H_2O and brine, and concentrated in vacuo to give a crude product which purified by column chromatography to afford 4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzonitrile (448.5 mg, 70.94%).

[122] **Step 3:** To a stirred solution of 4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzonitrile (448.5 mg 1.131 mmol) in THF (4.0 mL) was added Borane/THF(1M, 10.0 mL, 11.310 mmol) slowly at 0°C. After the addition, the reaction was stirred at room temperature for 5 h. The reaction was quenched with MeOH and the resulting mixture was stirred with HCl (1M, 1ml) at 70°C for 30 min. The reaction mixture was evaporated to remove MeOH. The residue was diluted with H_2O, adjusted to pH 8-9 with saturated $NaHCO_3$ solution, extracted with DCM. The organic layer was separated, washed with saturated $NaHCO_3$ solution, H_2O and brine, and concentrated in vacuo to give a crude product (4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (463.8 mg).

[123] **Step 4:** To a solution of 3-[(2,2-dimethyl-4-oxo-5-aza-3,8-dioxadec-10-yl)oxy]propanoic acid (138.51 mg, 0.499 mmol) in DMF (6.0 mL) was added HATU (284.88 mg, 0.749 mmol), then cooled in ice-water bath. To the reaction mixture was added Ethyldiisopropylamine (193.67 mg, 1.498 mmol). After stirred for 3 min, (4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (200.00 mg, 0.499 mmol) was added and the reaction was stirred at room temperature for 3 hr. The reaction was concentrated in vacuo, diluted with DCM and saturated NH_4Cl solution. The organic layer was separated, washed with further water, saturated $NaHCO_3$ solution, water and concentrated in vacuo. The residue was purified using silica gel column chromatography eluting with methanol in dichloroform to afford tert-butyl (2-(2-(3-oxo-3-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)propoxy)ethoxy)ethyl)carbamate (310.2 mg, 0.470 mmol, 94.14%).

[124] **Step 5:** To a flask containing tert-butyl (2-(2-(3-oxo-3-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)propoxy)ethoxy)ethyl)carbamate (310.2 mg, 0.470 mmol) was added HCl/dioxane (6.0 mL). The mixture was stirred at room temperature for 3h. The reaction was concentrated in vacuo and dried to afford 3-(2-(2-aminoethoxy)ethoxy)-N-(4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)propanamide (280.27 mg, 0.470 mmol, 100.00%).

[125] **Step 6:** To a solution of 4-(methoxycarbonyl)benzoic acid (84.68 mg, 0.470 mmol) in DMF (6.0 mL) was added HATU (268.07 mg, 0.705 mmol), then cooled in ice-water bath. To the reaction mixture was added Ethyldiisopropylamine (303.74 mg, 2.350 mmol). After stirred for 3 min, 3-(2-(2-aminoethoxy)ethoxy)-N-(4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-

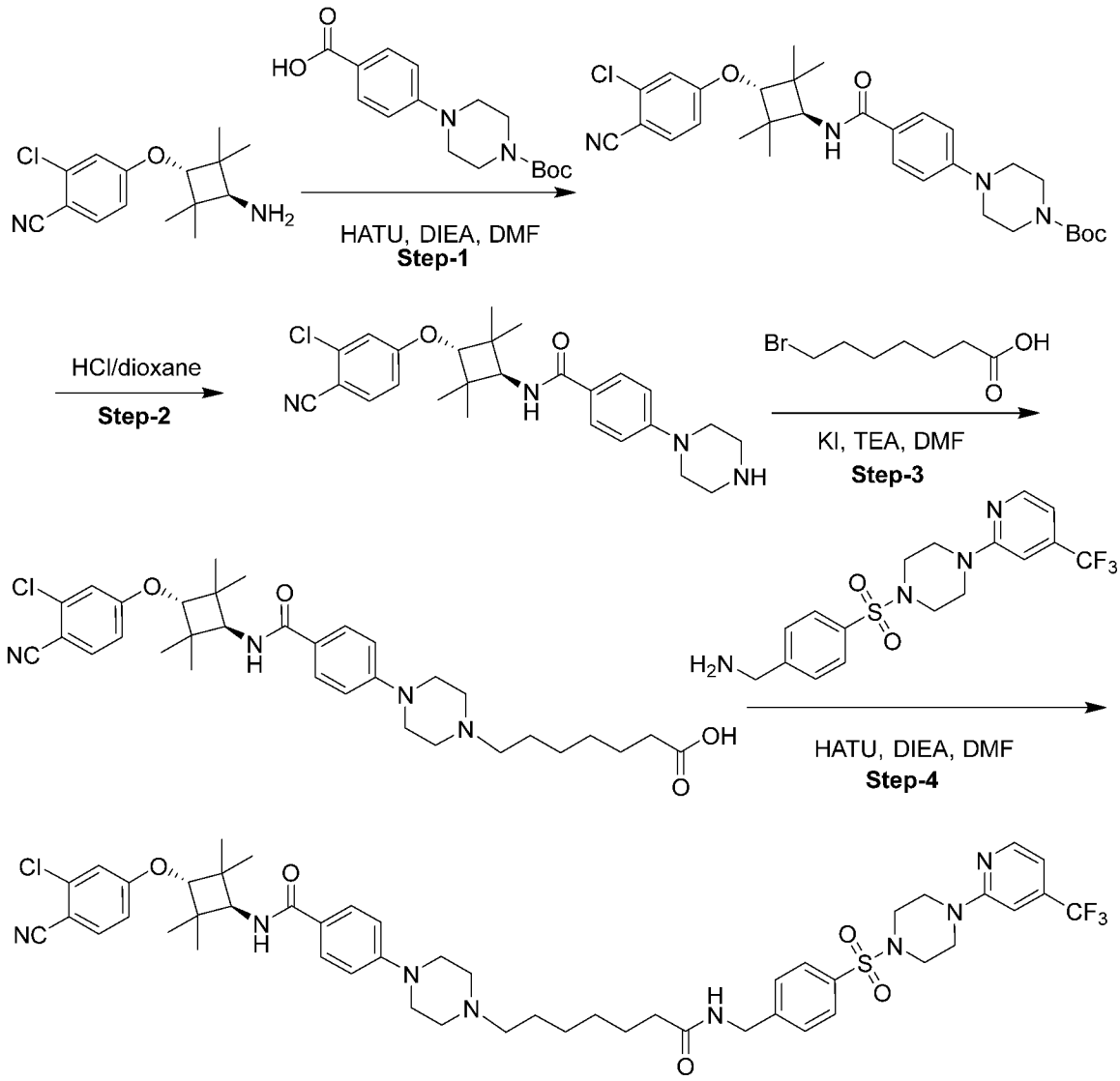
yl)sulfonyl)benzyl)propanamide (280.15 mg, 0.470 mmol) was added and the reaction was stirred at room temperature for 3 hr. The reaction was concentrated in vacuo, diluted with DCM and saturated NH_4Cl solution. The organic layer was separated, washed with further water, saturated $NaHCO_3$ solution and water, and concentrated in vacuo. The residue was purified using silica gel column chromatography eluting with methanol in dichloroform to afford methyl 4-((2-(2-(3-oxo-3-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)propoxy)ethoxy)ethyl)carbamoyl)benzoate (330.6 mg, 0.458 mmol, 97.46%).

[126] **Step 7:** To a solution of 4-((2-(2-(3-oxo-3-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)propoxy)ethoxy)ethyl)carbamoyl)benzoate (100.0 mg, 0.139 mmol) in MeOH (1.0 mL)/THF (1.0 mL)/H_2O (0.5 mL) was added NaOH (27.71 mg, 0.693 mmol) and the reaction was stirred at room temperature for overnight. The reaction mixture was ajusted to pH 3-4 with HCl (aq. 1M). The resulting mixture was concentrated in vacuo, diluted with EA and water. The organic layer was separated, washed with further water and saturated NaCl solutions, dried by anhydous Na_2SO_4 and concentrated in vacuo to afford 4-((2-(2-(3-oxo-3-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)propoxy)ethoxy)ethyl)carbamoyl)benzoic acid (81.2 mg, 0.115 mmol, 82.81%).

[127] **Step 8:** To a solution of 4-((2-(2-(3-oxo-3-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)propoxy)ethoxy)ethyl)carbamoyl)benzoic acid (81.2 mg, 0.115 mmol) in DMF (1.5 mL) was added HATU (65.44 mg, 0.172 mmol), then cooled in ice-water bath. To the reaction mixture was added Ethyldiisopropylamine (59.45 mg, 0.460 mmol). After stirred for 3 min, 4-((1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile hydrochloride (36.17 mg, 0.115 mmol) was added and the reaction was stirred at room temperature for 3 hr. The reaction was concentrated in vacuo, diluted with DCM and saturated NH_4Cl solution. The organic layer was separated, washed with further water, saturated $NaHCO_3$ solution and water, and concentrated in vacuo. The residue was purified by pre-TLC(methanol in EA) to afford N^1-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-N^4-(2-(2-(3-oxo-3-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)propoxy)ethoxy)ethyl)terephthalamide **(Compound 1**, 57.0 mg, 0.059 mmol, 51.30%). ESI-MS: 967.2$[M-H]^-$, 968.2、969.2$[M+H]^+$.

Example S2

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperaz-in-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 2)



[128] **Step 1:** To a solution of 4-((1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile (25 mg, 1 eq) in DMF (2 mL) were added 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)benzoic acid (28 mg, 1 eq), HATU (68 mg, 2 eq), and DIEA (35 mg, 3 eq), and the reaction was stirred at room temperature for 6 hours. TLC showed a new spot was observed, and no starting material remained. The reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (eluent: PE:EA=1:1)to afford tert-butyl 4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazine-1-carboxylate (45 mg). ESI- MS: 564.8 $[M-H]^-$.

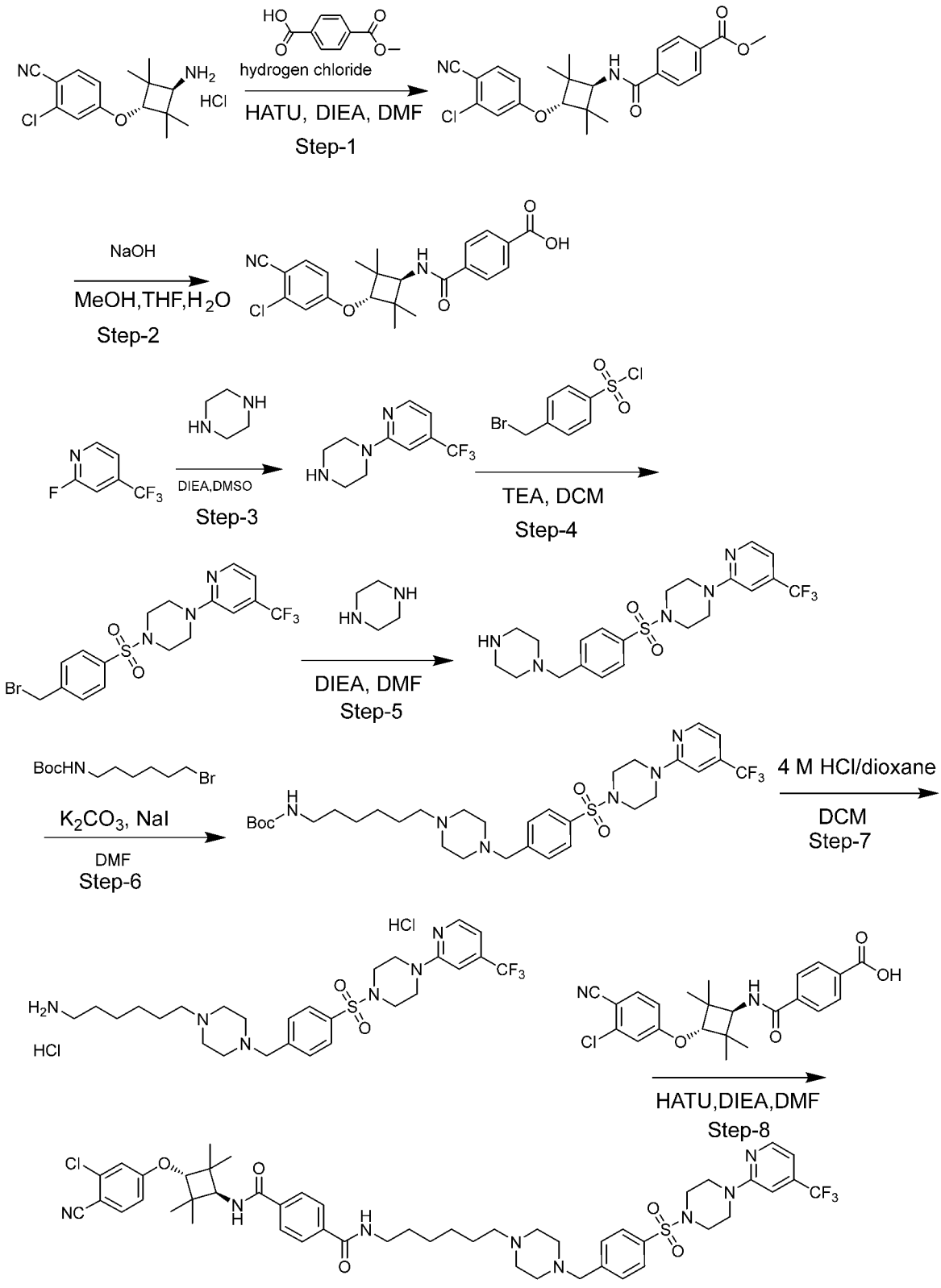
[129] **Step 2:** A solution of 4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazine-1-carboxylate (40 mg, 1 eq) in HCl/dioxane (3 mL) was stirred at room temperature for 3 hours. TLC showed new spot was observed, and no starting material remained. The reaction mixture was concentrated in vacuo to afford N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benzamide (60 mg) as a white solid.

[130] **Step 3:** To a solution of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benzamide (20 mg, 1 eq) in DMF (3 mL) were added 7-bromoheptanoic acid (9 mg, 1 eq), TEA (13 mg, 3 eq), and KI (8 mg, 1 eq), the reaction was stirred at 70 °C for 16 hours. TLC showed new spot was observed, and no starting material remained. The reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=10:1) to afford 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbam oyl)phenyl)piperazin-1-yl)heptanoic acid (10 mg). ESI-MS: 594.8 $[M+H]^+$.

[131] **Step 4:** To a solution of 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (10 mg, 1 eq) in DMF (3 mL) were added (4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (7 mg, 1 eq), HATU (20 mg, 3 eq), and DIEA (11 mg, 5 eq), and the reaction was stirred at room temperature for 3 hours. TLC showed new spot was observed, and no starting material remained. The reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=15:1) to give crude product, then the crude product was purified by preparative TLC (DCM: MeOH=10:1) to afford N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperaz-in-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 2**, 3.2 mg). ESI-Ms: 976.5 $[M+H]^+$.

Example S3

Synthesis of N^1-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-N^4-(6-(4-(4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)piperazin-1-yl)hexyl)terephthalamide (Compound 3)



[132] **Step 1:** To a solution of 4-((1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile (50 mg, 1.0 eq.) in DMF (1 mL) was added 4-(methoxycarbonyl)benzoic acid (62.8 mg, 1.0 eq.), HATU (90.4 mg, 1.2 eq.), and DIEA (61.4 mg, 3.0 eq.) at 0-5 ^{0}C, and the yellow mixture was stirred at r.t. for 2 h. TLC (EA/PE=1/5, Rf=0.5) showed the reactants were consumed, and mainly a new spot was

present. The mixture was quenched with water (10 mL), and lots of solid appeared, which was filtered, washed with water. Then, the cake was dissolved with EA (20 mL), dried over Na_2SO_4, and concentrated in vacuo to afford methyl 4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)benzoate (64 mg, white solid, crude).

[133] **Step 2:** To a solution of methyl 4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)benzoate (64 mg, 1.0 eq.) in MeOH (1 mL) and THF (1 mL) was added NaOH (29.1 mg, 5.0 eq.) and H_2O (1 mL) at 0-5 ^{0}C. The yellow mixture was stirred at r.t. for 1 h. TLC (EA/PE=1/5, Rf=0) showed the starting material was consumed, and mainly a new spot was present. The mixture was concentrated in vacuo, water was added (10 mL), the pH was adjusted to ~3 with 1 M HCl. Solid appeared, which was filtered and washed with water (2 mL*2). Then, the cake was dissolved with MeOH/DCM (1/15, 16 mL), dried over Na_2SO_4, and concentrated in vacuo to afford 4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)benzoic acid (64 mg, white solid, crude).

[134] **Step 3:** To a solution of 2-fluoro-4-(trifluoromethyl)pyridine (100 mg, 1.0 eq.) in DMSO (1 mL) was added DIEA (156 mg, 2.0 eq.) and piperazine (1 mL) at r.t., and the yellow mixture was stirred at 110 ^{0}C for 3 h. TLC (EA/PE=1/5, Rf=0.35) showed the starting material was consumed, and mainly a new spot was present. The mixture was quenched with water (15 mL), extracted with DCM (15 mL*4), dried over Na_2SO_4, and concentrated in vacuo and oil pump to get 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (110 mg, yellow semi-solid, crude).

[135] **Step 4:** To a solution of 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (110 mg, 1.0 eq.) in DCM (1 mL) was added TEA (121.2 mg, 2.5 eq.) and 4-(bromomethyl)benzenesulfonyl chloride (194.2 mg, 1.5 eq.) at 0-5 ^{0}C. The yellow mixture was stirred at r.t. for 1 h. TLC (EA/PE=1/2, Rf=0.2) showed the starting material was consumed, and mainly a new spot was present. The mixture was concentrated in vacuo. The residue was directly purified with pre-TLC (EA/PE=1/2) to get 1-((4-(bromomethyl)phenyl)sulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazine (90 mg, light yellow solid). LCMS: [M+H$^+$] 463.6.

[136] **Step 6:** To a solution of 1-((4-(bromomethyl)phenyl)sulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazine (90 mg, 1.0 eq.) in DMF (1 mL) was added piperazine (25 mg, 1.5 eq.) and DIEA (62.7 mg, 2.5 eq.) at r.t., and the yellow mixture was stirred at r.t. for 2 h. TLC (EA/PE=1/2, Rf=0) showed the starting material was consumed, and mainly a new spot was present. The mixture was quenched with water (10 mL). A solid appeared, which was filtered and washed with water (5 mL*1). The cake was dissolved with DCM (10 mL), dried over Na_2SO_4, and concentrated in vacuo to afford 1-((4-(piperazin-1-ylmethyl)phenyl)sulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazine (100 mg, off-white solid, crude).

[137] **Step 7:** To a solution of 1-((4-(piperazin-1-ylmethyl)phenyl)sulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazine (25 mg, 1.0 eq.) in DMF (1 mL) was added tert-butyl (6-bromohexyl)carbamate (22 mg, 1.5 eq.), K_2CO_3 (11 mg, 1.5 eq.), and NaI (4 mg, 0.5 eq.) at r.t. The yellow

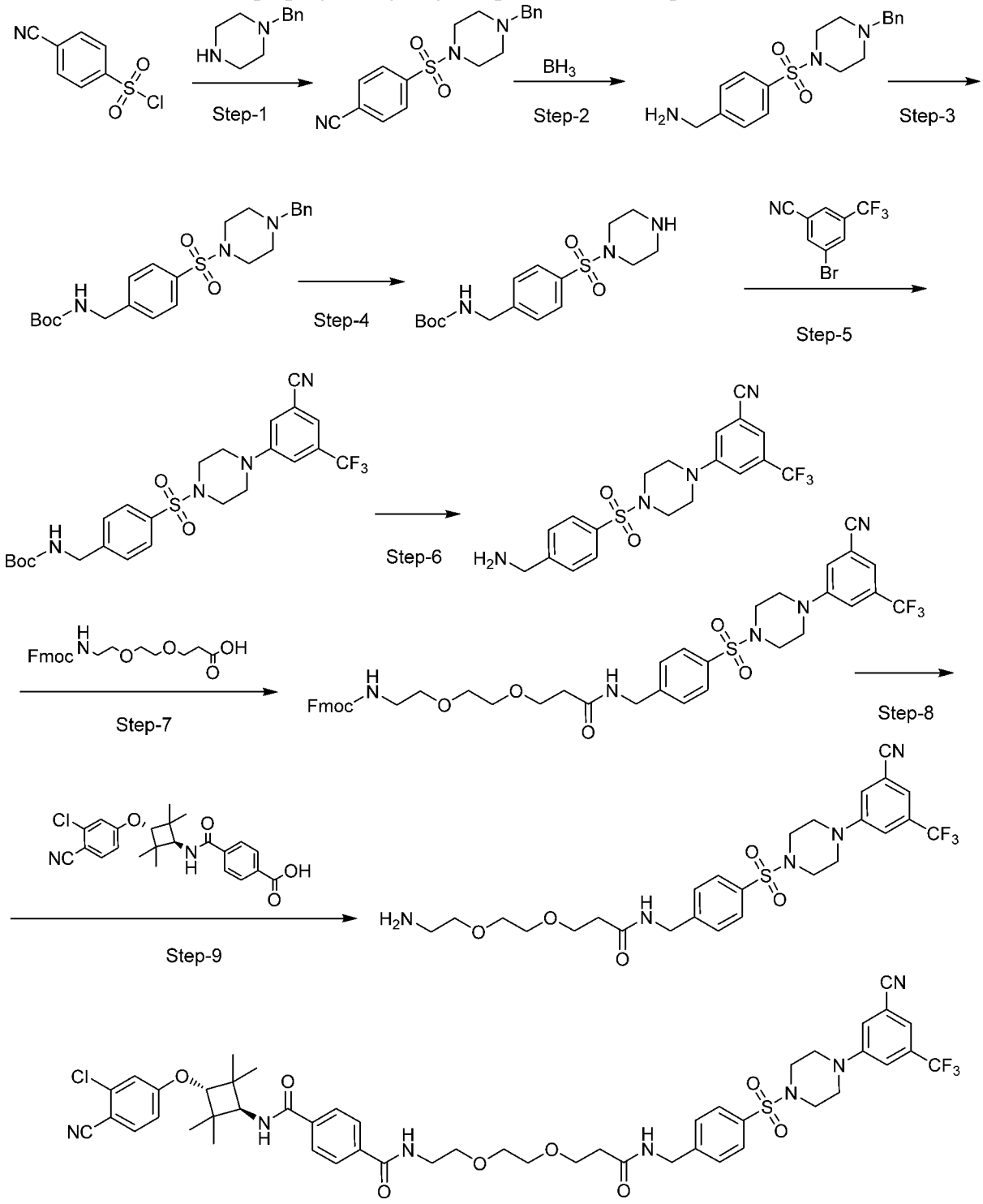
mixture was stirred at 70 ^{0}C for 6 h. TLC (EA/PE=1/1, Rf=1.5) showed the starting material still remained, and several spots were present. The mixture was concentrated in oil pump. The residue was directly purified with pre-TLC (MeOH/DCM=1/20) to afford tert-butyl (6-(4-(4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)piperazin-1-yl)hexyl)carbamate (32 mg, white solid). LCMS: [M+H$^+$] 668.7.

[138] **Step 8:** To a solution of tert-butyl (6-(4-(4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)piperazin-1-yl)hexyl)carbamate (32 mg, 1.0 eq.) in DCM (0.5 mL) was added 4 M HCl/dioxane (0.5 mL) at 0-5 ^{0}C. The yellow mixture was stirred at r.t. for 6 h. TLC (MeOH/DCM=1/10, Rf=0.02) showed the starting material was consumed, and mainly a new spot was present. The mixture was concentrated in vacuo to afford 6-(4-(4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)piperazin-1-yl)hexan-1-amine • 2 HCl (38 mg, yellow solid, crude).

[139] **Step 9:** To a solution of 6-(4-(4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)piperazin-1-yl)hexan-1-amine • 2 HCl (22.5 mg, 1.5 eq.) in DMF (1 mL) was added 4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)benzoic acid (10 mg, 1.0 eq.), HATU (13.4 mg, 1.5 eq.), and DIEA (15 mg, 5.0 eq.) at 0-5 ^{0}C. The yellow mixture was stirred at r.t. for 3 h. TLC (MeOH/DCM=1/10, Rf=0.3) showed 4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)benzoic acid was consumed and some starting material remained, but mainly a new spot was present. The mixture was quenched with water (10 mL), extracted with DCM (10 mL*5), dried over Na_2SO_4, concentrated in vacuo. The residue was directly purified with pre-TLC (MeOH/DCM=1/12) to get N^1-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-N^4-(6-(4-(4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)piperazin-1-yl)hexyl)terephthalamide (**Compound 3**, 8 mg, off-white solid). LCMS: [M+H$^+$] 976.3.

Example S4

Synthesis of N^1-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-N^4-(2-(2-(3-((4-((4-(3-cyano-5-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)amino)-3-oxopropoxy)ethoxy)ethyl)terephthalamide (Compound 4)



[140] **Step 1:** To a solution of 4-cyanobenzenesulfonyl chloride (100 mg, 1.0eq) in DCM (2 ml) was added 1-benzylpiperazine (111 mg, 1.05eq), Et_3N (130 mg, 2.5eq). The reaction was stirred at RT overnight. The mixture was purified by column chromatography on silica gel eluted with PE/EA (5:1~3:1) to give 4-((4-benzylpiperazin-1-yl)sulfonyl)benzonitrile. ESI-MS: 342.1$[M+H]^+$.

[141] **Step 2:** To a solution of 4-((4-benzylpiperazin-1-yl)sulfonyl)benzonitrile (135 mg,1.0 eq) in THF (2 ml) was added slowly BH_3/THF (1 M,1.6 ml,4.0 eq) at -10°C. Then stirred at RT for 3h. The reaction mixture was quenched by the addition of MeOH, stirred at RT for 5min, added HCl aqueous solution (0.5 ml), stirred at 70°C for 30min, the mixture was cooled to RT, $NaHCO_3$ aqueous solution was added to adjust to aqueous pH=8-9. The combined aqueous layers were extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by pre-TLC (DCM:MeOH =10:1) to afford (4-((4-benzylpiperazin-1-yl)sulfonyl)phenyl)methanamine (49 mg) ESI-MS: 346.1$[M+H]^+$.

[142] **Step 3:** To a solution of (4-((4-benzylpiperazin-1-yl)sulfonyl)phenyl)methanamine (49 mg,1.0 eq) in DCM (2 ml) was added TEA (29 mg, 2.0 eq), $(Boc)_2O$ (38 mg,1.2eq). The reaction was stirred at RT for 2h. The reaction mixture was quenched by the addition of NaCl aqueous solution, extracted with DCM, dried over $MgSO_4$ and concentrated to give crude tert-butyl (4-((4-benzylpiperazin-1-yl)sulfonyl)benzyl)carbamate (61 mg), ESI-MS: 446.2[M+H]+.

[143] **Step 4:** To a solution of tert-butyl (4-((4-benzylpiperazin-1-yl)sulfonyl)benzyl)carbamate (61 mg, 1.0 eq) in MeOH (2 ml) was added Raney Ni. The reaction was stirred under H_2 at RT overnight. The mixture was filtered through a Celite pad, and the filtrate was concentrated to give crude product. The crude product was purified by pre-TLC (DCM:MeOH=10:1) to afford tert-butyl (4-(piperazin-1-ylsulfonyl)benzyl)carbamate (12 mg), ESI-MS: 356.2$[M+H]^+$.

[144] **Step 5:** A solution of tert-butyl (4-(piperazin-1-ylsulfonyl)benzyl)carbamate (12 mg, 1.0 eq), 3-bromo-5-(trifluoromethyl)benzonitrile(13 mg, 1.5 eq), Ruphos Pd(3 mg, 0.1 eq), Cs_2CO_3(22 mg, 2.0 eq) in toluene (2 ml) was stirred under N_2 at 90 °C overnight. The solvent was removed. DCM and H_2O were added, the organic layers were washed with NaCl aqueous solution for 2 times, then dried over $MgSO_4$ and concentrated. The crude product was purified by pre-TLC (PE:EA=2:1)to afford tert-butyl (4-((4-(3-cyano-5-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)carbamate (11 mg), ESI-MS: 525.1[M+H]+.

[145] **Step 6:** To a solution of tert-butyl (4-((4-(3-cyano-5-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)carbamate (11 mg) in 1,4-dioxane (1 ml) was added HCl/dioxane (1 ml). The reaction was stirred at RT for 3h. The mixture was evaporated to afford 3-(4-((4-(aminomethyl)phenyl)sulfonyl)piperazin-1-yl)-5-(trifluoromethyl)benzonitrile (9 mg), ESI-MS: 425.1 [M+H]+.

[146] **Step 7:** A solution of 3-(4-((4-(aminomethyl)phenyl)sulfonyl)piperazin-1-yl)-5-(trifluoromethyl)benzonitrile (9 mg, 1.0 eq), 1-(9H-fluoren-9-yl)-3-oxo-2,7,10-trioxa-4-azatridecan-13-oic

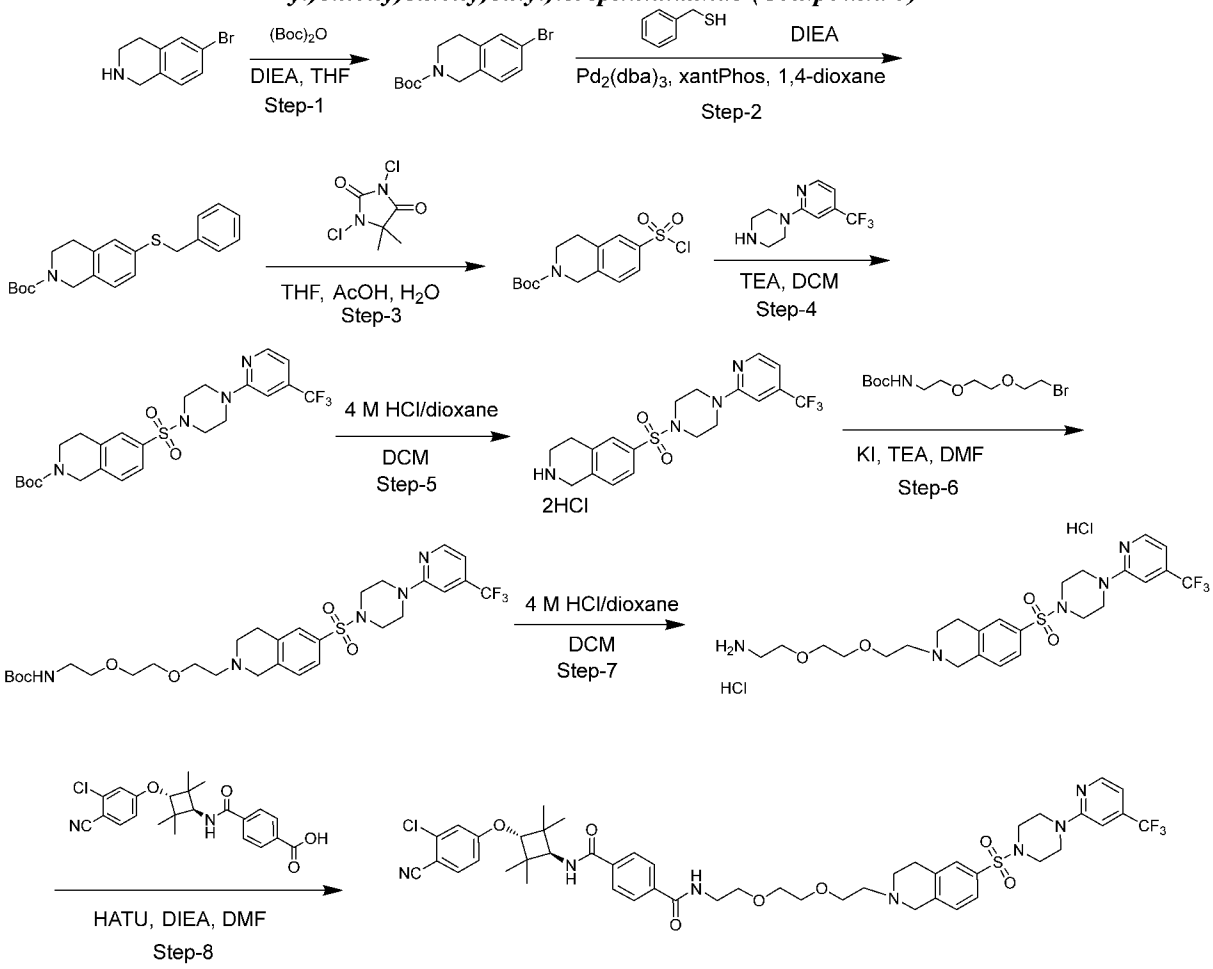
acid (9.3 mg, 1.1 eq), HATU (12.1 mg, 1.5 eq), DIEA (11 mg, 4.0 eq) in DMF (1.5 ml) was stirred at RT for 1h. DCM and H_2O were added, the organic layers were washed with NaCl aqueous solution for one time, dried over $MgSO_4$ and concentrated. The crude product was purified by pre-TLC (DCM:MeOH=20:1) to afford (9H-fluoren-9-yl)methyl (2-(2-(3-((4-((4-(3-cyano-5-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)amino)-3-oxopropoxy)ethoxy)ethyl)carbamate (14 mg) ESI-MS: 806.2[M+H]+.

[147] Step 8: To a solution of (9H-fluoren-9-yl)methyl (2-(2-(3-((4-((4-(3-cyano-5-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)amino)-3-oxopropoxy)ethoxy)ethyl)carbamate (14 mg) in DMF (1 ml) was added morpholine (0.5 ml). The mixture was stirred at RT for 40 min, then concentrated to afford 3-(2-(2-aminoethoxy)ethoxy)-N-(4-((4-(3-cyano-5-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)propanamide (10 mg), ESI-MS: 584.2[M+H]+.

[148] Step 9: A solution of 3-(2-(2-aminoethoxy)ethoxy)-N-(4-((4-(3-cyano-5-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)propanamide (10 mg, 1.0 eq), 4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)benzoic acid (7.3 mg, 1.0 eq), HATU (9.8 mg, 1.5 eq), DIEA (6.7 mg, 3.0 eq) in DMF (1.5ml) was stirred at RT for 1h. Added DCM and H2O, the organic layers was washed with NaCl aqueous solution for one time, dried over $MgSO_4$ and concentrated. The crude product was purified by pre-TLC (DCM: MeOH =10:1) to afford the product N^1-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-N^4-(2-(2-(3-((4-((4-(3-cyano-5-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)amino)-3-oxopropoxy)ethoxy)ethyl)terephthalamide (**Compound 4**, 12 mg) as a white solid. ESI-MS: 992.3[M+H]+.

Example S5

Synthesis of N^1-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-N^4-(2-(2-(2-(6-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethoxy)ethoxy)ethyl)terephthalamide (Compound 5)



[149] **Step 1:** To a solution of 6-bromo-1,2,3,4-tetrahydroisoquinoline (500 mg, 1.0 eq.) in THF (10 mL) was added DIEA (456 mg, 1.5 eq.), $(Boc)_2O$ (617 mg, 1.2 eq.) at r.t., the yellow mixture was stirred at r.t. for 1.5 h. TLC (EA/PE=1/10, Rf=0.5) showed starting material was consumed, and reaction contained a mainly new spot. The mixture was concentrated in vacuo. The residue was directly purified with silica gel. Chromatography column eluted EA in PE 10% to get tert-butyl 6-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate (740 mg, colorless oil).

[150] **Step 2:** To a solution of tert-butyl 6-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate (640 mg, 1.0 eq.) in 1,4-dioxane (10 mL) was added phenylmethanethiol (306 mg, 1.2 eq.), DIEA (530.9 mg, 2.0 eq.), $Pd_2(dba)_3$ (94 mg, 0.05 eq.), xantPhos (119 mg, 0.1 eq.) at r.t., the yellow mixture was exchanged with N_2 for 3 times and stirred at 100 °C for 5 h under N_2 atmosphere. TLC (EA/PE=1/10, Rf=0.35) showed starting materials were consumed, reaction had mainly a new spot. The mixture was filtered, washed with

EA (10 mL×2), the organic mixture was concentrated in vacuo. The residue was purified with silica gel. Chromatography column eluted EA in PE 15% to get tert-butyl 6-(benzylthio)-3,4-dihydroisoquinoline-2(1H)-carboxylate (770 mg, yellow oil). ESI-MS: 255.9 $[M+H-100]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ7.29-7.23 (m, 6H), 7.14-7.12 (dd, J = 8.0 Hz, J = 0.0 Hz,1H), 7.00 (d, J = 8.0 Hz, 1H), 4.52 (s, 2H), 4.09 (s, 2H), 3.61 (t, J = 6.0 Hz,, 2H), 2.75 (t, J = 6.0 Hz, 2H), 1.49 (s, 9H).

[151] **Step 3:** To a solution of tert-butyl 6-(benzylthio)-3,4-dihydroisoquinoline-2(1H)-carboxylate (200 mg, 1.0 eq.) in THF (3 mL), AcOH (0.05 mL), H_2O (0.1 mL) was slowly added 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (332 mg, 3.0 eq.) at 0-5 °C, the yellow mixture was stirred at 0-5 °C for 3 h. TLC (EA/PE=1/5, Rf=0.5) showed starting material was consumed, reaction had mainly a new spot. The mixture was added sat. $NaHCO_3$ (10 mL), extracted with EA (20 mL×2), dried over Na_2SO_4, concentrated in vacuo. The residue was purified with silica gel. Chromatography column eluted EA in PE 10-15% to get tert-butyl 6-(chlorosulfonyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (120 mg, white solid).

[152] **Step 4:** To a solution of tert-butyl 6-(chlorosulfonyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (120 mg, white solid) (120 mg, 1.0 eq.) in DCM (3 mL) was added 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (92 mg, 1.1 eq.), TEA (92 mg, 1.0 eq.) at 0-5 ^{0}C. The yellow mixture was stirred at r.t. for 2 h. TLC (EA/PE=1/2, Rf=0.45) showed starting material was consumed, and reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was directly purified with silica gel. Chromatography column eluted EA in PE 20% to get tert-butyl 6-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (175 mg, light yellow solid).

[153] **Step 5:** To a solution of tert-butyl 6-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (175 mg, 1.0 eq.) in DCM (0.5 mL) was dropped 4 M HCl/dioxane (1.0 mL) at 0-5 ^{0}C, the yellow mixture was stirred at r.t. for 2.5 h. TLC (EA/PE=1/2, Rf=0.0) showed start material was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo to get 6-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline (190 mg, yellow solid, crude).

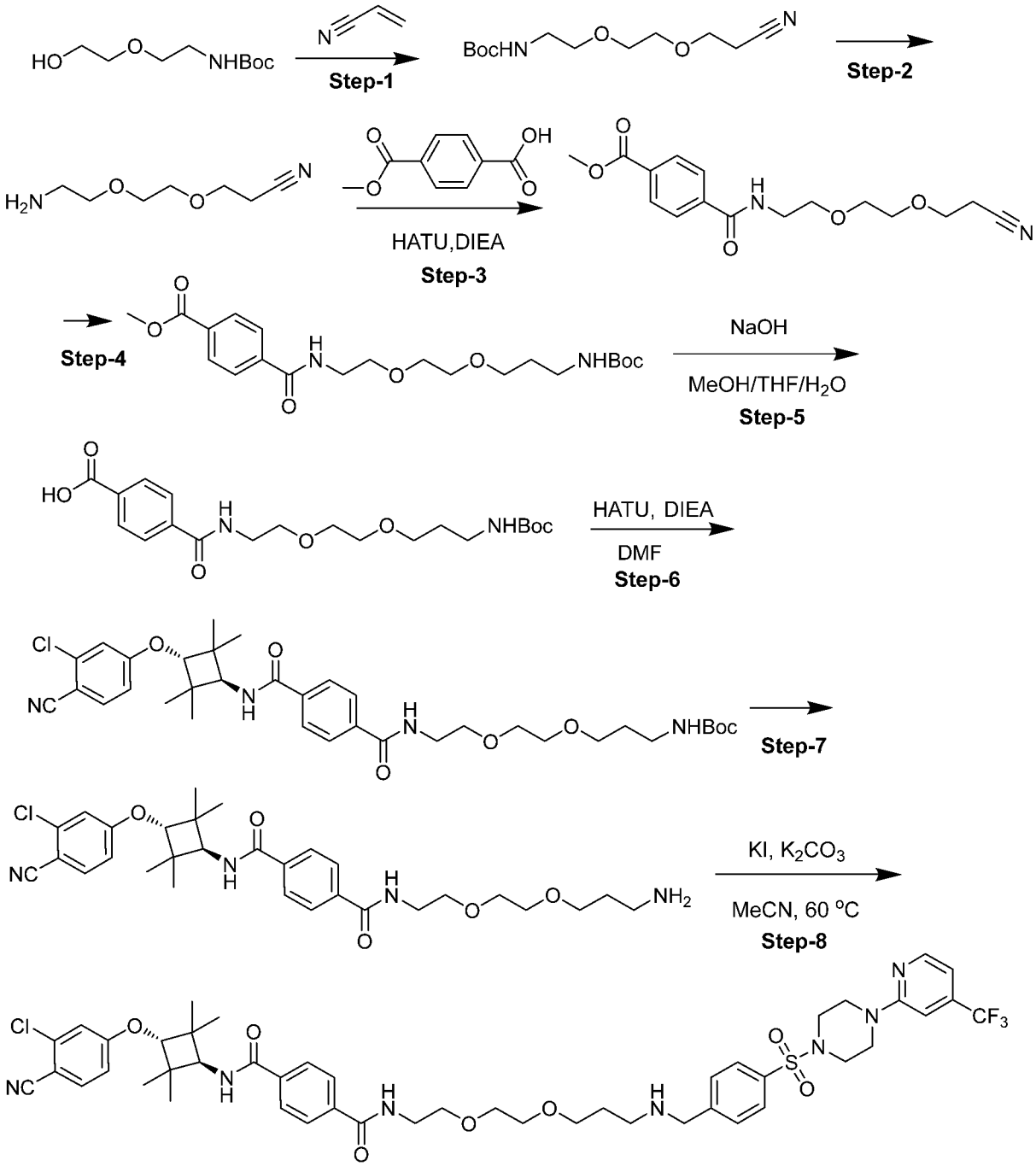
[154] **Step 6:** To a solution of 6-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline (50 mg, 1.0 eq.) in DMF (1 mL) was added tert-butyl (2-(2-(2-bromoethoxy)ethoxy)ethyl)carbamate (50 mg, 1.0 eq.), KI (1.5 mg, 0.1 eq.), TEA (47 mg, 5.0 eq.) at r.t. , the yellow mixture was stirred at r.t. for 2.5 h. TLC (MeOH/DCM=1/10, Rf=0.8) showed start material still remained, reaction had mainly a new spot. The mixture was filtered, concentrated in vacuo and oil pump. The residue was directly purified with pre-TLC (MeOH/DCM=1/30) to get tert-butyl tert-butyl (2-(2-(2-(6-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethoxy)ethoxy)ethyl)carbamate (28 mg, yellow oil). ESI-MS: 657.7 $[M+H]^+$.

[155] **Step 7:** To a solution of tert-butyl tert-butyl (2-(2-(2-(6-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethoxy)ethoxy)ethyl)carbamate (28 mg, 1.0 eq.) in DCM (0.5 mL) was dropped 4 M HCl/dioxane (1.0 mL) at 0-5 ^{0}C, the yellow mixture was stirred at r.t. for 3 h. TLC (MeOH/DCM=1/10, Rf=0.0) showed start material was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo to get 2-(2-(2-(6-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethoxy)ethoxy)ethan-1-amine (28 mg, light yellow solid, crude).

[156] **Step 8:** To a solution of 2-(2-(2-(6-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethoxy)ethoxy)ethan-1-amine (28 mg, 1.0 eq.) in DMF (1 mL) was added 4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)benzoic acid (28 mg, 1.0 eq.), HATU (13.3 mg, 1.5 eq.), DIEA (21.2 mg, 7.0 eq.) at 0-5 ^{0}C, the yellow mixture was stirred at r.t. for 3 h. TLC (MeOH/DCM=1/8, Rf=0.0) showed start materials were consumed, reaction had mainly a new spot. The mixture was quenched with water (5 mL), extracted with DCM (5 mL×2), dried over Na_2SO_4, concentrated in vacuo. The residue was purified with pre-TLC (MeOH/DCM=1/15) to get N^1-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-N^4-(2-(2-(2-(6-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethoxy)ethoxy)ethyl)terephthalamide (**Compound 5**, 10 mg, off-white solid). ESI-MS: 965.5 $[M+H]^+$.

Example S6

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperidin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 6)



[157] **Step 1:** To a mixture of tert-butyl (2-(2-hydroxyethoxy)ethyl)carbamate (1.025 g, 5 mmol) and acrylonitrile (530 mg, 10 mmol) in THF (10 ml) was added NaOMe (27 mg, 0.5 mmol). The reaction was stirred at 25 °C for 12h, quenched with H_2O and saturated aqueous NH_4Cl, and extracted with EA 3 times. The organic layers were combined, dried over Na_2SO_4, filtered, concentrated, purified by column chromatography on silica gel eluting with PE to PE/EA=1.5/1 to afford tert-butyl (2-(2-(2-cyanoethoxy)ethoxy)ethyl)carbamate (1.17 g) as a colorless oil.

[158] **Step 2:** To a solution of tert-butyl (2-(2-(2-cyanoethoxy)ethoxy)ethyl)carbamate (300 mg) in EA was added ethyl acetate hydrochloride (3 ml) and stirred at RT for 18h. The reaction was concentrated to afford 3-(2-(2-aminoethoxy)ethoxy)propanenitrile (226 mg) for next step.

[159] **Step 3:** To a mixture of 4-(methoxycarbonyl)benzoic acid (209 mg, 1.16 mmol), 3-(2-(2-aminoethoxy)ethoxy)propanenitrile (226 mg, 1.16 mmol), and HATU (530 mg, 1.39 mmol) in DMF was added DIEA (450 mg, 3.49 mmol) in an ice-bath. Then the reaction was stirred at RT for 2h, and purified by pre-TLC eluting with DCM/MeOH=30/1 for 2 times to afford the product methyl 4-((2-(2-(2-cyanoethoxy)ethoxy)ethyl)carbamoyl)benzoate (105 mg).

[160] **Step 4:** The atmosphere of a mixture of methyl 4-((2-(2-(2-cyanoethoxy)ethoxy)ethyl)carbamoyl)benzoate (105 mg, 0.29 mmol), Boc_2O (96.3 mg, 0.44 mmol) and Raney-Ni in MeOH was replaced with H_2 for 3 times. Then the reaction was stirred at RT under H_2 for 4h. The reaction was filtered, concentrated, and purified by pre-TLC eluting with DCM/MeOH=15/1 to afford the product methyl 4-((2,2-dimethyl-4-oxo-3,9,12-trioxa-5-azatetradecan-14-yl)carbamoyl)benzoate (64 mg).

[161] **Step 5:** To a solution of methyl 4-((2,2-dimethyl-4-oxo-3,9,12-trioxa-5-azatetradecan-14-yl)carbamoyl)benzoate (64 mg, 0.15 mmol) in THF/MeOH (1 ml/1.5 ml) was added NaOH (12.1 mg, 0.3 mmol) and H_2O (0.5 ml). The reaction was stirred at RT for 3 h. TLC indicated the reaction was completed. The mixture was acidified to pH=3-4, concentrated, and purified by pre-TLC eluting with DCM/MeOH=10/1 to afford the product 4-((2,2-dimethyl-4-oxo-3,9,12-trioxa-5-azatetradecan-14-yl)carbamoyl)benzoic acid (14mg).

[162] **Step 6:** To a solution of ((1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile hydrochloride (10.7 mg, 34.15 μmol), 4-((2,2-dimethyl-4-oxo-3,9,12-trioxa-5-azatetradecan-14-yl)carbamoyl)benzoic acid (14 mg, 34.15μmol) and HATU (15.6 mg, 40.98 μmol) in DMF (0.5 ml) was added DIEA (13.2 mg, 102.44 μmol) at ice-bath. Then the reaction was stirred at RT for 2h, and purified by pre-TLC eluting with DCM/MeOH=30/1 for 2 times to afford the product tert-butyl (3-(2-(2-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)benzamido)ethoxy)ethoxy)propyl)carbamate (10 mg).

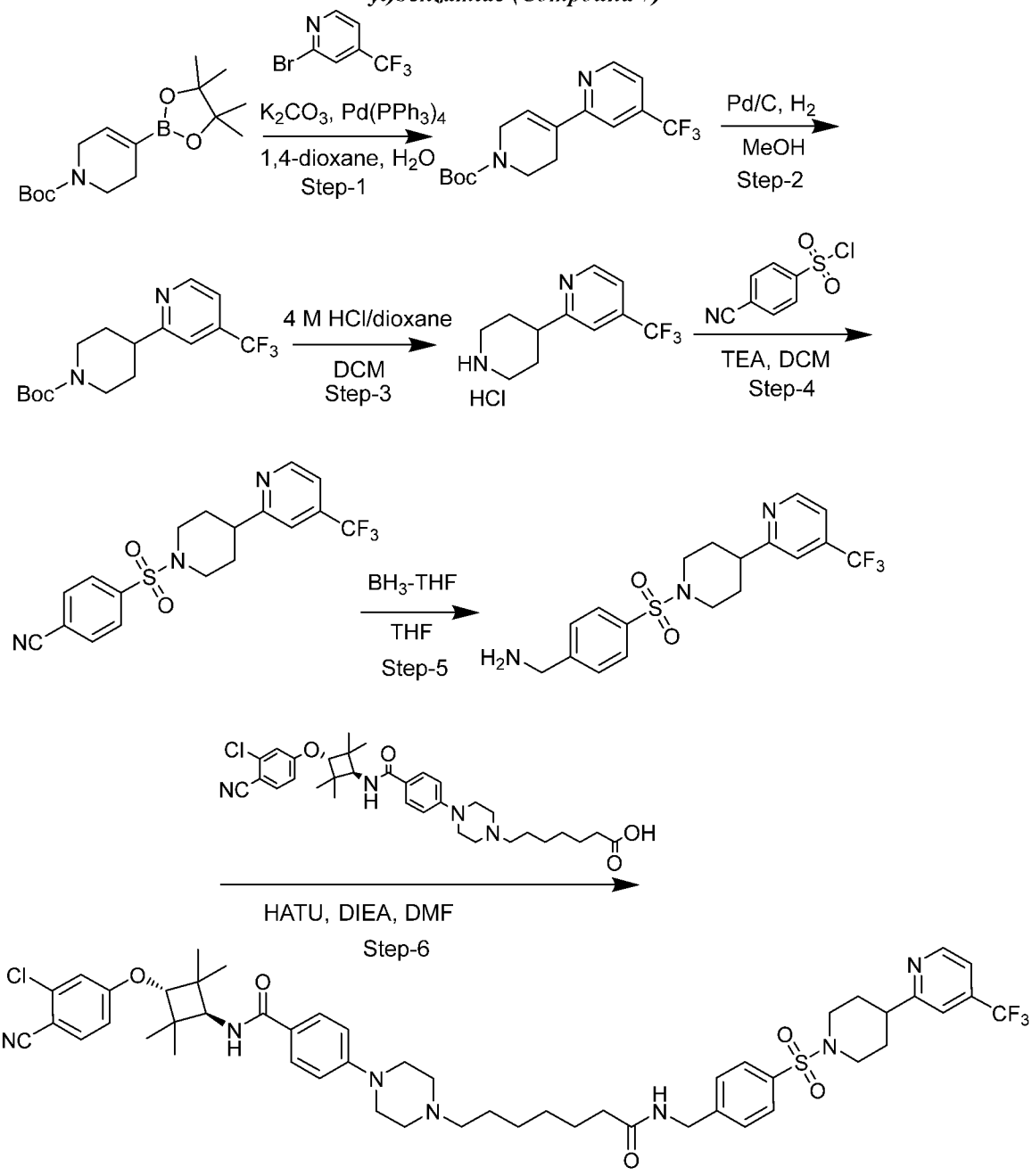
[163] **Step 7:** To a solution of tert-butyl (3-(2-(2-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)benzamido)ethoxy)ethoxy)propyl)carbamate (10 mg) in dioxane (0.5 ml) was added 1,4-dioxane hydrochloride (1 ml) and stirred at RT for 3h. The reaction was concentrated to afford N1-(2-(2-(3-aminopropoxy)ethoxy)ethyl)-N4-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)terephthalamide (10 mg) for next step.

[164] **Step 8:** A solution of ((4-(bromomethyl)phenyl)sulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazine (7.7 mg, 16.49μmol), N^1-(2-(2-(3-aminopropoxy)ethoxy)ethyl)-N^4-((1r,3r)-3-(3-chloro-4-

cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)terephthalamide (10 mg, 16.49μmol), KI (1 mg) and K_2CO_3 (6.9 mg, 49.47 μmol) in ACN (1.5 ml) was stirred at RT for 1h. Then the reaction was heated at 60 °C for 2h. Next, the reaction was concentrated and purified by pre-TLC eluting with DCM/MeOH=10/1 to afford *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperidin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 6** 8.1 mg). ESI-MS = 954.4, $[M+H]^+$.

Example S7

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperidin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 7)



[165] **Step 1:** To a solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.23 g, 1.5 eq.) in 1,4-dioxane (7 mL) was added 2-bromo-4-(trifluoromethyl)pyridine (600 mg, 1.0 eq.), K_2CO_3 (732.6 mg, 2.0 eq.), $Pd(PPh_3)_4$ (153.3 mg, 0.05 eq.), H_2O (1.75 mL) at r.t., the yellow mixture was stirred at 95 ^{0}C for o/n. TLC (EA/PE=1/5, Rf=0.25) showed starting materials were consumed, the reaction had mainly a new spot. The mixture was added water (20 mL), extracted with EA (20 mL×2), dried over Na_2SO_4, concentrated in vacuo. The residue was purified with silica gel. Chromatography column eluted EA in PE 20% to get tert-butyl 4-(trifluoromethyl)-3',6'-dihydro-[2,4'-bipyridine]-1'(2'H)-carboxylate (860 mg, colorless oil). ESI-MS: 272.8 $[M+H-56]^+$.

[166] **Step 2:** To a solution of tert-butyl 4-(trifluoromethyl)-3',6'-dihydro-[2,4'-bipyridine]-1'(2'H)-carboxylate (860 mg, 1.0 eq.) in MeOH (20 mL) was added Pd/C (10%) (100 mg) at r.t., and the atmosphere of the black mixture was exchanged with H_2 for 3 times. The reaction was stirred at r.t. overnight under H_2 atmosphere. TLC (EA/PE=1/5, Rf=0.05) showed starting material consumed, the reaction had mainly a new spot. The mixture was filtered and concentrated in vacuo to get tert-butyl 4-(4-(trifluoromethyl)pyridin-2-yl)piperidine-1-carboxylate (820 mg, colorless oil).

[167] **Step 3:** To a solution of tert-butyl 4-(4-(trifluoromethyl)pyridin-2-yl)piperidine-1-carboxylate (200 mg, 1.0 eq.) in DCM (2 mL) was added dropwise 4 M HCl/dioxane (2.5 mL) at 0-5 ^{0}C, and the colorless mixture was stirred at r.t. for 6 h. TLC (EA/PE=1/5, Rf=0.0) showed starting material consumed, the reaction had mainly a new spot. The mixture was concentrated in vacuo to get 2-(piperidin-4-yl)-4-(trifluoromethyl)pyridine hydrochloride (260 mg, white solid, crude).

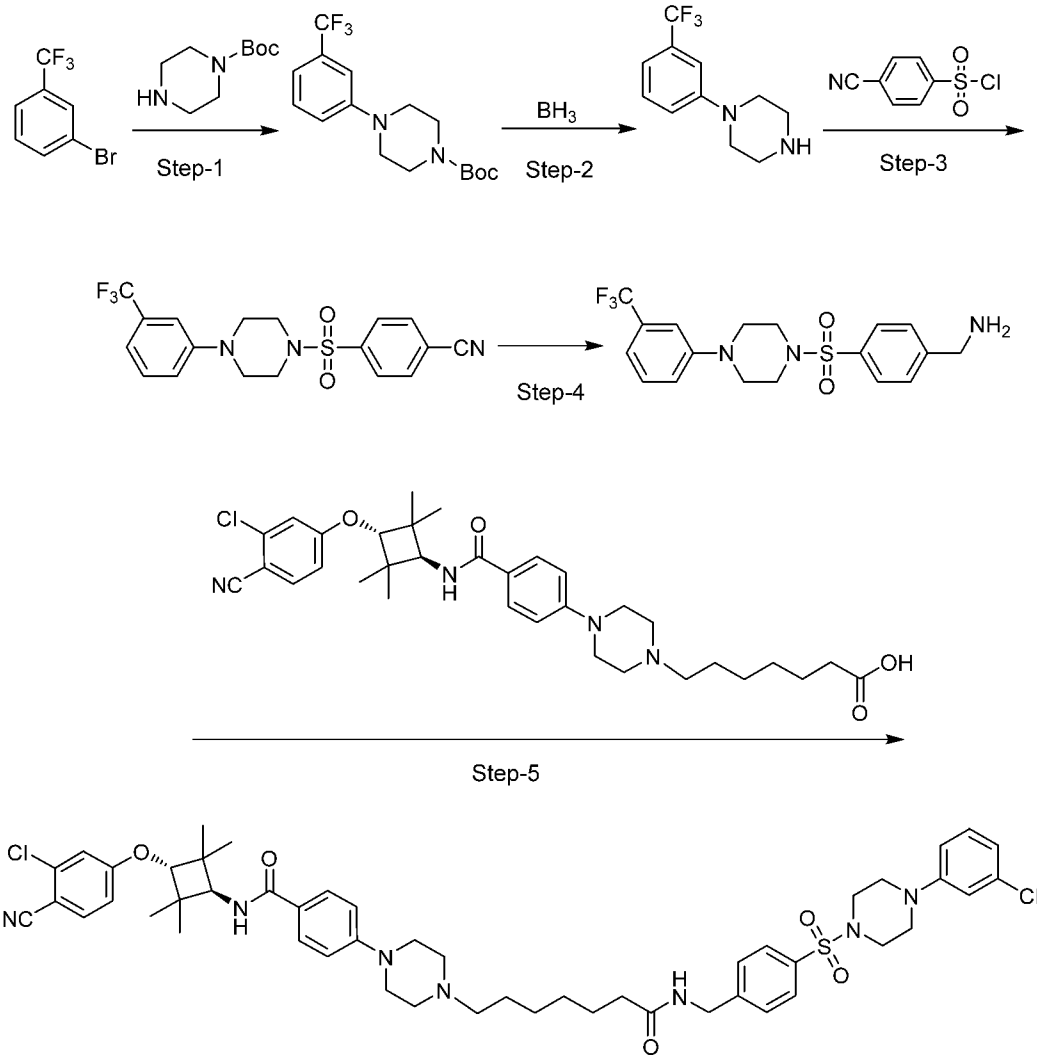
[168] **Step 4:** To a solution of 2-(piperidin-4-yl)-4-(trifluoromethyl)pyridine hydrochloride (160 mg, 1.0 eq.) in DCM (5 mL) was added 4-cyanobenzenesulfonyl chloride (112.5 mg, 1.05 eq.), TEA (241.5 mg, 4.5 eq.) at 0-5 ^{0}C, and the yellow mixture was stirred at r.t. for 2 h. TLC (EA/PE=1/1, Rf=0.25) showed starting materials were consumed, the reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was purified with silica gel. Chromatography column eluted EA in PE 50% to get 4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperidin-1-yl)sulfonyl)benzonitrile (130 mg, white solid).

[169] **Step 5:** To a solution of 4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperidin-1-yl)sulfonyl)benzonitrile (80 mg, 1.0 eq.) in THF (1 mL) was added BH_3-THF (1.0 M in THF) (2 mL, 10.0 eq.) at -10 ~ -5 ^{0}C, the colorless mixture was stirred at -10 ~ -5 ^{0}C for 10 mins, then stirred at r.t. for 2 h. TLC (EA/PE=1/1, Rf=0.25) showed starting material consumed, the reaction had mainly a new spot. The mixture was quenched with MeOH (1 mL), added 1 M HCl (5 drops), then stirred at 70 ^{0}C for 20 min. The mixture was concentrated in vacuo. Then the pH was adjusted to ~ 9 with sat. $NaHCO_3$, and the mixture was extracted with DCM (15 mL*3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with silica gel. Chromatography column eluted MeOH in DCM 3% ~ 5% to get (4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperidin-1-yl)sulfonyl)phenyl)methanamine (54 mg, light yellow solid).

[170] **Step 6:** To a solution of (4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperidin-1-yl)sulfonyl)phenyl)methanamine (5 mg, 1.0 eq.) in DMF (0.5 mL) was added 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (4 mg, 1.2 eq.), HATU (4.1 mg, 1.3 eq.), DIEA (2.7 mg, 2.5 eq.) at 0 ~ 5 ^{0}C, the yellow mixture was stirred at r.t. for 1 h. TLC (MeOH/DCM=1/15, Rf=0.2) showed starting materials were consumed, the reaction had mainly a new spot. The mixture was quenched with water (5 mL), extracted with DCM (10 mL×2), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with pre-TLC (MeOH/DCM=1/12.5) to get N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(trifluoromethyl)pyridin-2-yl)piperidin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 7**, 4.0 mg, off-white solid). ESI-MS: 976.4 $[M+H]^+$.

Example S8

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 8)



[171] **Step 1:** A solution of 1-bromo-3-(trifluoromethyl)benzene (100 mg, 1.0 eq), tert-butyl-piperazine-1-carboxylate (124 mg, 1.5 eq), Ruphos Pd (37.2 mg, 0.1 eq), Cs_2CO_3 (290 mg, 2.0 eq) in toluene (2 ml) was stirred under N_2 at 90 °C overnight. The solvent was removed. The mixture was purified by column chromatography on silica gel eluted with PE/EA (9:1) to give tert-butyl 4-(3-(trifluoromethyl)phenyl)piperazine-1-carboxylate (125 mg), ESI-MS: 331.2$[M+H]^+$.

[172] **Step 2:** To a solution of tert-butyl tert-butyl 4-(3-(trifluoromethyl)phenyl)piperazine-1-carboxylate (125 mg) in 1,4-dioxane (1 ml) was added HCl/dioxane (2 ml). The reaction was stirred at RT for 1h. The mixture was evaporated to afford 1-(3-(trifluoromethyl)phenyl)piperazine (80 mg), ESI-MS: =231.2 $[M+H]^+$.

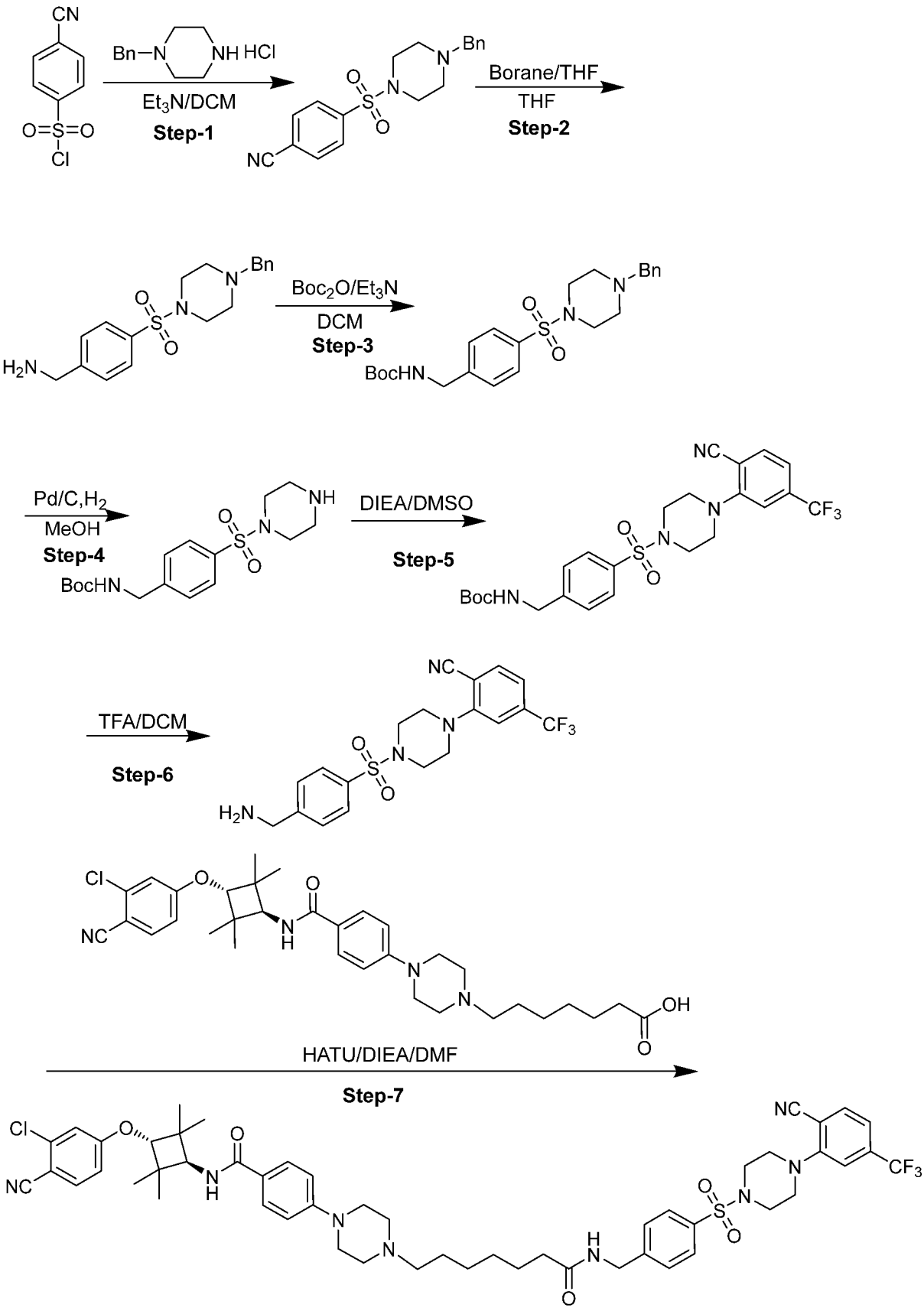
[173] **Step 3:** To a solution of 1-(3-(trifluoromethyl)phenyl)piperazine (80 mg, 1.0 eq) in DCM (2 ml) was added Et_3N (88 mg, 2.5 eq), and 4-cyanobenzenesulfonyl chloride (71 mg, 1.0 eq). The reaction was stirred at RT overnight. TLC showed complete reaction of raw materials. The mixture was purified by column chromatography on silica gel eluted with PE/EA (5:1-4:1) to give 4-((4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzonitrile (115 mg), ESI-MS: 396.1$[M+H]^+$.

[174] **Step 4:** To a solution of 4-((4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzonitrile(115 mg, 1.0 eq) in THF (2 ml) was added slowly BH_3/THF (1M/L, 1.2ml, 4.0eq) at -10°C, then stirred at RT for 3h. The reaction mixture was quenched by the addition of MeOH, stirred at RT for 5min, added 1M HCl aqueous solution (0.5 ml), stirred at 70°C for 30min, the mixture was cooled to RT, $NaHCO_3$ aqueous solution was added to adjust to aqueous PH=8-9. The combined aqueous layers were extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by pre-TLC (DCM:MeOH=10:1) to afford (4-((4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)phenyl)methanamine (85 mg), ESI-MS: 400.1$[M+H]^+$.

[175] **Step 5:** A solution of 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (5 mg, 1.0 eq), (4-((4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)phenyl)methanamine (3.5 mg, 1.0 eq), HATU (4.8 mg, 1.5 eq), and DIEA (3.5 mg, 3.0 eq) in DMF (1 ml) was stirred at RT for 1h. TLC showed complete reaction of raw materials. The solvent was removed and the mixture was purified by pre-TLC (DCM:MeOH=10:1) to afford the product *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 8**, 3.5 mg), ESI-MS: 976.4$[M+H]^+$.

Example S9

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-((4-((4-(2-cyano-5-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)amino)-7-oxoheptyl)piperazin-1-yl)benzamide (Compound 9)


Et3N/DCM
Step-1
Borane/THF
THF
Step-2
Boc2O/Et3N
DCM
Step-3
Pd/C,H2
MeOH
Step-4
DIEA/DMSO
Step-5
TFA/DCM
Step-6
HATU/DIEA/DMF
Step-7

[176] **Step 1:** To a stirred solution in DCM (5 mL) of 1-benzylpiperazine hydrochloride (133.4 mg 0.627 mmol) and 4-cyanobenzenesulfonyl chloride (126.4 mg, 0.627mmol) was added Et_3N (158.6 mg, 1.567 mmol) and the reaction was stirred at room temperature for 3 h. The reaction was diluted with DCM and H_2O. The organic layer was separated, washed with saturated NH_4Cl solution, water, saturated $NaHCO_3$ solution, water and brine, dried by anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give a crude product 4-((4-benzylpiperazin-1-yl)sulfonyl)benzonitrile (230.5 mg, 107.7%).

[177] **Step 2:** To a stirred solution in THF (6 mL) of 4-((4-benzylpiperazin-1-yl)sulfonyl)benzonitrile (230.5 mg, 0.675 mmol) was added Borane/THF (1.0 M, 6.7 mL, 6.751 mmol) dropwise at 0-5°C. After the addition, the reaction was stirred at room temperature for 4 h. The reaction was quenched with MeOH. To the resulting mixture was added HCl solution (1M, 1mL) and stirred at 70°C for 0.5 h. The resulting mixture was concentrated, diluted with DCM, adjusted to pH 9-10. The water layer was separated, extracted with DCM. The all organic layer was combined and washed with saturated $NaHCO_3$ solution, water and brine, dried by anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give a crude product (4-((4-benzylpiperazin-1-yl)sulfonyl)phenyl)methanamine (221.4 mg, 0.641 mmol, 94.93%).

[178] **Step 3:** To a stirred solution in DCM (6 mL) of (4-((4-benzylpiperazin-1-yl)sulfonyl)phenyl)methanamine (221.4 mg, 0.641 mmol) were added Boc_2O (139.9 mg, 0.641 mmol) and Et_3N (129.7 mg, 1.282 mmol), and stirred at room temperature for 1 h. The reaction was diluted with DCM and water. The organic layer was separated, washed with water, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give tert-butyl (4-((4-benzylpiperazin-1-yl)sulfonyl)benzyl)carbamate (224.3 mg, 0.503 mmol, 78.55%). ESI-MS: 445.8$[M+H]^+$.

[179] **Step 4:** To a stirred solution in MeOH (14 mL) of tert-butyl (4-((4-benzylpiperazin-1-yl)sulfonyl)benzyl)carbamate (224.3 mg, 0.503 mmol) was added 10%Pd/C (44.8mg), purged 4 times with H_2 and stirred at 40°C under H_2 for 1.5 h. The reaction was filtered with MeOH. The organic layer was concentrated in vacuo to give tert-butyl (4-(piperazin-1-ylsulfonyl)benzyl)carbamate (156.1 mg, 0.439 mmol, 87.24%).

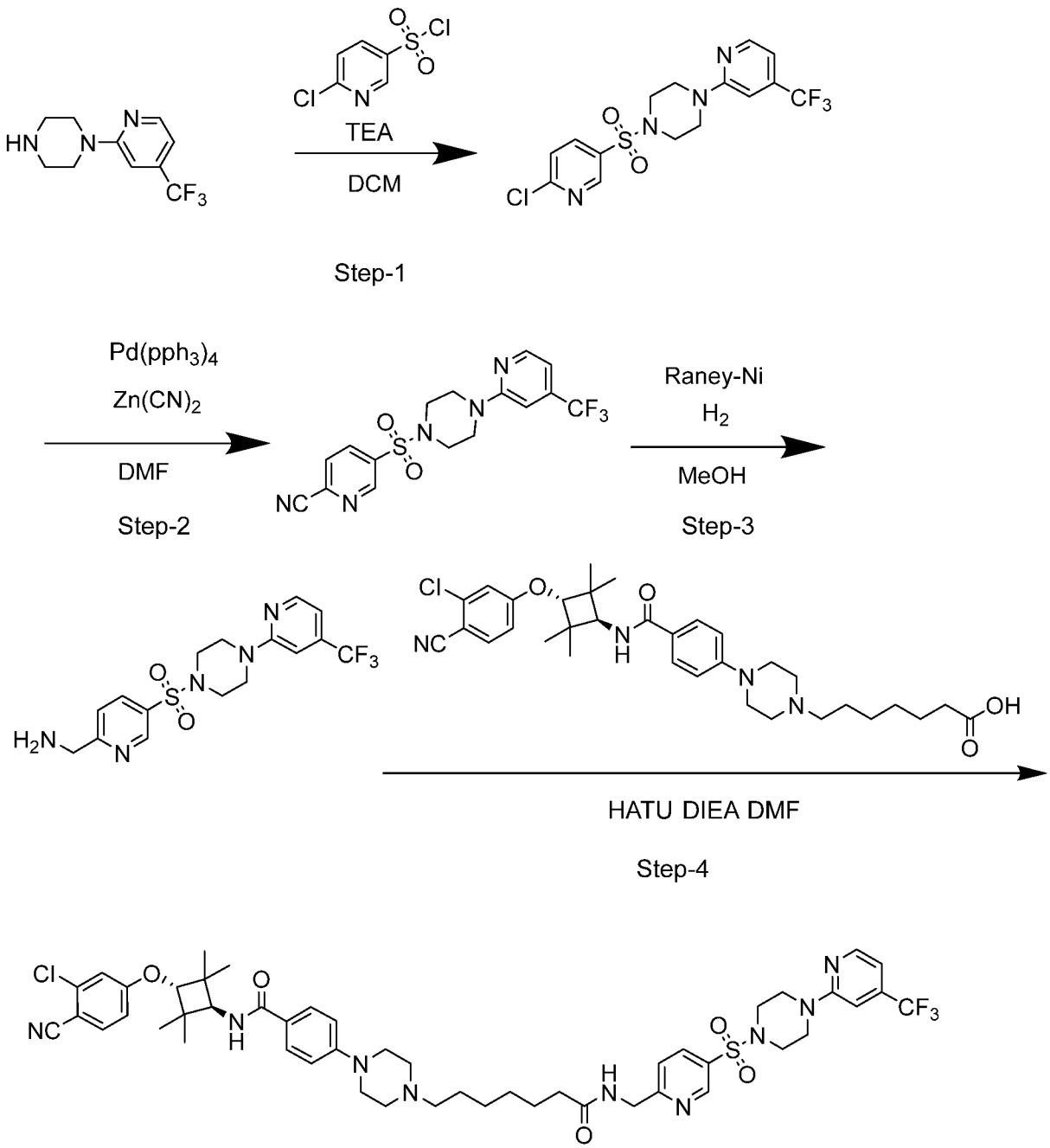
[180] **Step 5:** To a stirred solution in DMSO (4 mL) of tert-butyl (4-(piperazin-1-ylsulfonyl)benzyl)carbamate (156.1 mg, 0.439 mmol) were added 2-fluoro-4-(trifluoromethyl)benzonitrile(91.4 mg, 0.483 mmol) and DIEA (113.5 mg, 0.878 mmol), and the atmosphere was purged 4 times with N_2 and the reaction stirred at 110°C under N_2 for 4 h. The reaction was diluted with water and extracted with DCM. The organic layer was washed with saturated NH_4Cl solution, water, saturated $NaHCO_3$ solution, water and brine, dried by anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give tert-butyl (4-((4-(2-cyano-5-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)carbamate (1150.0 mg, 0.286 mmol, 65.11%).

[181] **Step 6:** To a stirred solution in DCM (1 mL) of tert-butyl (4-((4-(2-cyano-5-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)carbamate (16.0 mg, 30.502 μmol) was added TFA (0.5ml) and stirred at room temperature for 1 h. The reaction was concentrated in vacuo. The residue was dissolved in DCM, washed with $NaHCO_3$ solution, water and brine, dried by anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give 2-(4-((4-(aminomethyl)phenyl)sulfonyl)piperazin-1-yl)-4-(trifluoromethyl)benzonitrile (4.1 mg, 9.660 μmol, 31.67%).

[182] **Step 7:** To stirred solution in DMF (1.5 mL) of 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (5.7 mg, 9.660 μmol) and HATU (5.5 mg, 14.490 μmol) were added DIEA (3.7 mg, 28.980 μmol) and 2-(4-((4-(aminomethyl)phenyl)sulfonyl)piperazin-1-yl)-4-(trifluoromethyl)benzonitrile (4.1 mg, 9.660 μmol), and the reaction stirred at room temperature for 3 h. The reaction was concentrated in vacuo. The residue was purified by pre-TLC to give ***N***-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-((4-((4-(2-cyano-5-(trifluoromethyl)phenyl)piperazin-1-yl)sulfonyl)benzyl)amino)-7-oxoheptyl)piperazin-1-yl)benzamide (**Compound 9**, 2.7 mg, 27.9%). ESI-MS: 1001.7$[M+H]^+$.

Example S10

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-(((5-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyridin-2-yl)methyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 10)



[183] **Step 1:** To a solution of 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (160 mg, 1.0 eq) in DCM (3 mL) was added 6-chloropyridine-3-sulfonyl chloride (147 mg, 1.0 eq), and TEA (175 mg, 2.5 eq), and the yellow mixture was stirred at rt for 3 h. TLC (PE/EA=2/1, Rf=0.4) showed starting material was consumed, the reaction had mainly a new spot. The combined aqueous layers were extracted with DCM (5 mL×4) to remove neutral impurities. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was directly purified with pre-TLC (PE/EA=2/1) to get 1-((6-chloropyridin-3-yl)sulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazine (250.0 mg, white solid).

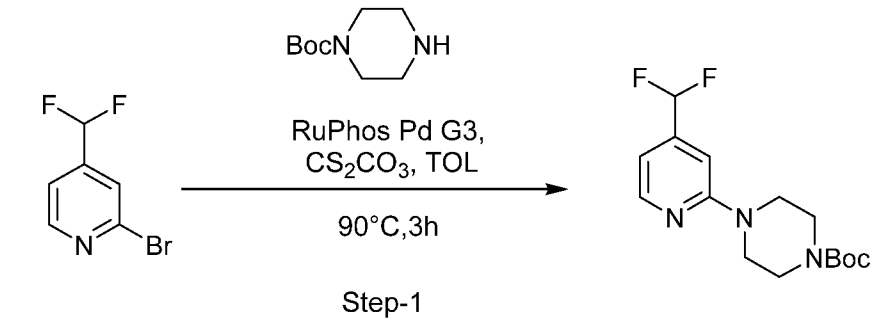
[184] **Step 2:** To a solution of 1-((6-chloropyridin-3-yl)sulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazine (100 mg, 1.0 eq.) in DMF (2 mL) was added $Pd(pph_3)_4$ (127 mg, 0.4 eq.), $Zn(CN)_2$ (23 mg, 0.8 eq.) at room temperature. The atmosphere was replaced with nitrogen 5 times. The yellow mixture was stirred at 100 °C for 4 h. TLC (PE/EA=2/1, Rf=0.3) showed starting material was consumed, the reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was directly purified with pre-TLC (EA/PE=1/3) to get 5-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)picolinonitrile (40 mg, white solid).

[185] **Step 3:** To a solution of 5-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)picolinonitrile (20 mg, 1.0 eq) in $MeOH/NH_3$ (2 mL) was added H_2,Raney-Ni (3 mg), the black mixture was stirred at r.t. for 3 h. TLC (EA/PE=1/1, Rf=0.1) showed starting material was consumed, the reaction has a mainly new spot. Filtration of reaction solution, The mixture was concentrated in vacuo, to get (5-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyridin-2-yl)methanamine (18 mg, white solid). ESI-MS: 404.1[M+H]+.

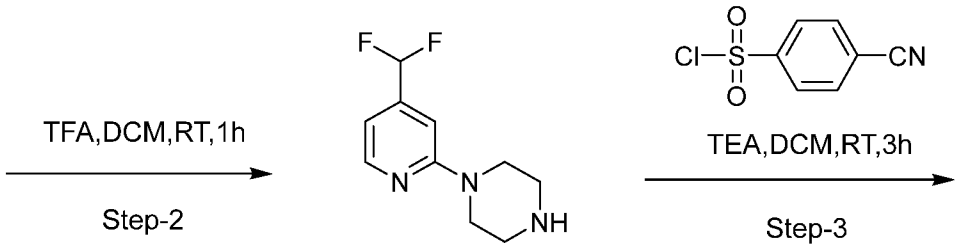
[186] **Step 4:** To a solution of (5-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyridin-2-yl)methanamine (3.4 mg, 1.0 eq.) in DMF (1 mL) was added 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (5.0 mg, 1.0 eq.), HATU (4.7 mg, 1.5 eq.), DIEA (3.5 mg, 3.0 eq.) at 0-5 °C, and the yellow mixture was stirred at r.t. for 3 h. TLC (MeOH/DCM=1/10, Rf=0.6) showed starting material was consumed, the reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was directly purified with pre-TLC (MeOH/DCM=1/10) to get N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-(((5-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyridin-2-yl)methyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 10**, 1.6mg, off-white solid). ESI-MS: 979.3$[M+H]^+$.

Example S11

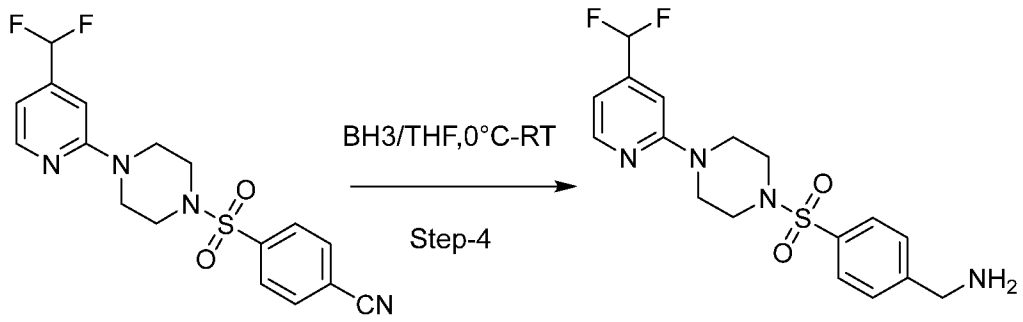
Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-((4-((4-(4-(difluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)-7-oxoheptyl)piperazin-1-yl)benzamide (Compound 11)



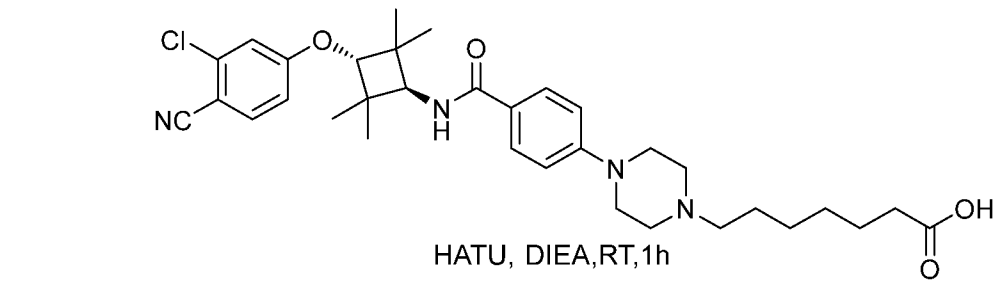
Step-1



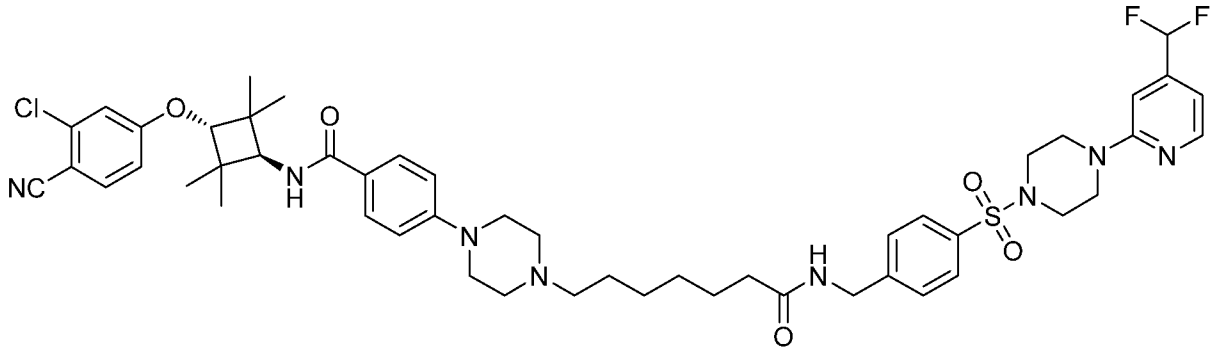
Step-2 Step-3



Step-4



Step-5



[187] **Step 1:** 2-bromo-4-(difluoromethyl)pyridine (61 mg, 0.29 mmol), tert-butyl piperazine-1-carboxylate(64 mg, 0.34 mmol), RuPhos Pd G3(28.8 mg, 0.034 mmol) and Cs_2CO_3 were dissolved in toluene (4 ml), and the reaction mixture was stirred at 90 °C for 3 hours under N_2 atomsphere, filtered and concentrated in vacuo to give the crude product which was purified by Pre-TLC with PE/EA(3/1) to give tert-butyl 4-(4-(difluoromethyl)pyridin-2-yl)piperazine-1-carboxylate (41 mg 0.13 mmol 45%) as yellow oil.

[188] **Step 2:** tert-butyl 4-(4-(difluoromethyl)pyridin-2-yl)piperazine-1-carboxylate (41 mg 0.13 mmol) and TFA (2 mL) were dissolved in DCM (2 mL), and the reaction mixture was stirred at RT for 1 hour, and then concentrated in vacuo to give the crude product 1-(4-(difluoromethyl)pyridin-2-yl)piperazine (29 mg, 0.13mmol,99%) as yellow oil.

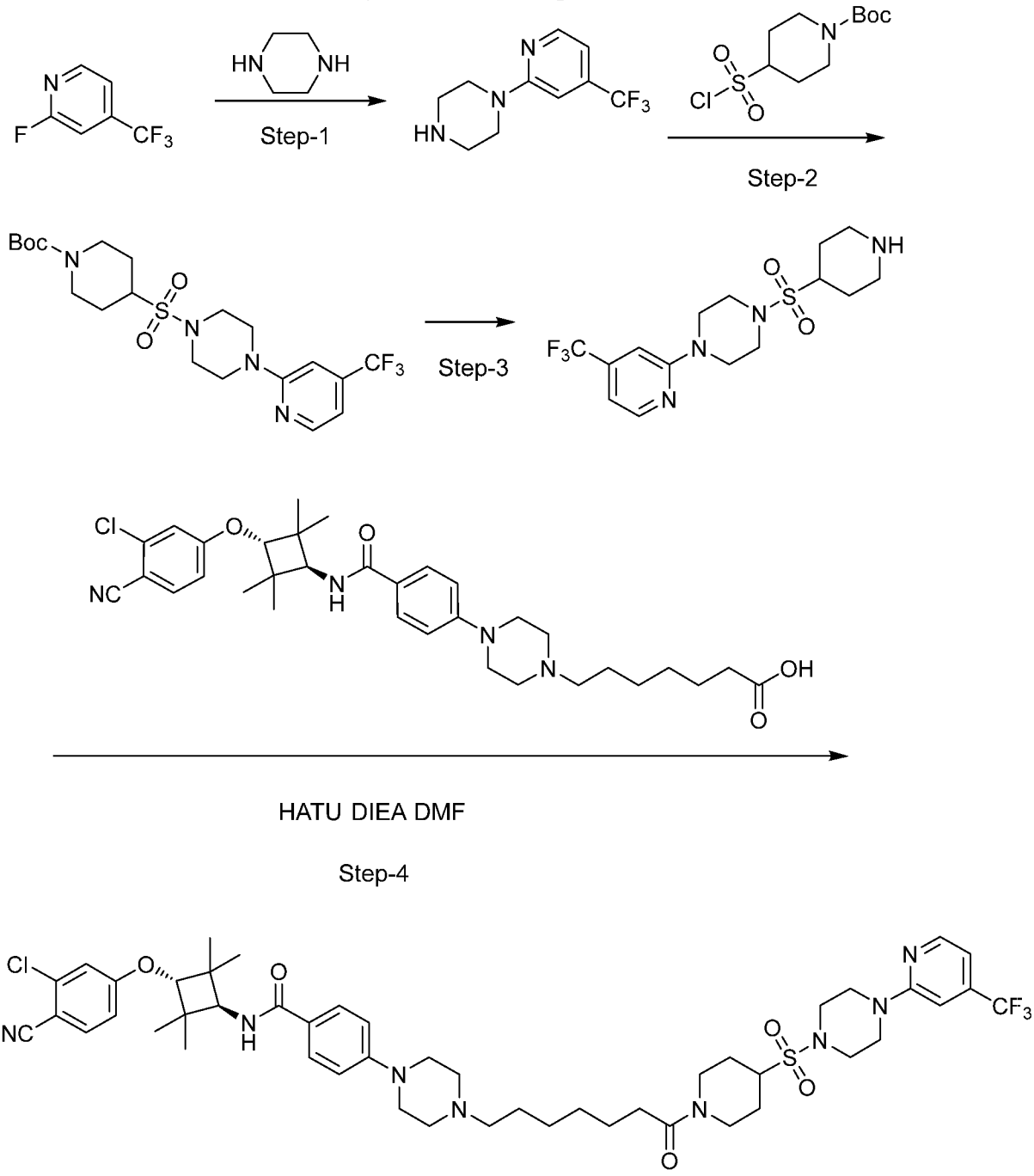
[189] **Step 3:** To a mixture of 1-(4-(difluoromethyl)pyridin-2-yl)piperazine (29 mg, 0.13mmol) and TEA (90 mg, 0.89 mmol) was added 4-cyanobenzenesulfonyl chloride (26 mg, 0.13mmol) in DCM (2 mL), and the mixture stirred at RT for 3 hours, and was concentrated in vacuo to give the crude product which was purified by P-TLC with PE/EA(3/1) to give 4-((4-(4-(difluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzonitrile (35 mg, 0.092 mmol, 71%) as a white solid.

[190] **Step 4:** To a stirred solution of the 4-((4-(4-(difluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzonitrile (15 mg, 0.039 mmol) in anhydrous THF (20 mL) under N_2 was added a solution of BH_3 in THF (1.0M, 0.4 mL, 0.4 mmol, 10 eq) at 0 °C. The mixture was stirred at room temperature for 3 hours. Aqueous HCl (2M, 0.5 mL) was added and refluxed for 0.5 hours. The mixture was basified to pH 9 by addition of aq. $NaHCO_3$, extracted with CH_2Cl_2 (3×10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (DCM/MeOH = 50/1 to 15:1) to give (4-((4-(4-(difluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (8.7 mg, 0.011mmol,29%) as a white solid.

[191] **Step 5:** To a solution of 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (5.3 mg, 1.0 eq.) in DMF (0.5 mL) was added (4-((4-(4-(difluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (4 mg, 1.2 eq.), HATU (4.4 mg, 1.3 eq.), and DIEA (2.8 mg, 2.5 eq.) at 0-5 ^{0}C, and the yellow mixture was stirred at r.t. for 1 h. TLC (MeOH/DCM=1/10, Rf=0.65) showed starting meterials were consumed, the reaction had mainly a new spot. The mixture was quenched with water (5 mL), extracted with DCM (10 mL*3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with pre-TLC (MeOH/DCM=1/12.5) to get N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-((4-((4-(4-(difluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)-7-oxoheptyl)piperazin-1-yl)benzamide (**Compound 11**, 2.0 mg, off-white solid). ESI-MS: 958.7 [M+H]+.

Example S12

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-(4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)heptyl)piperazin-1-yl)benzamide (Compound 12)



[192] **Step 1:** A mixture of 2-fluoro-4-(trifluoromethyl)pyridine (495 mg, 3 mmol), piperazine (309.6 mg, 3.6 mmol) and DIEA (774 mg, 6 mmol) in DMSO (8 ml) was heated at 110 °C for 2.5 h, poured into H_2O, extracted with MTBE for 4 times, dried over Na_2SO_4, filtered, and concentrated to afford the crude 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (700 mg).

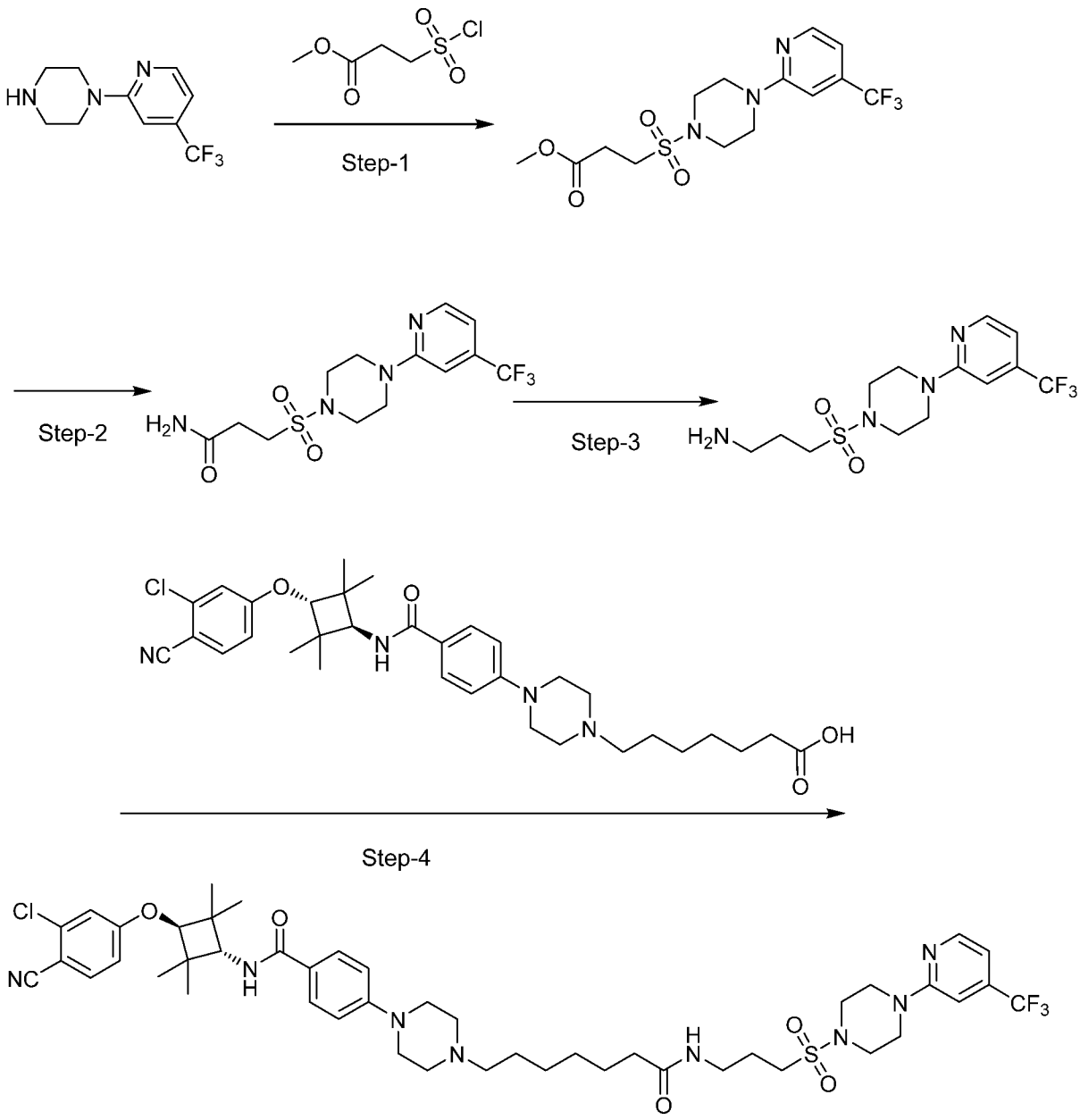
[193] **Step 2:** To a solution of 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (46.2 mg, 0.2 mmol) in DCM (2 mL) was added Et_3N (40.4 mg, 0.4 mmol) and tert-butyl 4-(chlorosulfonyl)piperidine-1-carboxylate (56.8 mg, 0.2 mmol) in DCM (1 mL), dropwise, in an ice-bath. After addition, the reaction was stirred at RT for 3h, and purified by pre-TLC eluting with PE/EA=2/1 and got tert-butyl 4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)piperidine-1-carboxylate (43.6 mg).

[194] **Step 3:** tert-butyl 4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)piperidine-1-carboxylate (10 mg) was dissolved in 1,4-dioxane (1 mL). 1,4-dioxane hydrochloride (1 mL) was added to the reaction in an ice-bath and stirred at RT for 1h. The reaction was concentrated to afford crude 1-(piperidin-4-ylsulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazine (8 mg).

[195] **Step 4:** To a solution of 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (5 mg, 8.42 μmol), 1-(piperidin-4-ylsulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazine (3.5 mg, 8.42 μmol) and HATU (3.8 mg, 10.1 μmol) in DMF (0.5 mL) was added DIEA (3.3 mg, 25.25 μmol) and stirred at RT for 18h. The reaction was quenched with H_2O, extracted with EA for 3 times. The organic layers were combined, concentrated, and purified by pre-TLC eluting with DCM/MeOH=15/1 to afford *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-(4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)heptyl)piperazin-1-yl)benzamide (**Compound 12**, 4 mg). ESI-MS:952.6$[M-H]^-$.

Example S13

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 13)



[196] **Step 1:** To a solution of 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (60 mg, 1.0 eq) and Et_3N (66 mg, 2.5 eq) in DCM was added methyl 3-(chlorosulfonyl)propanoate (48.5 mg, 1.0 eq). The reaction was stirred at RT for 6h. The solvent was removed and the mixture was purified by pre-TLC(PE:EA=2:1) to afford methyl 3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propanoate (88 mg), ESI-MS: 382.1[M+H]+.

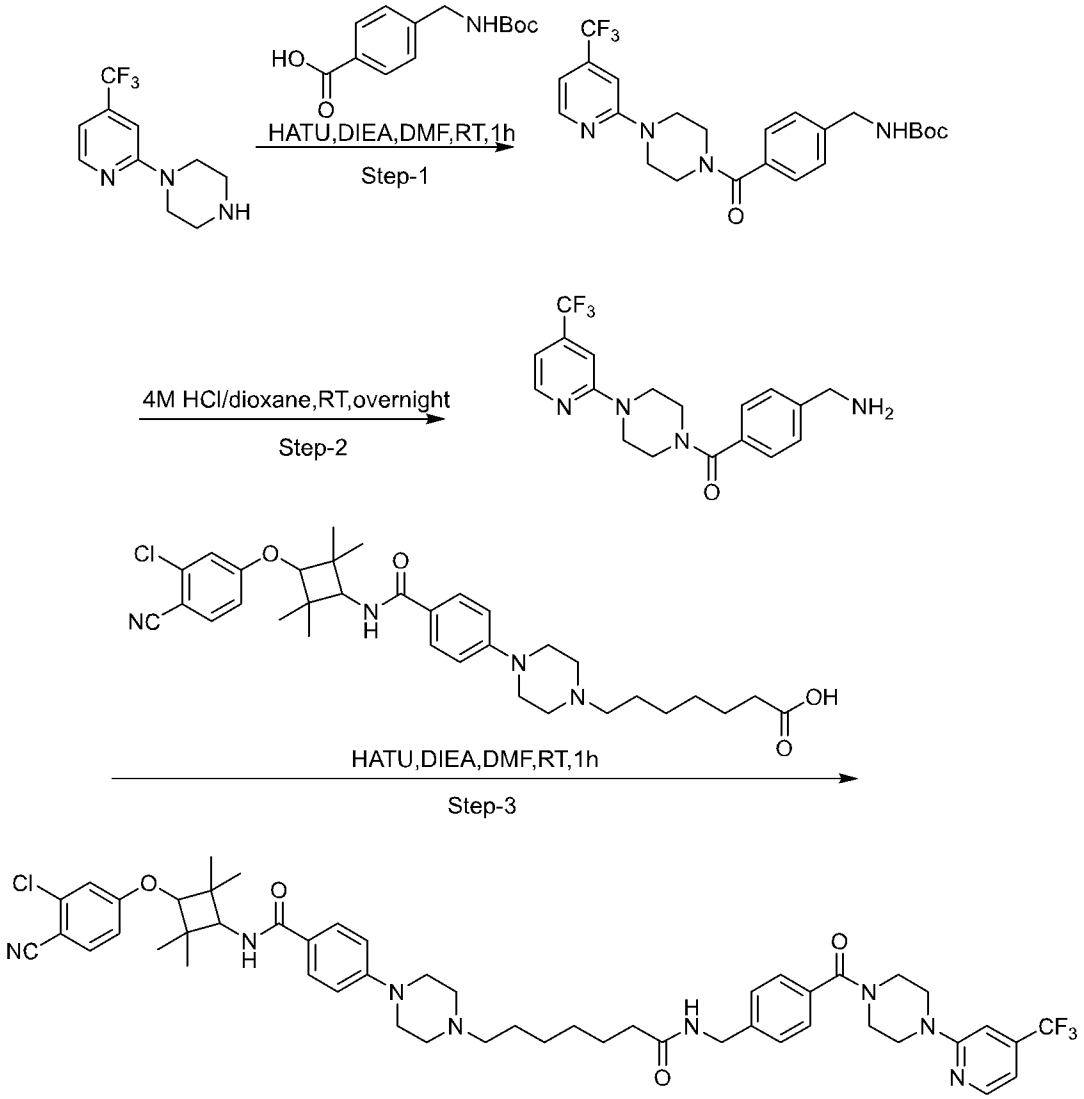
[197] **Step 2:** To a solultion of methyl 3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propanoate (80 mg, 1.0 eq) in MeOH (4ml) was added ammonium hydroxide (2 ml). The reaction was stirred in a sealed tube at 40 °C overnight. The solvent was removed and the mixture was purified by pre-TLC (DCM:MeOH=10:1) to afford 3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propanamide (16 mg), ESI-MS: 367.1[M+H]+ .

[198] **Step 3:** To a solution of 3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propanamide(16 mg, 1.0 eq) in THF (1.5 ml) was added in dropwise LAH (1 M, 0.1 ml, 2.0 eq) at 0 °C. Then the reaction was stirred at RT overnight. The reaction mixture was quenched by the addition of NH_4Cl aqueous solution, extracted with EA. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by pre-TLC (DCM:MeOH=8:1) to afford 3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propan-1-amine (3 mg), ESI-MS: 353.1 [M+H]+.

[199] **Step 4:** A solution of 3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propan-1-amine (3 mg, 1.0 eq), 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (5 mg, 1.0 eq), HATU(4.9 mg, 1.5 eq), and DIEA (3.3 mg, 3.0 eq) in DMF (1 ml) was stirred at RT for 30min. TLC showed complete reaction of raw materials. The solvent was removed and the mixture was purified by pre-TLC(DCM:MeOH=10:1) to afford the product N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 13**, 2 mg) ESI-MS: 929.4[M+H]+.

Example S14

Synthesis of N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-(4-(4-(trifluoromethyl)pyridin-2-yl)piperazine-1-carbonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 14)



[200] **Step 1:** To a mixture of 4-(((tert-butoxycarbonyl)amino)methyl)benzoic acid (44 mg, 0.17 mol) and HATU (129 mg, 0.34 mmol) in DMF (2 ml) was added 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (40 mg, 0.17mmol) and DIEA (66mg, 0.51mmol) ,the reaction mixture was stirred at RT for 1 hour, and concentrated in vacuo to give the crude product which was purified by silica gel column chromatography eluting with PE/EA (1/1) to give tert-butyl tert-butyl (4-(4-(4-(trifluoromethyl)pyridin-2-yl)piperazine-1-carbonyl)benzyl)carbamate (60 mg, 0.13 mmol, 76%) as white solid.

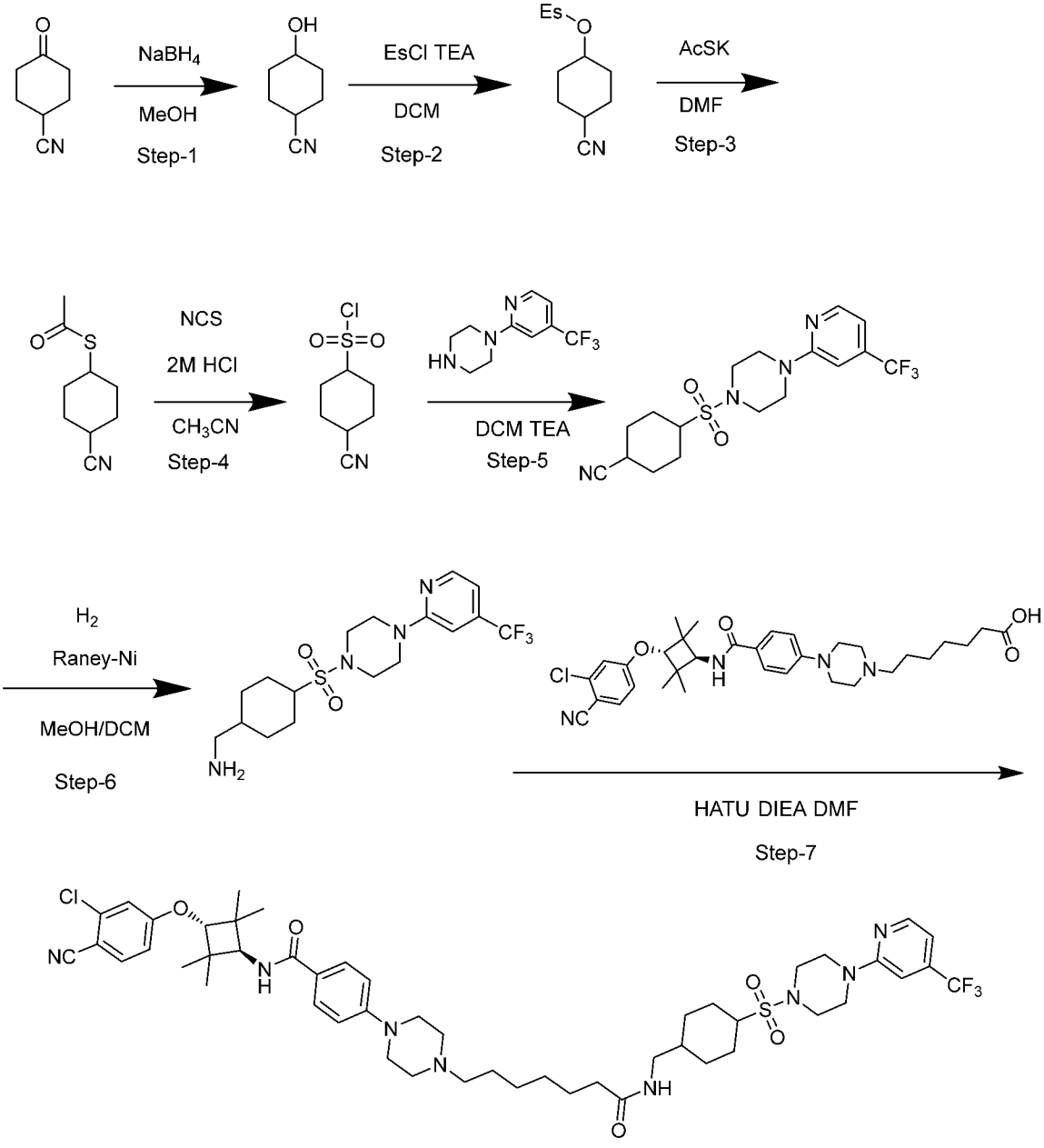
[201] **Step 2:** To a mixture of tert-butyl (4-(4-(4-(trifluoromethyl)pyridin-2-yl)piperazine-1-carbonyl)benzyl)carbamate (15 mg,0.032 mmol) was added 4M HCl/dioxane (2ml). The reaction mixture was stirred at RT overnight, and then concentrated in vacuo to give the crude product (4-(aminomethyl)phenyl)(4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)methanone (10 mg, 0.027mmol,85%) as white solid.

[202] **Step 3:** 7-(4-(4-((3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (5 mg, 0.0084 mmol), (4-(aminomethyl)phenyl)(4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)methanone (10 mg, 0.027 mmol),

and DIEA (12 mg, 0.1 mmol) were dissolved in DMF (1 mL), and HATU (6.4 mg, 0.017 mmol) was added to the solution. After 1 hour the reaction was completed. 2 mL of a saturated NaCl solution were then added and the product extracted with EtOAc (3×2 mL). The organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude product which was purified by P-TLC with DCM/MeOH (10/1) to give N-(3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-(4-(4-(trifluoromethyl)pyridin-2-yl)piperazine-1-carbonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 14**, 2.7 mg, 0.0028 mol, 10%) as a white solid.

Example S15

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-(((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)cyclohexyl)methyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 15)



[203] **Step 1:** To a stirred 0 °C solution of 4-oxocyclohexane-1-carbonitrile (500 mg, 1 eq.) in MeOH (3 mL) under nitrogen was added $NaBH_4$ (76.82 mg, 0.5 eq.), and the white mixture was stirred at r.t. for 1 h. TLC (PE/EA=3/1, Rf=0.2) showed starting material was consumed, the reaction had mainly a new spot. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl. The combined aqueous layers were extracted with EtOAc (5 mL×4) to remove neutral impurities. The mixture was concentrated in vacuo, to get 4-hydroxycyclohexane-1-carbonitrile (507 mg, white solid). ESI-MS: 126.1$[M+H]^+$.

[204] **Step 2:** To a solution of 4-hydroxycyclohexane-1-carbonitrile (500 mg, 1.0 eq.) in DCM (5mL) was added TEA (530 mg, 1.3 eq.) and EsCl (501 mg, 1.2 eq.), and the yellow mixture was stirred at rt. for 3 h. TLC (PE/EA=1/1, Rf=0.4) showed starting material was consumed, the reaction had mainly a new spot. The combined aqueous layers were extracted with DCM (5 mL×4) to remove neutral impurities. The combined organic layers were dried over $MgSO_4$. The mixture was concentrated in vacuo, to get ((4-cyanocyclohexyl)oxy)einsteinium (1010 mg, yellow liquid).

[205] **Step 3:** To a solution of AcSK (788 mg, 1.5 eq.) in DMF (10 mL) was added ((4-cyanocyclohexyl)oxy)einsteinium (1000 mg, 1.0 eq.), and the yellow mixture was stirred at 50 °C for 5 h. TLC (PE/EA=2/1, Rf=0.8) showed starting material was consumed, the reaction had mainly a new spot. The reaction mixture was quenched by addition H_2O. The combined aqueous layers were extracted with EtOAc (5 mL×4), The combined organic layers were dried over $MgSO_4$. The mixture was concentrated in vacuo to get S-(4-cyanocyclohexyl) ethanethioate (800mg, yellow liquid).

[206] **Step 4:** To a solution of S-(4-cyanocyclohexyl) ethanethioate (800 mg, 1.0 eq.) in CH_3CN (15 mL) was added 2M HCl (1 mL) and NCS (2300 mg, 4.0 eq.) at 10 ^{0}C, and the yellow mixture was stirred at r.t. for 2 h. The reaction mixture was concentrated, and then was quenched by the addition of H_2O. The combined aqueous layers were extracted with EtOAc (5 mL×4), The combined organic layers were dried over $MgSO_4$. The mixture was concentrated in vacuo, to get 4-cyanocyclohexane-1-sulfonyl chloride (500 mg, yellow liquid).

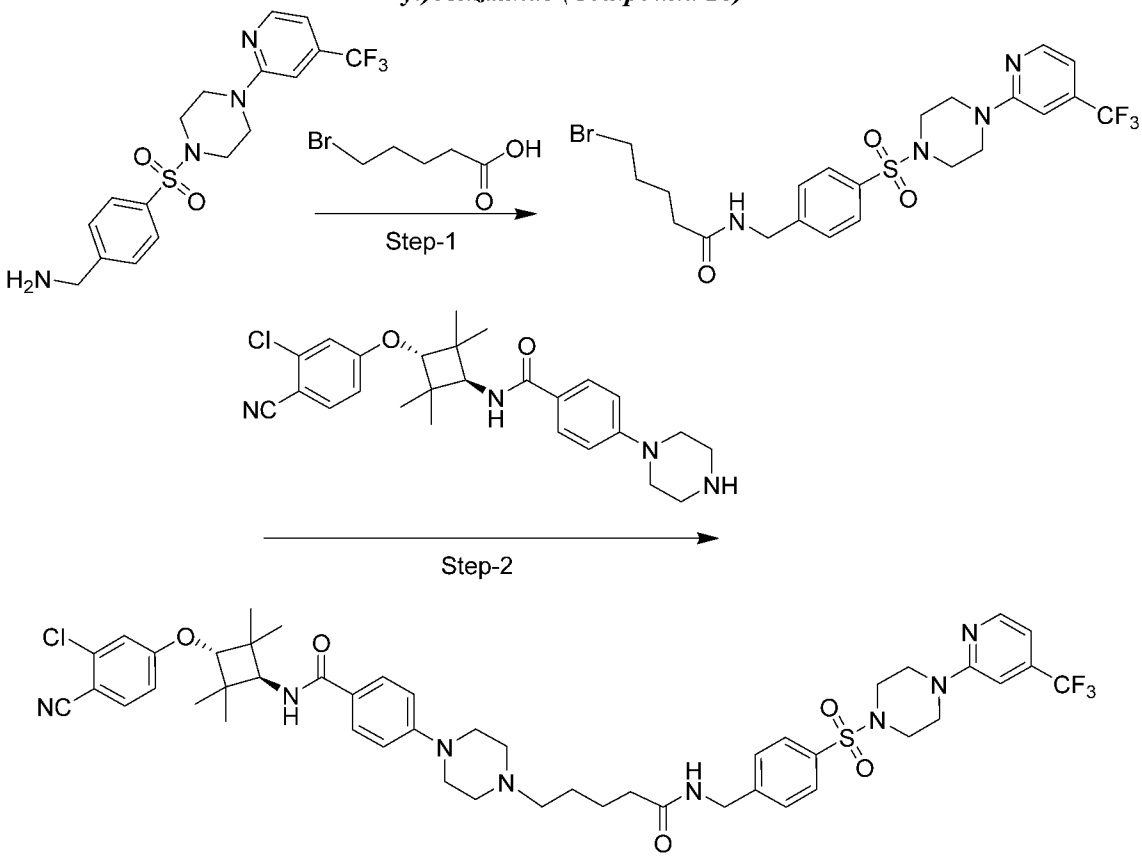
[207] **Step 5:** To a solution of 4-cyanocyclohexane-1-sulfonyl chloride (300 mg, 1.0 eq.) in DCM (5 mL) was added 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (200 mg, 0.6 eq.) and TEA (370 mg, 2.5 eq), and the yellow mixture was stirred at rt for 13 h. TLC (PE/EA=2/1, Rf=0.5) showed starting material was consumed, the reaction had mainly a new spot. Added 10mL of water to the reaction solution. The combined aqueous layers were extracted with DCM (5 mL×3) to remove neutral impurities. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was directly purified with pre-TLC (PE/EA=2/1) to get 4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)cyclohexane-1-carbonitrile (90.0 mg, colorless liquid). ESI-MS: 402.1$[M+H]^+$.

[208] **Step 6:** A mixture of 4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)cyclohexane-1-carbonitrile (5.4 mg, 1.0 eq.) and Raney Ni (2 mg) in MeOH (1 mL) and DCM (1 mL) was stirred under 1 atm of H_2 at room temperature for 0.5 hour. TLC (DCM/MeOH=10/1, Rf=0.2) showed starting material was consumed, ther reaction had mainly new spot. The mixture was filtered through a Celite pad, and the filtrate was concentrated to give crude product (4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)cyclohexyl)methanamine (3.6 mg). ESI-MS: 407.3$[M+H]^+$.

[209] **Step 7:** To a solution of (4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)cyclohexyl)methanamine (3.0 mg, 1.0 eq.) in DMF (1 mL) was added 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (4.5 mg, 1.0 eq.), HATU (4.2 mg, 1.5 eq.), and DIEA (2.9 mg, 3.0 eq.) at 0-5 °C, and the yellow mixture was stirred at r.t. for 0.5 h. TLC (MeOH/DCM=1/10, Rf=0.7) showed starting material was consumed, the reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was directly purified with pre-TLC (MeOH/DCM=1/10) to get *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-(((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)cyclohexyl)methyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 15**, 1.4mg, off-white solid). ESI-MS: 984.3$[M+H]^+$.

Example S16

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(5-oxo-5-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)pentyl)piperazin-1-yl)benzamide (Compound 16)



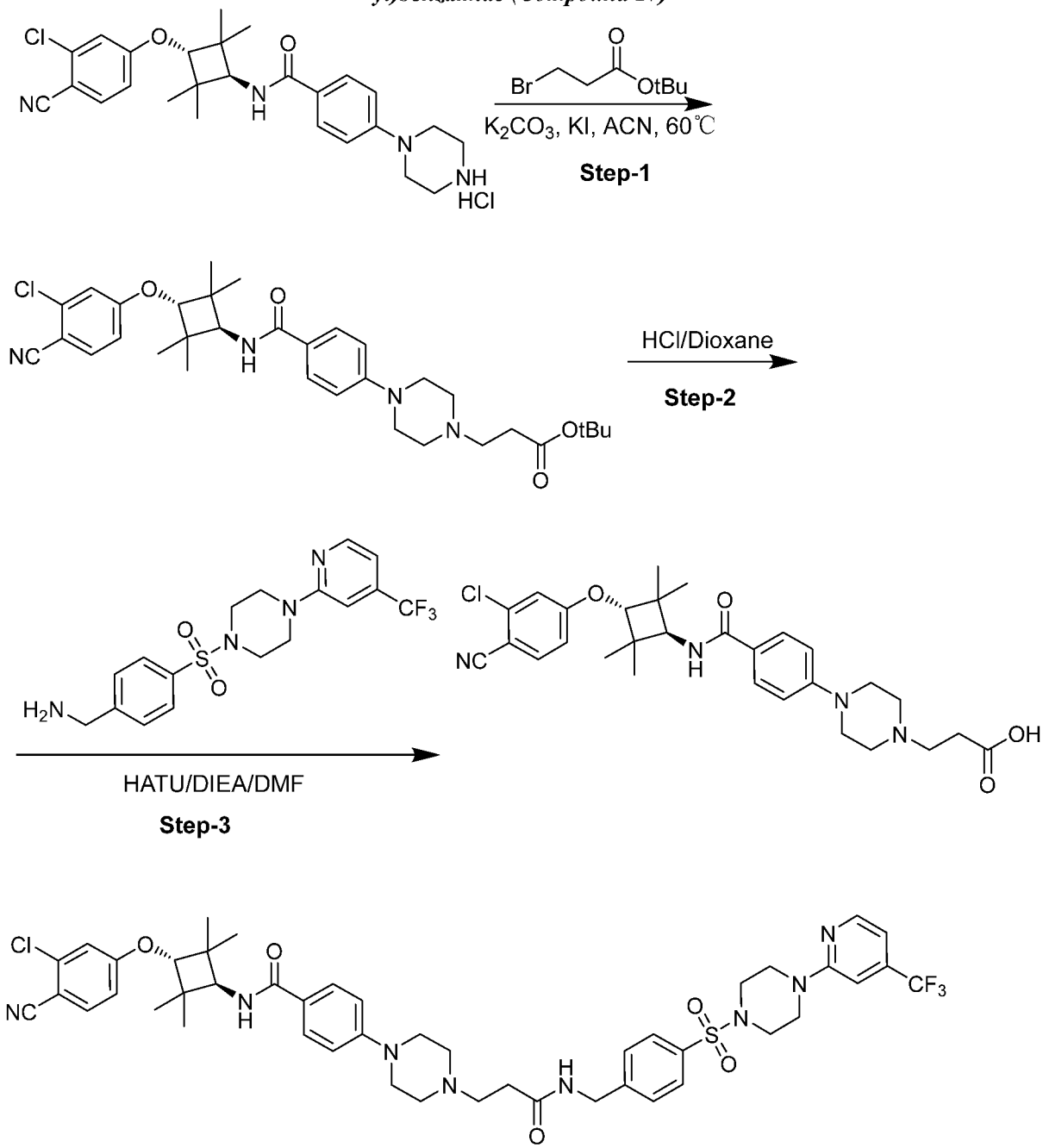
[210] **Step 1:** To a solution of (4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (5 mg, 1 eq) in DMF (2 mL) were added 5-bromopentanoic acid (3 mg, 1.2 eq), HATU (10 mg, 2 eq), and DIEA (5 mg, 3 eq), and the reaction was stirred at room temperature for 3 hours. TLC showed new spot was observed, and no starting material remained. The reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (PE:EA=1:1) to afford tert-butyl 5-bromo-N-(4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)pentanamide (10 mg) as a white solid.

[211] **Step 2:** To a solution of 5-bromo-N-(4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)pentanamide (4 mg, 1 eq) in DMF (2 mL) were added N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benza mide (5 mg, 1 eq), and K_2CO_3 (6 mg, 5 eq), and the reaction was stirred at room temperature for 16 hours. TLC showed all starting material remained, and the reaction was stirred at 80°C for 6 hours. A new spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=15:1) to afford N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(5-oxo-5-((4-((4-(4-

(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)pentyl)piperazin-1-yl)benzamide (**Compound 16**, 1.4 mg) as a white solid. ESI-MS: 948.5 $[M+H]^+$.

Example S17

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(3-oxo-3-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)propyl)piperazin-1-yl)benzamide (Compound 17)



[212] **Step 1:** To a solution in CAN (1.0ml) of *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benzamide (10.0 mg, 0.020 mmol) were added tert-butyl 3-

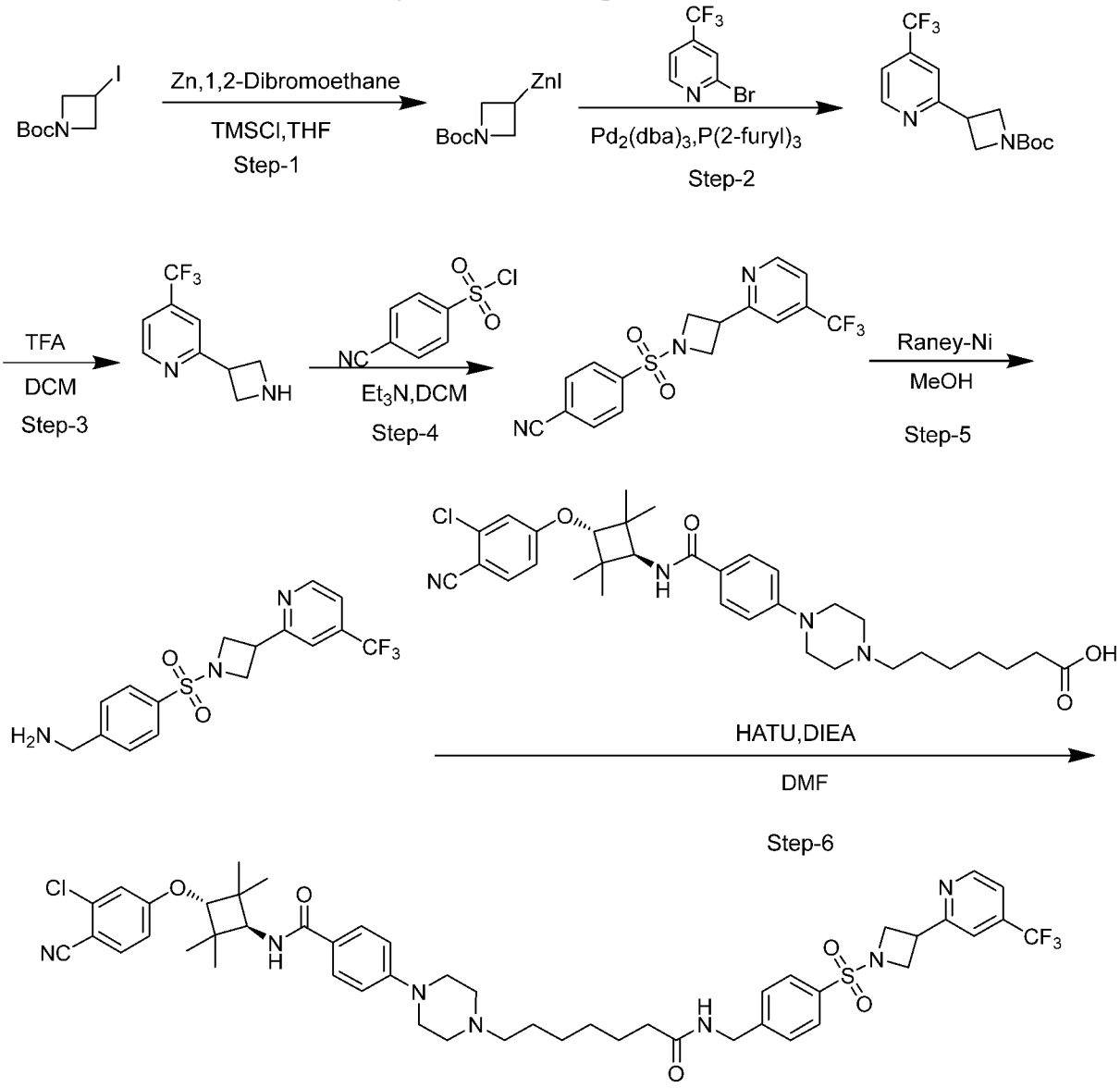
bromopropanoate (6.2 mg, 0.030 mmol), K_2CO_3 (8.3 mg, 0.060 mmol) and KI (1.6 mg, 0.010 mmol), and the reaction was stirred at 80 °C under N_2 for 15 h. The reaction was concentrated in vacuo. The residue was diluted with DCM and water. The organic layer was separated, washed with further water, and concentrated in vacuo. The residue was purified by pre-TLC to afford tert-butyl 3-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)propanoate (8.4 mg, 0.014 mmol, 42.00%). ESI-MS: 592.8, 593.8$[M-H]^-$, 594.8, 596.8 $[M+H]^+$.

[213] **Step 2:** HCl/1,4-dioxane (4M, 1.0 mL) was added to a solution of tert-butyl 3-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)propanoate (8.4 mg, 0.014 mmol) in 1,4-dioxane (0.5 ml). The reaction was stirred at room temperature for 3 h. The reaction was concentrated in vacuo and dried to afford 3-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)propanoic acid (0.014 mmol). ESI-MS: 536.8$[M-H]^-$, 538.8$[M+H]^+$.

[214] **Step 3:** To a solution in DMF (1.0 mL) of 3-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)propanoic acid (0.014 mmol) and HATU (8.0 mg, 0.021 mmol) was added Ethyldiisopropylamine (9.1 mg, 0.070 mmol) followed by (4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (5.9 mg, 0.015 mmol). The reaction was stirred at room temperature for 3 h. The reaction was concentrated in vacuo, and diluted with DCM and water. The organic layer was separated and concentrated in vacuo. The residue was purified by pre-TLC to afford *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(3-oxo-3-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)propyl)piperazin-1-yl)benzamide (**Compound 17**, 6.0 mg, 0.007 mmol, 46.5%). ESI-MS: 918.6, 920.6$[M-H]^-$; 920.5, 922.5$[M+H]^+$.

Example S18

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((3-(4-(trifluoromethyl)pyridin-2-yl)azetidin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 19)



[215] **Step 1:** Zinc dust (169 mg, 2.6 mmol) was stirred in THF (0.5mL) under N_2 and 1,2-dibromoethane (45.1 mg, 0.24 mmol) was added at RT. The mixture was heated to 65 °C for 5 min and allowed to cool to RT while stirring. TMSCl (24 mg, 0.22 mmol) was then added and the mixture was stirred at RT for 30 min. A solution of tert-butyl 3-iodoazetidine-1-carboxylate (566 mg, 2 mmol) in THF (2 mL) was added slowly. The mixture was allowed to stir at RT for 45 min for next step.

[216] **Step 2:** In a separate flask, $Pd_2(dba)_3$ (18.3 mg, 0.02 mmol), P(2-furyl)$_3$ (18.6 mg, 0.08 mmol) and 2-bromo-4-(trifluoromethyl)pyridine (542.4 mg, 2.4mmol) were mixed in THF(1 mL) under N_2 for 10

min. This mixture was added to the organozinc reagent solution mentioned above followed by iodobenzene in THF (3 mL). The mixture was heated at 65 °C for 2 h, filtered, washed with $NaHCO_3$ and brine, concentrated, purified by colunm chromatography on silic gel eluting with PE to PE/EA=10/1 to afford tert-butyl 3-(4-(trifluoromethyl)pyridin-2-yl)azetidine-1-carboxylate (40 mg).

[217] **Step 3:** To a solution of tert-butyl 3-(4-(trifluoromethyl)pyridin-2-yl)azetidine-1-carboxylate (40 mg) in DCM (1 mL) was added TFA (0.6 mL) at RT. The reaction was stirred at RT for 1h and concentrated to yield crude 2-(azetidin-3-yl)-4-(trifluoromethyl)pyridine (41.6 mg).

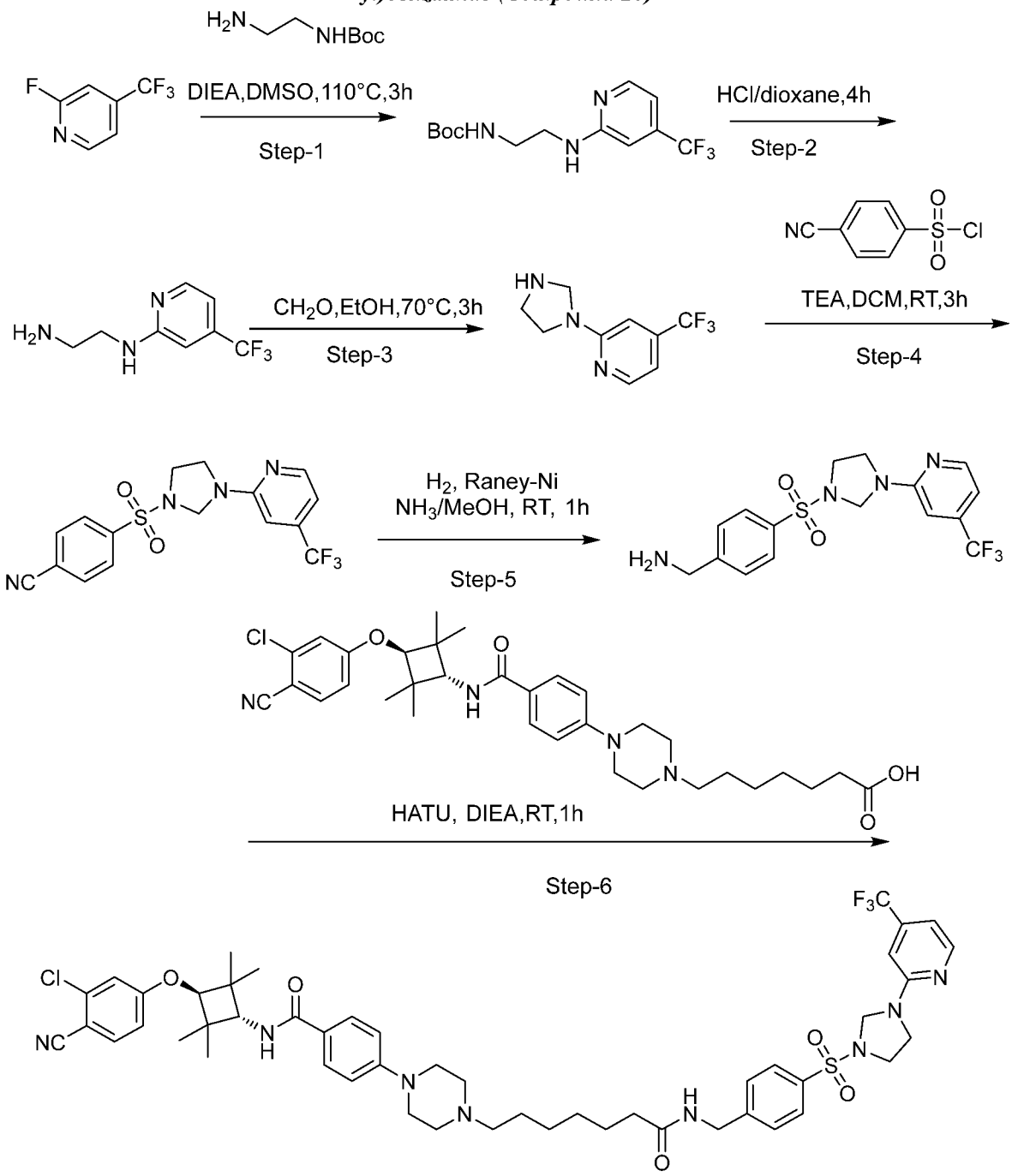
[218] **Step 4:** To a solution of 2-(azetidin-3-yl)-4-(trifluoromethyl)pyridine (41.6 mg, 0.079 mmol) and TEA (23.9 mg, 0.237 mmol) in DCM (2 mL) was added 4-cyanobenzenesulfonyl chloride (15.9 mg,0.079 mmol) in DCM (1 mL) in dropwise. After addition, the mixture was stirred at RT for 1h, concentrated, purified by pre-TLC eluting with PE/EA=4/1 and got 4-((3-(4-(trifluoromethyl)pyridin-2-yl)azetidin-1-yl)sulfonyl)benzonitrile (17 mg).

[219] **Step 5:** To a mixture of 4-((3-(4-(trifluoromethyl)pyridin-2-yl)azetidin-1-yl)sulfonyl)benzonitrile (5.6 mg) and Raney-Ni (100 mg) in MeOH (1 mL) was added ammonia methanol and the atmosphere was replaced with H_2 3 times. The reaction was stirred at RT under H_2 atmosphere for 0.5h, filtered, and concentrated to afford the crude (4-((3-(4-(trifluoromethyl)pyridin-2-yl)azetidin-1-yl)sulfonyl)phenyl)methanamine (5 mg).

[220] **Step 6:** To a solution of 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (8 mg, 13.48 μmol), (4-((3-(4-(trifluoromethyl)pyridin-2-yl)azetidin-1-yl)sulfonyl)phenyl)methanamine (5 mg, 13.48 μmol), and HATU (6.1 mg, 16.17 μmol) in DMF(0.5 mL) was added DIEA(5.2 mg, 40.43 μmol) and stirred at RT for 1h, quenched with H_2O, extracted with DCM 3 times. Combined the organic layer, concentrated, purified by pre-TLC eluting with DCM/MeOH=15/1 to afford the product *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((3-(4-(trifluoromethyl)pyridin-2-yl)azetidin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 19**, 4.5 mg). ESI-MS: 945.6$[M+H]^+$.

Example S19

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((3-(4-(trifluoromethyl)pyridin-2-yl)imidazolidin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 20)



[221] **Step 1:** 2-fluoro-4-(trifluoromethyl)pyridine (200 mg, 0.88 mmol), tert-butyl (2-aminoethyl)carbamate (140 mg, 0.875 mmol), and DIEA (230 mg, 1.78 mmol) were dissolved in DMSO (5 mL). The reaction mixture was stirred at 110 °C. After 3 hours the reaction was completed. 10 mL of a saturated NaCl solution was then added and the product extracted with EtOAc (3×10 mL). The organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude product which was purified

by silica gel column chromatography eluting with PE/EA (3/1) to give tert-butyl tert-butyl (2-((4-(trifluoromethyl)pyridin-2-yl)amino)ethyl)carbamate (250 mg, 0.81 mmol, 92%) as a white solid.

[222] **Step 2:** Tert-butyl (2-((4-(trifluoromethyl)pyridin-2-yl)amino)ethyl)carbamate (250 mg, 0.81 mol) was dissolved in 4 mL HCl/dioxane, the reaction mixture was stirred at room temperature for 4 h, concentrated and the residue was washed by Et_2O to give N^1-(4-(trifluoromethyl)pyridin-2-yl)ethane-1,2-diamine (166 mg, 0.81 mmol, 99%) as white solid.

[223] **Step 3:** To the mixture of N^1-(4-(trifluoromethyl)pyridin-2-yl)ethane-1,2-diamine (166 mg, 0.81 mmol), in EtOH (2 ml) was added formaldehyde (3 ml) at 70 °C for 3 hours, and concentrated in vacuo to give the crude product which was purified by silica gel column chromatography eluting with DCM/MeOH (20/1) to give 2-(imidazolidin-1-yl)-4-(trifluoromethyl)pyridine (150 mg, 0.69 mmol, 85%) as oil.

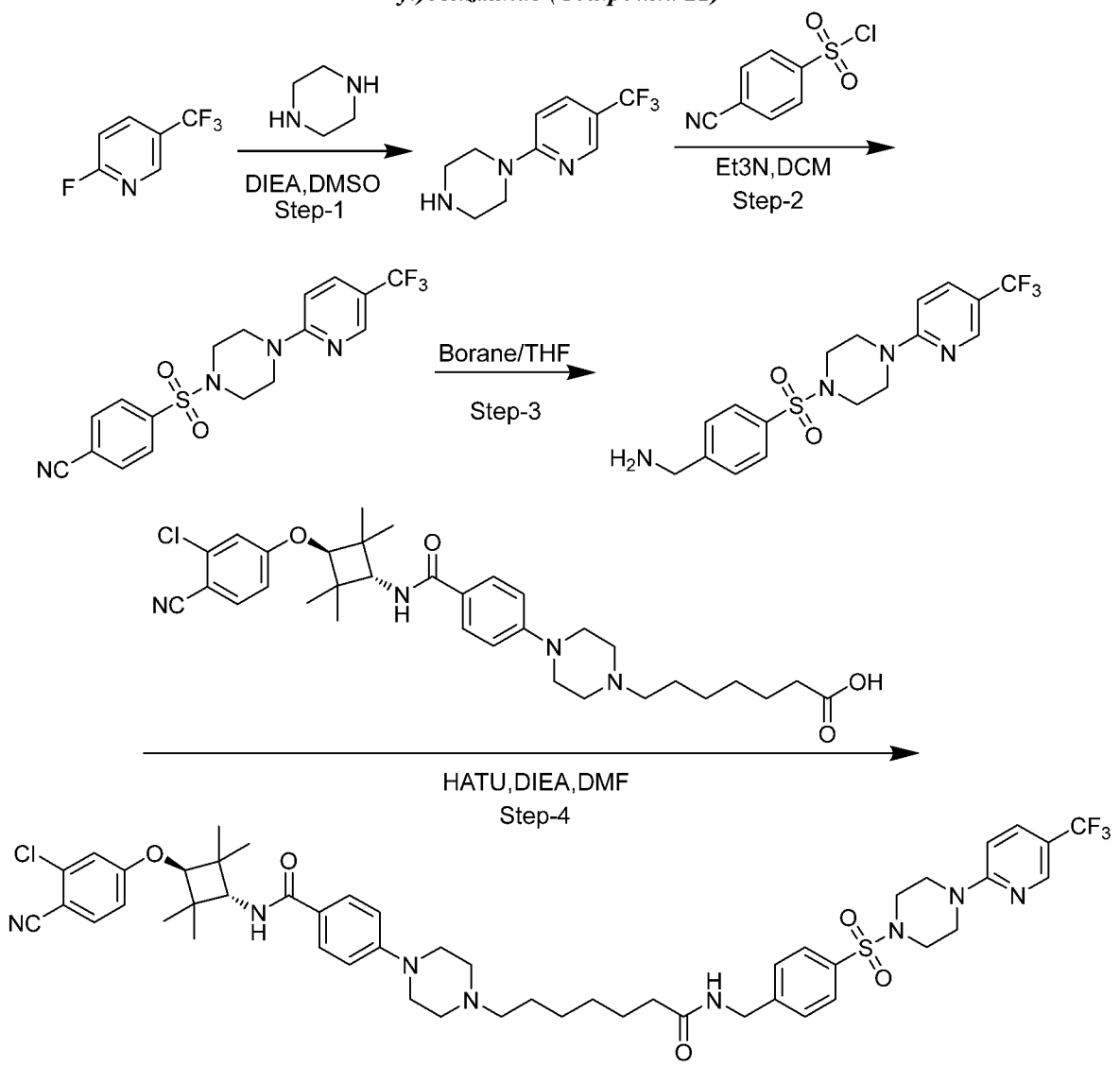
[224] **Step 4:** To the mixture of 2-(imidazolidin-1-yl)-4-(trifluoromethyl)pyridine (150 mg, 0.69 mmol) and TEA (263 mg, 2.6 mmol) in DCM (10ml) was added 4-cyanobenzenesulfonyl chloride (264 mg, 1.3 mmol), the reaction mixture was stirred at RT for 3 hours and concentrated in vacuo to give the crude product which was purified by silica gel column chromatography eluting with PE/EA (3/1) to give 4-((3-(4-(trifluoromethyl)pyridin-2-yl)imidazolidin-1-yl)sulfonyl)benzonitrile (125 mg, 0.32 mmol, 47%) as white solid.

[225] **Step 5:** To the mixture of 4-((3-(4-(trifluoromethyl)pyridin-2-yl)imidazolidin-1-yl)sulfonyl)benzonitrile (10 mg, 0.026 mmol) in NH_3/MeOH was added Raney-Ni (10mg). The reaction mixture was stirred at RT under H_2 for 1 hour , filtered and concentrated in vacuo to give the crude product (4-((3-(4-(trifluoromethyl)pyridin-2-yl)imidazolidin-1-yl)sulfonyl)phenyl)methanamine (6.7 mg) as white solid.

[226] **Step 6:** 7-(4-(4-((3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (12 mg, 0.021 mmol), (4-((3-(4-(trifluoromethyl)pyridin-2-yl)imidazolidin-1-yl)sulfonyl)phenyl)methanamine (6.7 mg, 0.021 mmol), and DIEA (8.3 mg, 0.064 mmol) were dissolved in DMF (1 mL), and HATU (12 mg, 0.032 mmol) was added to the solution. After 1 hour the reaction was completed. 2 mL of a saturated NaCl solution was then added and the product extracted with EtOAc (3×2 mL). The organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude product which was purified by P-TLC with DCM/MeOH (10/1) to give *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((3-(4-(trifluoromethyl)pyridin-2-yl)imidazolidin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 20**, 4 mg, 0.0041 mol,20%) as a white solid.

Example S20

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 21)



[227] **Step 1:** To a stirred solution of 2-fluoro-5-(trifluoromethyl)pyridine (500.0 mg, 3.029 mmol) in DMSO (5 mL) were added piperazine (313.1 mg, 3.634 mmol) and DIEA (782.8 mg, 6.058 mmol) and the reaction was stirred at 110 °C for 6 h. The reaction was diluted with DCM and H_2O. The organic layer was separated, washed with H_2O and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford crude product of 1-(5-(trifluoromethyl)pyridin-2-yl)piperazine (748.2 mg, 106.83%).

[228] **Step 2:** To a stirred solution of 1-(5-(trifluoromethyl)pyridin-2-yl)piperazine (748.2 mg 3.236 mmol) in DCM (8 mL) were added 4-cyanobenzenesulfonyl chloride (456.7 mg, 2.265 mmol) and Et_3N (458.4 mg, 4.530 mmol) and the reaction was stirred at room temperature for 2 h. The reaction was diluted with DCM and H_2O. The organic layer was separated, washed with H_2O and brine, and concentrated in

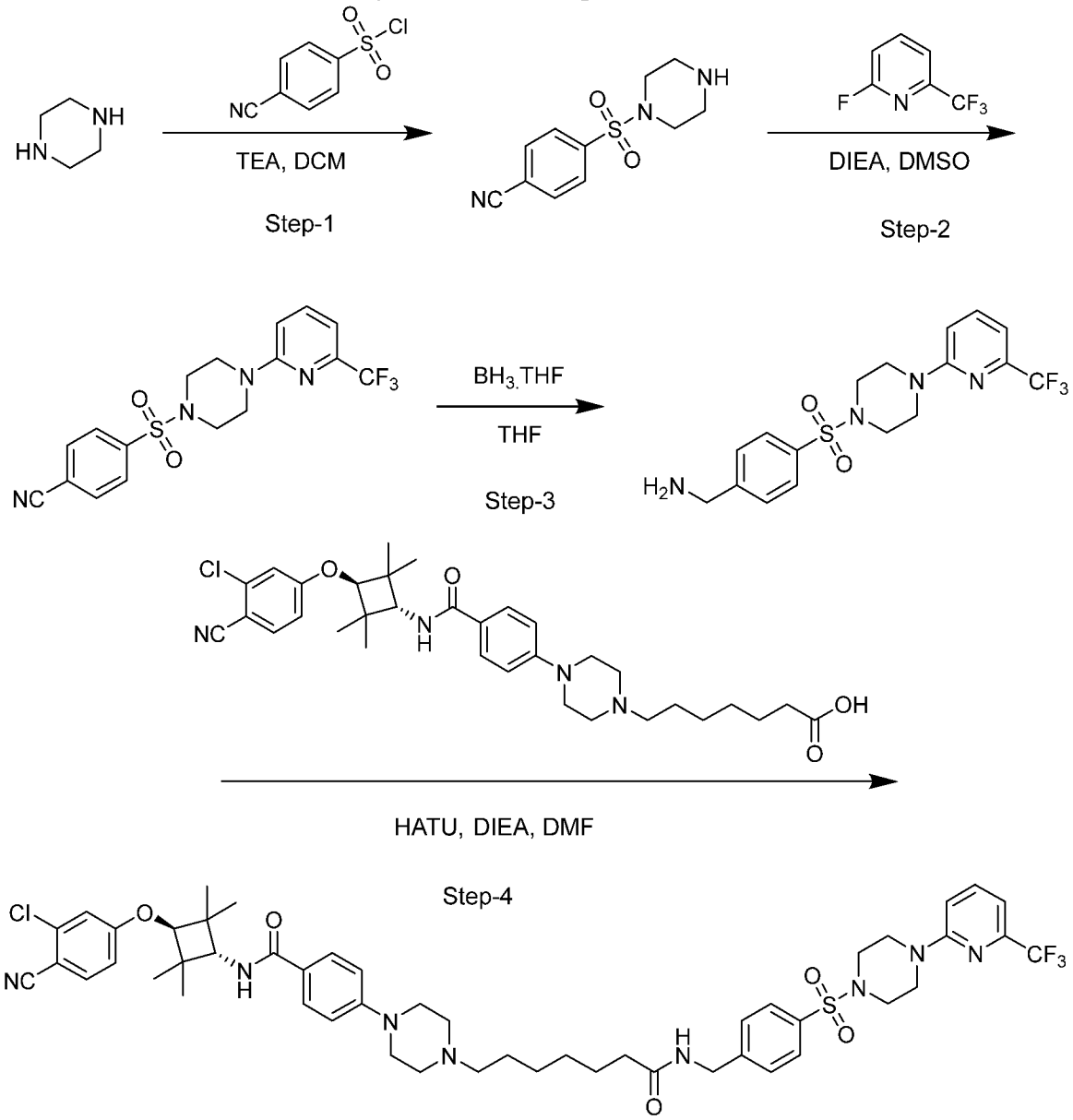
vacuo to give a crude product which was purified by column chromatography to afford 4-((4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzonitrile (809.3 mg, 90.14%).

[229] **Step 3:** To a stirred solution of 4-((4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzonitrile (100.0 mg 0.252 mmol) in THF (2.5 mL) was added Borane/THF(1M, 2.5 mL, 2.522 mmol) slowly at 0 °C. After the addition, the reaction was stirred at room temperature for 5 h. The reaction was quenched with MeOH and the resulting mixture was stirred with HCl (1M, 1ml) at 70 °C for 30 min. The reaction mixture was evaporated to remove MeOH. The residue was diluted with H_2O, adjusted to pH 8-9 with saturated $NaHCO_3$ solution, extracted with DCM. The organic layer was separated, washed with saturated $NaHCO_3$ solution, H_2O and brine. The organic layer was concentrated in vacuo and purified by pre-TLC to give (4-((4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (57.5 mg).

[230] **Step 4:** To a stirred solution in DMF (1.5 mL) of 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (6.0 mg, 10.076 μmol) and HATU (5.7 mg, 15.114 μmol) were added DIEA (3.9 mg, 30.228 μmol) and (4-((4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (4.0 mg, 10.076 μmol), and stirred at room temperature for 2 h. The reaction was concentrated in vacuo. The residue was purified by pre-TLC to give *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 21**, 7.2 mg, 73.09%). ESI-MS: 974.6$[M+H]^+$.

Example S21

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 22)



[231] **Step 1:** To a solution of piperazine (43 mg, 1 eq) in DCM (3 mL) were added 4-cyanobenzenesulfonyl chloride (100 mg, 1 eq) and TEA (101 mg, 2 eq), and the reaction was stirred at room temperature for 3 hours. TLC showed new spot was observed, and no starting material remained. The reaction mixture was diluted with water and saturated $NaHCO_3$ solution. The combined aqueous layers were extracted with DCM. The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo to afford 4-(piperazin-1-ylsulfonyl)benzonitrile (124 mg) as a yellow solid.

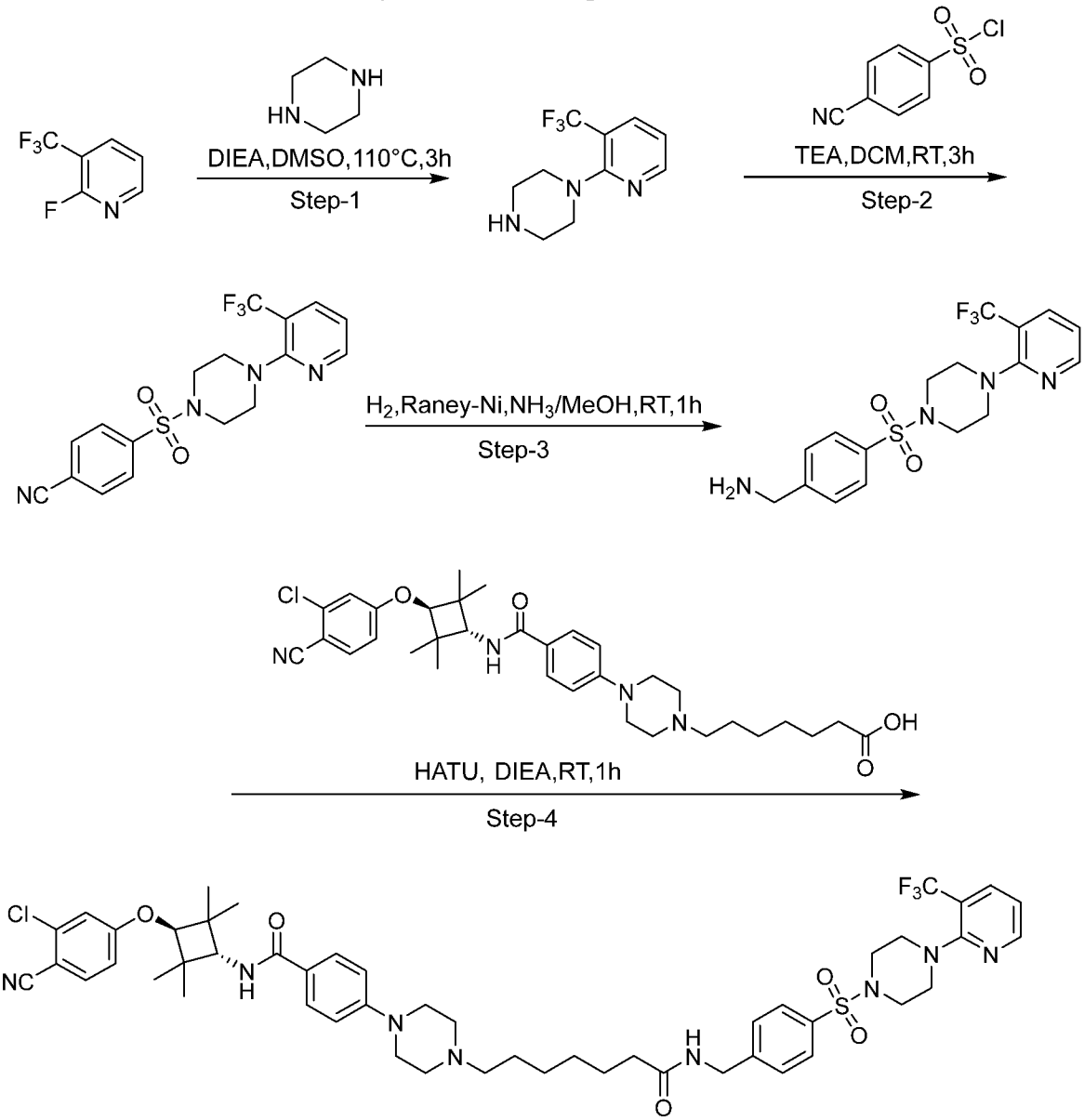
[232] **Step 2:** To a solution of 4-(piperazin-1-ylsulfonyl)benzonitrile (60 mg, 1 eq) in DMSO (3 mL) were added 2-fluoro-6-(trifluoromethyl)pyridine (47 mg, 1.2 eq), and DIEA (62 mg, 2 eq). The reaction was stirred at 110 °C for 6 hours. TLC showed new spot was observed, and no starting material remained. The reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (PE: EA=1:1) to afford 4-((4-(6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzonitrile (40 mg) as a white solid.

[233] **Step 3:** To a solution of 4-((4-(6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzonitrile (40 mg, 1 eq) in THF (3 mL) was added BH_3•THF (1mL, 10 eq). The reaction was stirred at room temperature for 2 hours. TLC showed new spot was observed, and no material was remained. The reaction mixture was quenched by the addition of MeOH, then 0.5 mL HCl (1 M) was added. The reaction mixture was stirred at 70 °C for 30 minutes. The reaction mixture was concentrated in vacuo. The residue was neutralized with saturated $NaHCO_3$ solution and extracted with DCM (10 mL × 4), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=10:1) to afford (4-((4-(6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (20 mg) as a yellow solid.

[234] **Step 4:** To a solution of 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (5 mg, 1 eq) in DMF (2 mL) were added (4-((4-(6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (4 mg, 1.1 eq), HATU (10 mg, 3 eq), and DIEA (6 mg, 5 eq), and the reaction was stirred at room temperature for 2 hours. TLC showed new spot was observed, and no material was remained, the reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=10:1) to afford *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 22**, 5.4 mg) as a white solid. ESI-MS: 976.5 $[M+H]^+$.

Example S22

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 23)



[235] **Step 1:** 2-fluoro-3-(trifluoromethyl)pyridine (200 mg, 1.21 mmol), piperazine (125 mg, 1.45 mmol) and DIEA (313 mg, 2.42 mmol) were dissolved in DMSO (5 mL). The reaction mixture was stirred at 110 °C. After 3 hours the reaction was completed. 10 mL of a saturated NaCl solution was then added and the product extracted with EtOAc (3×10 mL).The organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 1-(3-(trifluoromethyl)pyridin-2-yl)piperazine (250 mg, 1.08 mol, 89%) as oil.

[236] **Step 2:** To the mixture of 1-(3-(trifluoromethyl)pyridin-2-yl)piperazine (250 mg, 1.08 mol) and TEA (186 mg, 2.84 mmol) in DCM (10ml) was added 4-cyanobenzenesulfonyl chloride (286 mg, 1.42

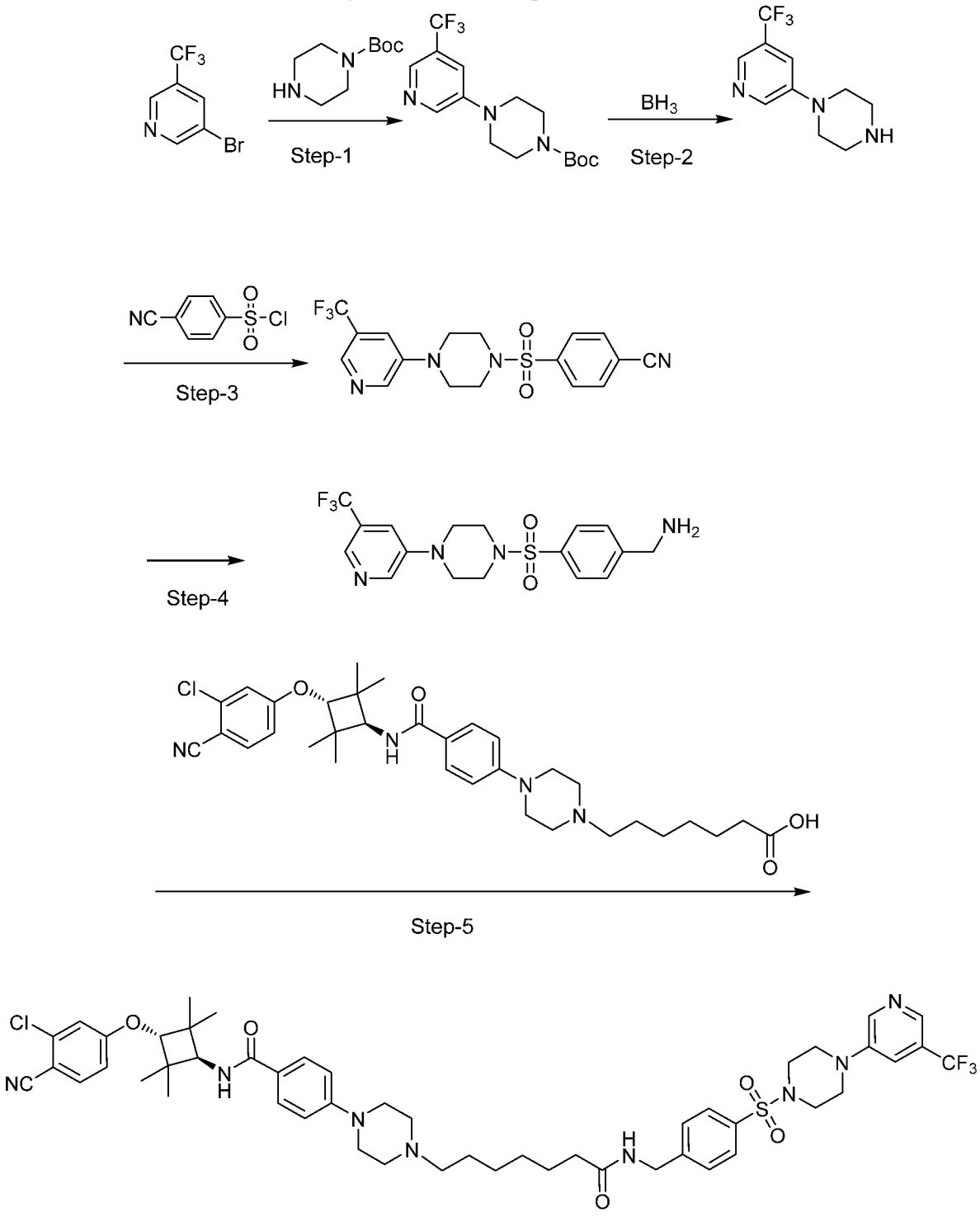
mmol), the reaction mixture was stirred at RT for 3 hours and concentrated in vacuo to give the crude product which was purified by silica gel column chromatography eluting with PE/EA (5/1) to give 4-((4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzonitrile (180 mg,0.45 mmol, 41%) as white solid.

[237] **Step 3:** To the mixture of 4-((4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzonitrile (180 mg 0.45 mmol) in NH_3/MeOH was added Raney-Ni (10 mg), the reaction mixture was stirred at RT under H_2 for 1 hour, filtered and concentrated in vacuo to give the crude product (4-((4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (61 mg, 0.15 mmol, 0.34%) as white solid.

[238] **Step 4:** 7-(4-(4-((3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (12 mg, 0.021 mmol), (4-((4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (8 mg, 0.02 mmol) and DIEA (8.3 mg, 0.064 mmol) were dissolved in DMF (1 mL), and HATU (12 mg, 0.032 mmol) was added to the solution. After 1 hour the reaction was completed. 2 mL of a saturated NaCl solution was then added and the product extracted with EtOAc (3×2 mL). The organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude product which was purified by P-TLC with DCM/MeOH (10/1) to give *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 23**, 9 mg, 0.0092 mol, 46%) as a white solid.

Example S23

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 24)



[239] **Step 1:** A solution of 3-bromo-5-(trifluoromethyl)pyridine (50 mg, 1.0 eq), tert-butyl piperazine-1-carboxylate (61.7 mg, 1.5 eq), Ruphos Pd (18.5 mg, 0.1 eq), Cs_2CO_3 (144.3 mg, 2.0 eq) in Tol (2 ml) was stirred under N_2 at 90°C for 3h. The solvent was removed. The mixture was purified by

Pre-TLC(2:1) to give tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-carboxylate (32 mg) ESI-MS: 332.2 [M+H]+.

[240] **Step 2:** To a solution of tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-carboxylate (32 mg) in 1,4-dioxane (1 ml) was added HCl/dioxane (1 ml). the reaction was stirred at RT for 1h. The mixture was evaporated to afford 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine (22 mg), ESI-MS: 232.2[M+H]+.

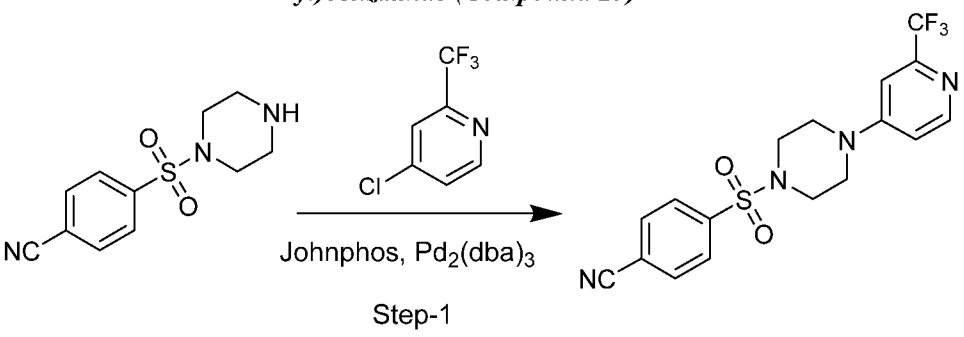
[241] **Step 3:** To a solution of 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine (22 mg, 1.0 eq), in DCM (2 ml) was added Et_3N (24 mg, 2.5 eq), 4-cyanobenzenesulfonyl chloride (19.2 mg, 1.0 eq). The reaction was stirred at RT for 4h. TLC showed complete reaction of starting materials. The mixture was purified by Pre-TLC (DCM:MeOH=1.5:1) to give 4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)benzonitrile (18 mg), ESI-MS: 397.1[M+H]+.

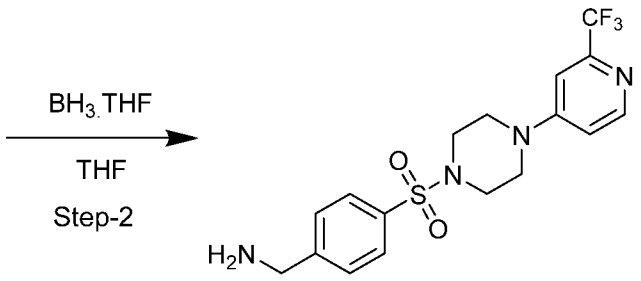
[242] **Step 4:** To a solution of 4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)benzonitrile (18 mg, 1.0 eq) in THF (2 ml) was added slowly BH_3/THF (1M/L, 0.3 ml, 5.0 eq) at -5°C, then stirred at RT for 3h. The reaction mixture was quenched by the addition of MeOH, stirred at RT for 5min, added 1M HCl aqueous solution (0.3 ml), stirred at 70 °C for 30 min, the mixture was cooled to RT, $NaHCO_3$ aqueous solution was added to adjust to aqueous pH=8-9. The combined aqueous layers were extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by pre-TLC (DCM:MeOH=8:1) to afford (4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (7 mg), ESI-MS: 401.1[M+H]+.

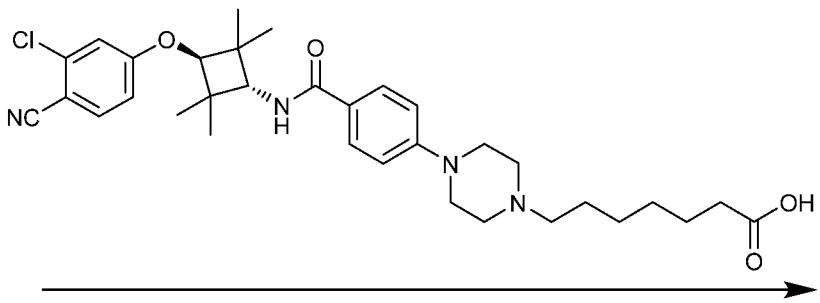
[243] **Step 5:** A solution of (4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (5 mg, 1.0 eq), 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (7.5 mg, 1.0 eq), HATU(7.2 mg, 1.5 eq), DIEA (5 mg, 3.0 eq) in DMF(1 ml) was stirred at RT for 1h. TLC showed complete reaction of starting materials. The solvent was removed and the mixture was purified by pre-TLC (DCM:MeOH=10:1) to afford the product *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 24**, 9 mg), ESI-MS: 977.4[M+H]+.

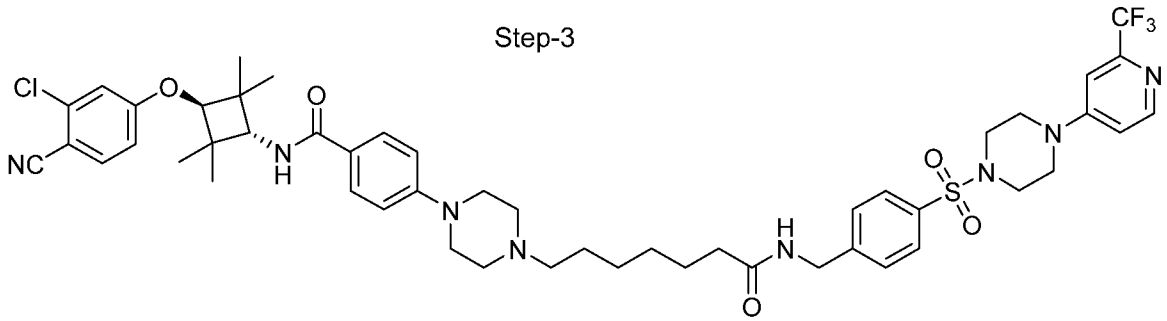
Example S24

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(2-(trifluoromethyl)pyridin-4-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 25)









[244] **Step 1:** To a solution of 4-(piperazin-1-ylsulfonyl)benzonitrile (40 mg, 1 eq) in toluene (3 mL) were added 4-chloro-2-(trifluoromethyl)pyridine (58mg, 2 eq), JohnPhos (20 mg, 0.4 eq), $Pd_2(dba)_3$ (30 mg, 0.2 eq) and K_2CO_3 (66 mg, 3 eq), and the reaction was stirred at 120 °C for 8 hours under nitrogen atmosphere. TLC showed new spot was observed, and no starting material was remained. The reaction

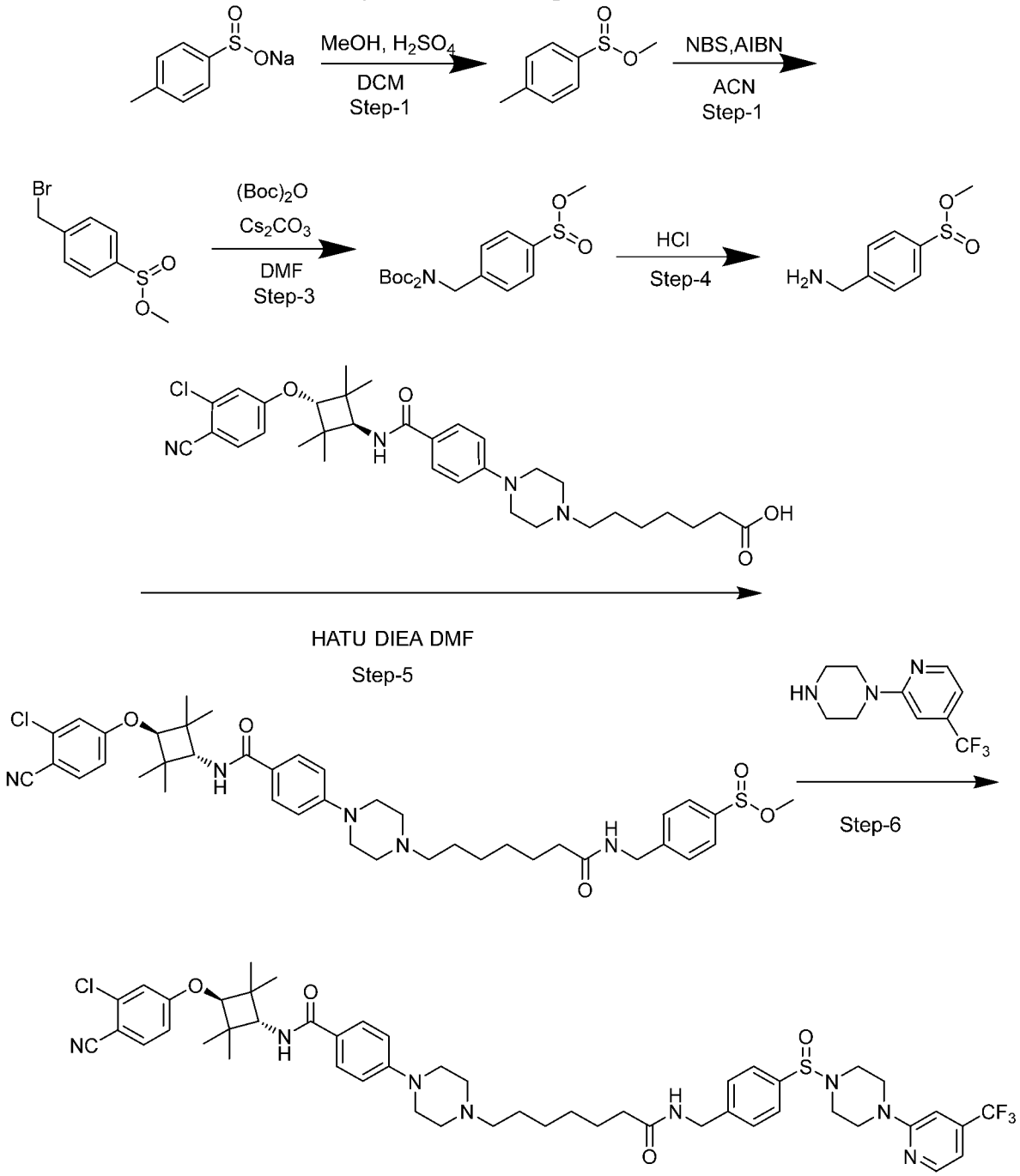
mixture was diluted with water and extracted with DCM. The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4. The residue was purified by preparative TLC (PE: EA=2:1) to afford 4-((4-(2-(trifluoromethyl)pyridin-4-yl)piperazin-1-yl)sulfonyl)benzonitrile (40 mg). ESI-MS: 396.8 $[M+H]^+$.

[245] **Step 2:** To a solution of 4-((4-(2-(trifluoromethyl)pyridin-4-yl)piperazin-1-yl)sulfonyl)benzonitrile (40 mg, 1 eq) in THF (3 mL) was added BH_3•THF (1 mL, 10 eq), the reaction was stirred at room temperature for 2 hours. TLC showed new spot was observed, and no material was remained, the reaction mixture was quenched by the addition of MeOH, 2 mL HCl (1 M) was added. The reaction mixture was stirred at 70°C for 30 minutes. The reaction mixture was concentrated in vacuo. The residue was neutralized with saturated $NaHCO_3$ solution and extracted with DCM (10 mL × 4), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=10:1) to afford (4-((4-(2-(trifluoromethyl)pyridin-4-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (8 mg) as a white solid. ESI-MS: 401.1 $[M+H]^+$.

[246] **Step 3:** To a solution of 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (5 mg, 1 eq) in DMF (2 mL) were added (4-((4-(2-(trifluoromethyl)pyridin-4-yl)piperazin-1-yl)sulfonyl)phenyl)methanamine (4 mg, 1.1 eq), HATU (10 mg, 3 eq), and DIEA (6 mg, 5 eq), and the reaction was stirred at room temperature for 3 hours. TLC showed new spot was observed, and no material was remained. The reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=10:1) to afford *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(2-(trifluoromethyl)pyridin-4-yl)piperazin-1-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (***Compound 25***, 4.2 mg) as a white solid. ESI-MS: 489.3 $[M/2+H]^+$.

Example S25

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfinyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 26)



[247] **Step 1:** To a mixture of sodium 4-methylbenzenesulfinate (3.5 g, 19.6 mmol) and MeOH (2.4 mL) in DCM (25 mL) was added con. H_2SO_4. After addition, the reaction was stirred at RT for 0.5h, and molecular sieves (3.2 g) were added. Then the mixture was stirred overnight. The reaction was diluted with

DCM, filtered, washed with H_2O 3 times, concentrated, and purified by column chromatography on silica gel eluting with PE to PE/EA=50/1, 25/1 to afford the product methyl 4-methylbenzenesulfinate (3.2 g).

[248] **Step 2:** A solution of methyl methyl 4-methylbenzenesulfinate (170 mg, 1 mmol) in acetonitrile (3 mL) was added NBS (195.8 mg, 1.1 mmol) and AIBN (16.4 mg, 0.1 mmol) under N_2 atmosphere. After addition, the reaction mixture was heated at 70 °C for 16h. The reaction was then concentrated, and then purified by column chromatography on silica gel eluting with PE to PE/EA=10/1 to afford the product methyl 4-(bromomethyl)benzenesulfinate (55 mg).

[249] **Step 3:** A mixture of methyl 4-(bromomethyl)benzenesulfinate (124 mg, 0.5 mmol), di-tert-butyl iminodicarbonate (130.2 mg, 0.6 mmol) and Cs_2CO_3 (326 mmol, 1 mmol) in DMF(2 mL) was heated at 70 °C under N_2 atmosphere for 2h. The reaction mixture was poured into H_2O, extracted with EA 4 times, washed with NH_4Cl aqueous, dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel eluting with PE to PE/EA=10/1 to afford the product methyl 4-((bis(tert-butoxycarbonyl)amino)methyl)benzenesulfinate (97 mg).

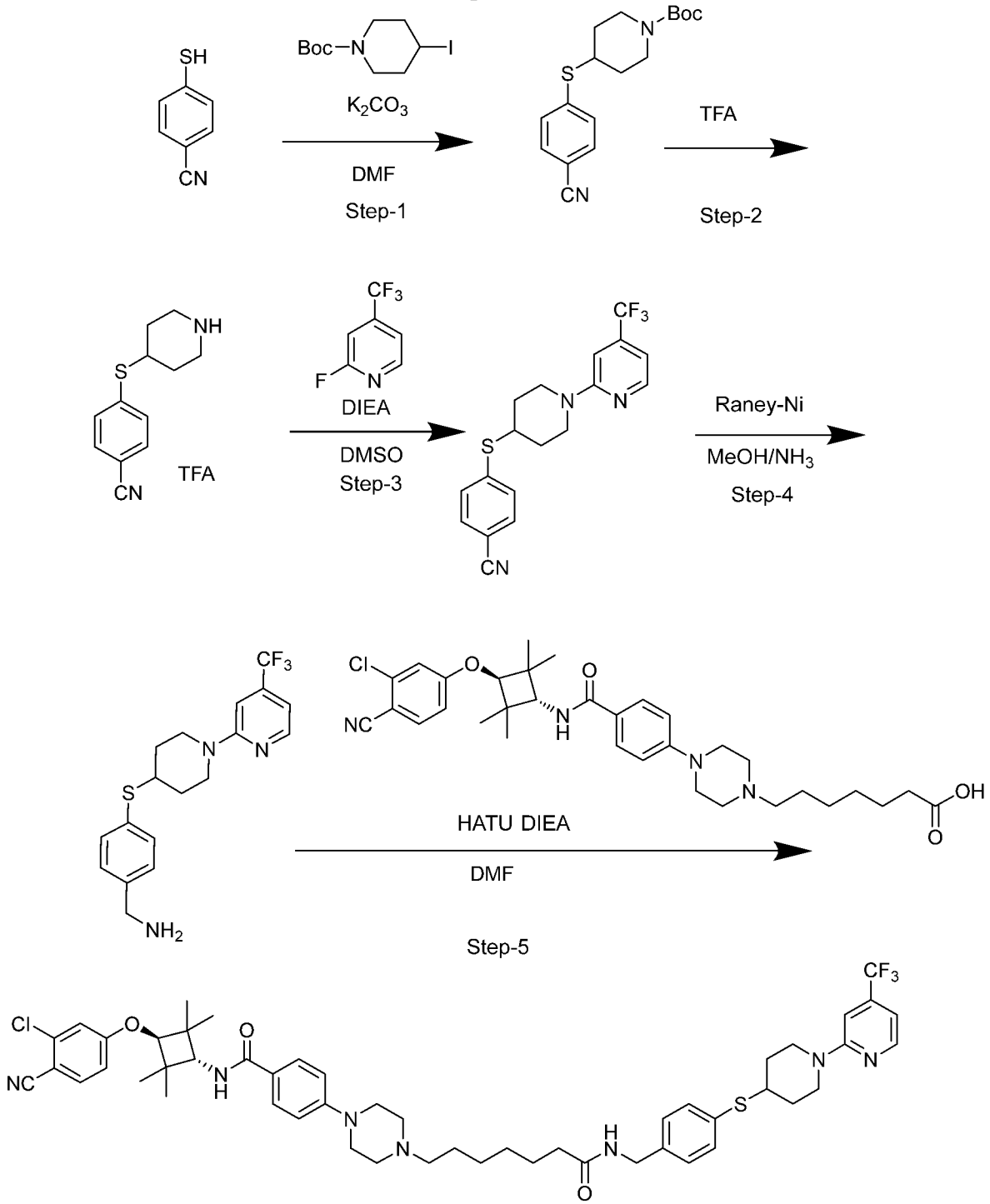
[250] **Step 4:** To a solution of methyl methyl 4-((bis(tert-butoxycarbonyl)amino)methyl)benzenesulfinate (97 mg) in dioxane (0.3 mL) was added 1,4-dioxane hydrochloride (1 mL) at ice-bath temperature and stirred at RT for 18h. The reaction was concentrated to afford crude methyl 4-(aminomethyl)benzenesulfinate (65 mg).

[251] **Step 5:** To a mixture of methyl 4-(aminomethyl)benzenesulfinate (4.1 mg, 18.52 μmol), 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (10 mg, 16.84 μmol) and HATU (7.7 mg, 20.20 μmol) in DMF (0.5 mL) was added DIEA (6.5 mg, 50.51 μmol) and the reaction stirred at RT for 1h. The reaction was concentrated and purified by column chromatography on silica gel eluting with DCM/MeOH=15/1 to afford the product methyl 4-((7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanamido)methyl)benzenesulfinate (9.3 mg).

[252] **Step 6:** An oven-dried pressure tube was charged with a magnetic stir bar, $NiCl_2$ (77.6 μg, 0.60 μmol), and IPr•HCl (1 mg, 2.39 μmol). The solvent THF was then added. Afterwards methyl 4-((7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanamido)methyl)benzenesulfinate (9.3 mg, 11.94 μmol) and 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine hydrochloride (5.5 mg, 23.88 μmol) were subsequently added into the reaction mixture. The reaction was stirred under N_2 atmosphere at 100 °C for 16h, and the was concentrated, and purified by pre-TLC eluting with DCM/MeOH=15/1 to afford the product *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfinyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 26**, 4.5 mg), ESI-MS: 958.6$[M+H]^+$.

Example S26

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)thio)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 27)



[253] **Step 1:** To a solution of 4-mercaptobenzonitrile (120 mg, 1.0 eq) in DMF (3 mL) was added K_2CO_3 (245 mg, 2.0 eq) and tert-butyl 4-iodopiperidine-1-carboxylate (304.8 mg, 1.1 eq.), and at 90 °C the yellow mixture was stirred at for 3 h. TLC (PE/EA=8/1, Rf=0.8) showed 4-mercaptobenzonitrile was

consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was directly purified with pre-TLC (PE/EA=8/1) to afford tert-butyl 4-((4-cyanophenyl)thio)piperidine-1-carboxylate (230.0 mg, white solid).

[254] **Step 2:** To a solution of tert-butyl 4-((4-cyanophenyl)thio)piperidine-1-carboxylate (22 mg, 1.0 eq) in DCM(1 mL) was added TFA (1 mL), the yellow mixture was stirred at r.t. for 3 h. TLC (DCM/MeOH=10/1, Rf=0.2) showed tert-butyl 4-((4-cyanophenyl)thio)piperidine-1-carboxylate was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo to afford 4-(piperidin-4-ylthio)benzonitrile•TFA (20.0 mg, white solid).

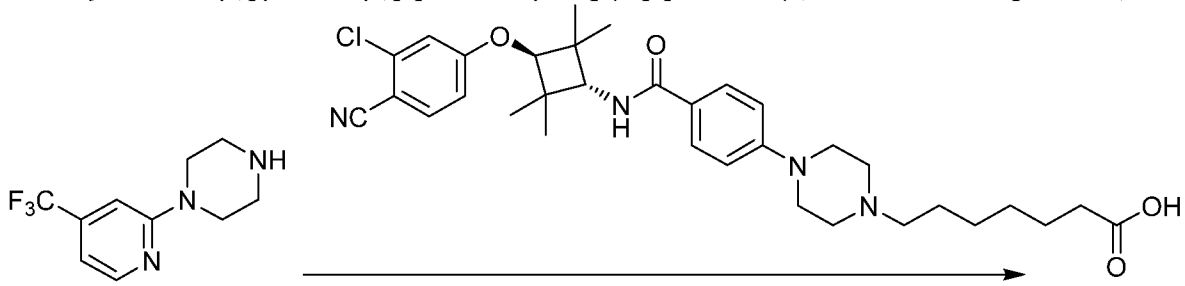
[255] **Step 3:** To a solution of 4-(piperidin-4-ylthio)benzonitrile•TFA (20mg, 1.0eq) in DMSO(1 mL) was added 2-fluoro-4-(trifluoromethyl)pyridine (10.9mg, 1.1eq) and DIEA (23.3 mg, 3.0 eq), and the yellow mixture was stirred at 110 °C for 3 h. TLC (DCM/MeOH=10/1, Rf=0.2) showed 4-(piperidin-4-ylthio)benzonitrile•TFA was consumed, reaction had mainly a new spot. The combined aqueous layers were extracted with EtOAc (5 mL×4) to remove neutral impurities. The combined organic layers were dried over MgSO4 and concentrated. The residue was directly purified with pre-TLC (PE/EA=8/1) to afford 4-((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)thio)benzonitrile (13.0 mg, white solid). ESI-MS: 364.3[M+H]+.

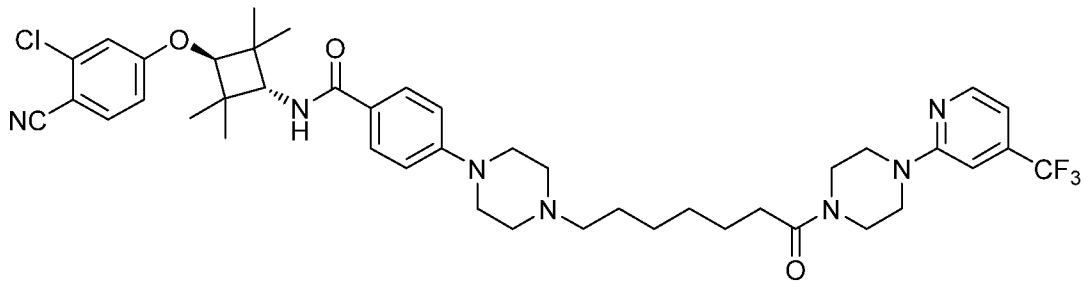
[256] **Step 4:** To a solution of 4-((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)thio)benzonitrile (13 mg, 1.0 eq) in MeOH/NH_3 (2 mL) was added H_2, Raney-Ni (2 mg), the black mixture was stirred at r.t. for 3 h. TLC (DCM/MeOH=10/1, Rf=0.3) showed 4-((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)thio)benzonitrile was consumed, reaction had mainly a new spot. The reaction solution was filtered. The mixture was then concentrated in vacuo, to afford (4-((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)thio)phenyl)methanamine (11mg, white solid). ESI-MS: 368.3[M+H]+.

[257] **Step 5:** A solution of (4-((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)thio)phenyl)methanamine (3.0 mg, 1.0 eq.) in DMF (1 mL) was added to 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (5.0 mg, 1.0 eq.), HATU (4.7 mg, 1.5 eq.), and DIEA (15 mg, 3.0 eq.) at 0-5 °C, and the yellow mixture was stirred at r.t. for 3 h. TLC (MeOH/DCM=1/10, Rf=0.6) showed (4-((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)thio)phenyl)methanamine was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was directly purified with pre-TLC (MeOH/DCM=1/12) to afford *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)thio)benzyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 27**, 3.5mg, off-white solid). ESI-MS: 942.3[M+H]+.

Example S27

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-(4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)heptyl)piperazin-1-yl)benzamide (Compound 28)

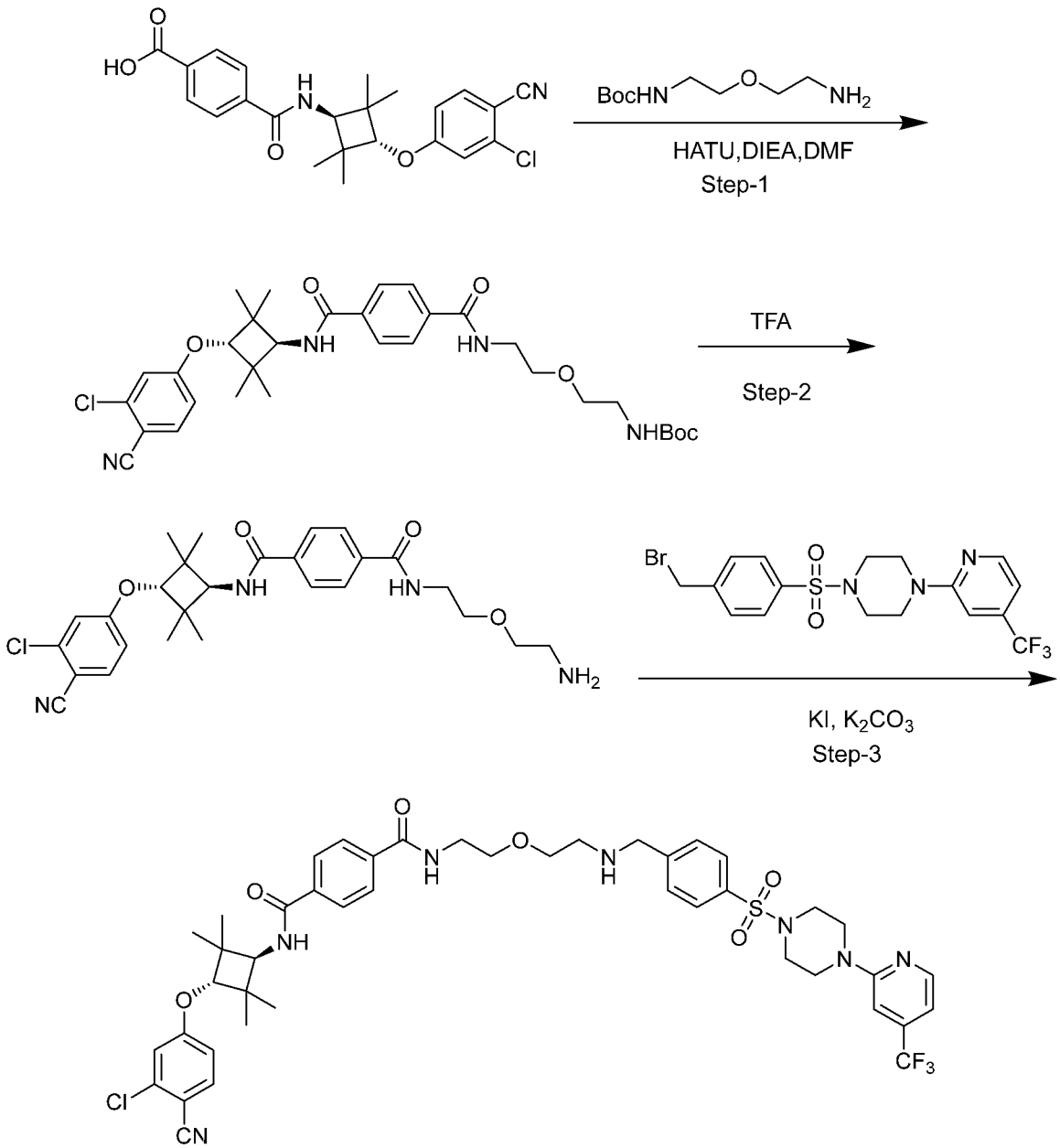




[258] A solution of 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (3 mg, 1.0 eq), 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (5.1 mg, 1.0 eq), HATU (4.9 mg, 1.5 eq), and DIEA (3.3 mg, 3.0 eq) in DMF (1 ml) was stirred at RT for 30 min. TLC showed complete reaction of starting materials. The solvent was removed and the mixture was purified by pre-TLC(DCM:MeOH=10:1) to afford the product *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-(4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)heptyl)piperazin-1-yl)benzamide (**Compound 28**, 1.5mg) ESI-MS: 808.4 [M+H]+.

Example S28

Synthesis of N^1-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-N^4-(2-(2-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)ethoxy)ethyl)terephthalamide (Compound 29)



[259] **Step 1:** To a mixture of 4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)benzoic acid (18 mg, 42.25 μmol), tert-butyl (2-(2-aminoethoxy)ethyl)carbamate (8.6 mg, 42.52 μmol) and HATU (19.3 mg, 50.70 μmol) in DMF (1 mL) was added DIEA (16.4 mg, 126.76 μmol) at RT. Then the reaction was stirred at RT overnight. Then the reaction was poured into H_2O, extracted with DCM 4 times. Ther organic layers were combined, concentrated, and purified by pre-TLC eltuting with DCM/MeOH=15/1 for 3 times to afford the product tert-butyl (2-(2-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)benzamido)ethoxy)ethyl)carbamate (20 mg).

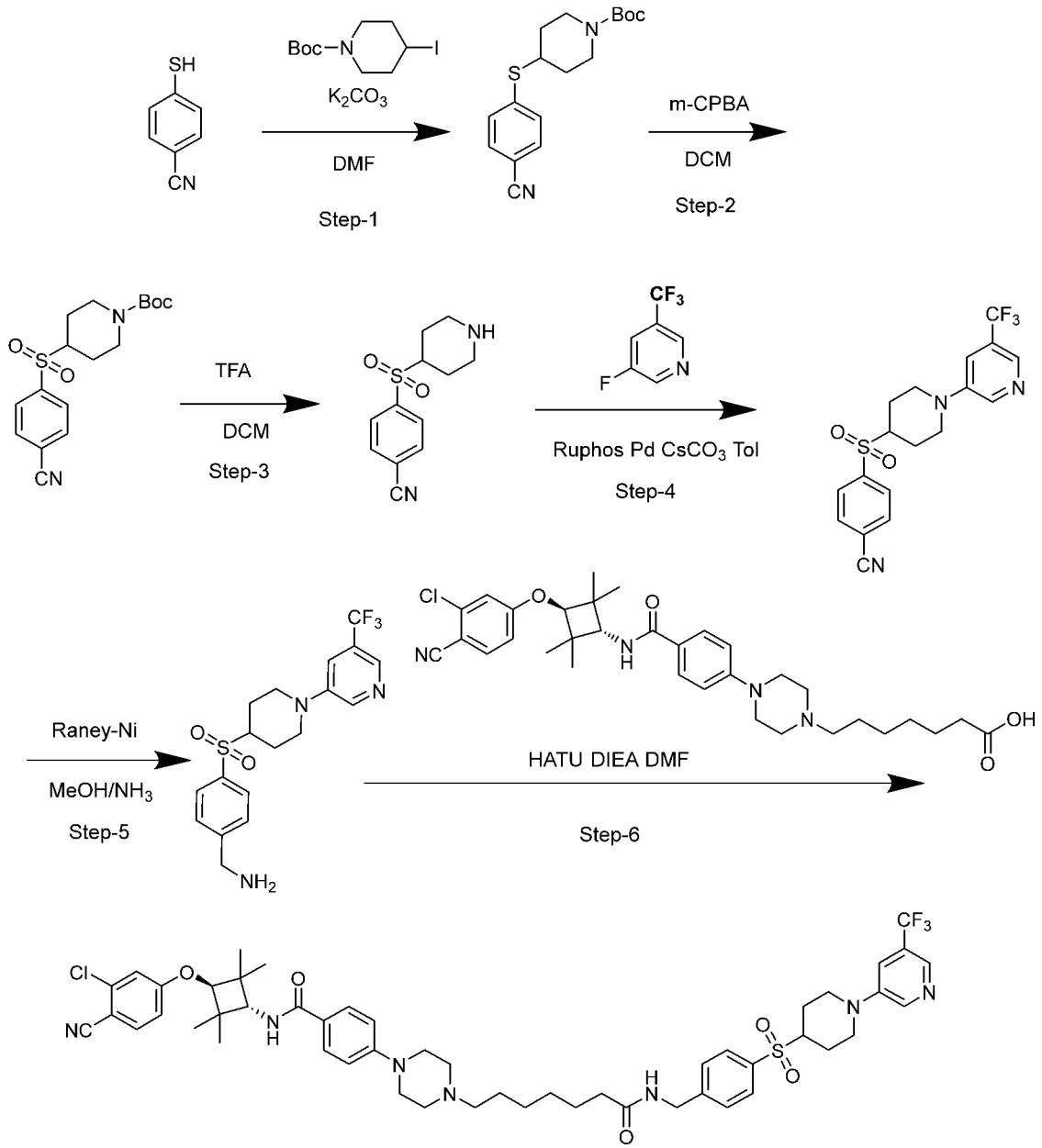
[260] **Step 2:** Tert-butyl (2-(2-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)benzamido)ethoxy)ethyl)carbamate (20 mg) was dissolved in dioxane and added 1,4-dioxane hydrochloride (1 mL) at ice-bath. Then the reaction was stirred at RT for 1h.

Concentrated to afford the crude product N^1-(2-(2-aminoethoxy)ethyl)-N^4-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)terephthalamide (30 mg) for next step.

[261] **Step 3:** N^1-(2-(2-aminoethoxy)ethyl)-N^4-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)terephthalamide (10 mg, 18.25 μmol), 1-((4-(bromomethyl)phenyl)sulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazine (7.7 mg, 18.25 μmol), KI (1 mg) and K_2CO_3 (7.6 mg,54.74 μmol) in ACN (1.5 mL) was stirred at RT for 1h. Then heated at 60 °C for 2h. Purified by pre-TLC eluting with DCM/MeOH=12/1 to afford the product *N*^{1}-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-*N*^{4}-(2-(2-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzyl)amino)ethoxy)ethyl)terephthalamide (**Compound 29**, 6.4 mg), ESI-MS: 895.6$[M+1]^+$.

Example S29

Synthesis N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 30)



[262] **Step 1:** To a solution of 4-mercaptobenzonitrile (120mg, 1.0eq) in DMF (3 mL) was added K_2CO_3 (245 mg, 2.0 eq) and tert-butyl 4-iodopiperidine-1-carboxylate (304.8 mg, 1.1 eq.), at 90 °C. The yellow mixture was stirred for 3 h. TLC (PE/EA=8/1, Rf=0.8) showed 4-mercaptobenzonitrile was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was directly purified with pre-TLC (PE/EA=8/1) to afford tert-butyl 4-((4-cyanophenyl)thio)piperidine-1-carboxylate (230.0 mg, white solid).

[263] **Step 2:** To a solution of tert-butyl 4-((4-cyanophenyl)thio)piperidine-1-carboxylate (50 mg, 1.0 eq) in DCM (5 mL) was added m-CPBA (72.0 mg, 2.0 eq), and the yellow mixture was stirred at r.t. for 3 h. TLC (PE/EA=2/1, Rf=0.3) showed tert-butyl 4-((4-cyanophenyl)thio)piperidine-1-carboxylate was consumed, reaction had mainly a new spot. $NaHCO_3$ aqueous solution was added, then extracted with DCM 6ml×3, dried over Na_2SO_4, The mixture was concentrated in vacuo. The residue was directly

purified with pre-TLC (PE/EA=2/1) to afford tert-butyl 4-((4-cyanophenyl)sulfonyl)piperidine-1-carboxylate (57.0mg, white solid). ESI-MS: 356.4[M+H]+.

[264] **Step 3:** To a solution of tert-butyl 4-((4-cyanophenyl)sulfonyl)piperidine-1-carboxylate (58 mg, 1.0 eq) in DCM (2 mL) was added TFA (2 ml), and the yellow mixture was stirred at r.t. for 3 h. TLC (DCM/MeOH=10/1, Rf=0.2) showed tert-butyl 4-((4-cyanophenyl)sulfonyl)piperidine-1-carboxylate was consumed, reaction had mainly a new spot. K_2CO_3 aqueous solution was added, then extracted with DCM 3ml×3, The mixture was concentrated in vacuo to afford 4-(piperidin-4-ylsulfonyl)benzonitrile (40.0mg, white solid).

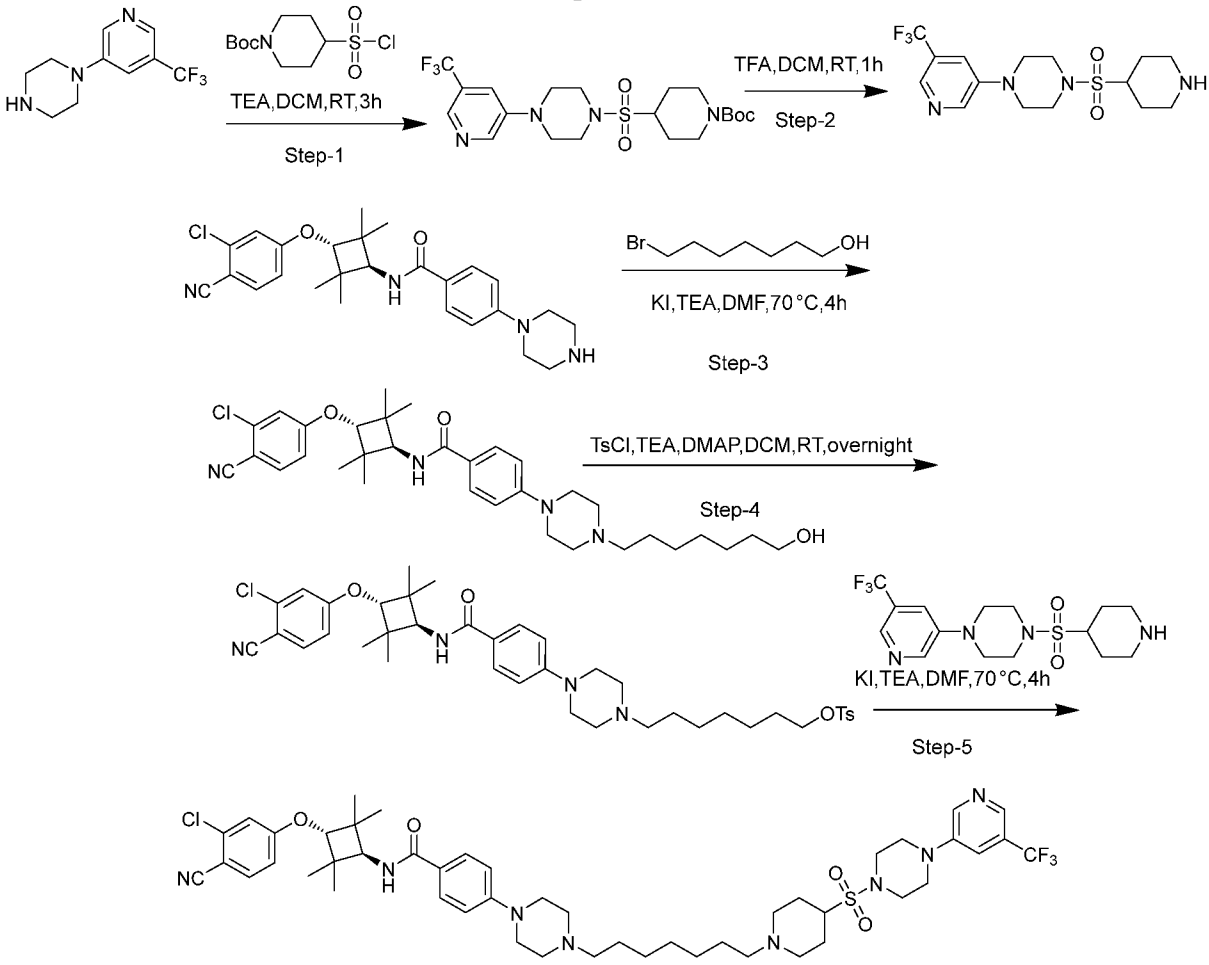
[265] **Step 4:** To a solution of 4-(piperidin-4-ylsulfonyl)benzonitrile (40 mg, 1.0 eq.) in toluene (1 mL) was added 3-fluoro-5-(trifluoromethyl)pyridine (28.8 mg, 1.0 eq.), Ruphos Pd (10.6 mg, 0.1 eq.), and Cs_2CO_3 (61.4 mg, 3.0 eq.) at room temperature. Nitrogen atmosphere was replaced 5 times. The yellow mixture was stirred at 90 ^{0}C. for 4 h. TLC (PE/EA=2/1, Rf=0.3) showed 4-(piperidin-4-ylsulfonyl)benzonitrile was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was directly purified with pre-TLC (EA/PE=1/1) to afford 4-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)benzonitrile (27 mg, white solid). ESI-MS: 397.6 [M+H]+.

[266] **Step 5:** To a solution of 4-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)benzonitrile (8.5 mg, 1.0 eq) in MeOH/NH_3 (2 mL) was added H_2 and Raney-Ni (2 ml), and the black mixture was stirred at r.t. for 3 h. TLC (DCM/MeOH=10/1, Rf=0.3) showed 4-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)benzonitrile was consumed, reaction had mainly a new spot. The reaction was filtered and the mixture was concentrated in vacuo, to afford (4-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)phenyl)methanamine (8.0 mg, white solid).

[267] **Step 6:** To a solution of (4-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)phenyl)methanamine (6.0 mg, 1.0 eq.) in DMF (1 mL) was added 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptanoic acid (5.0 mg, 1.0 eq.), HATU (13.4 mg, 1.5 eq.), and DIEA (15 mg, 5.0 eq.) at 0-5 ^{o}C, and the yellow mixture was stirred at r.t. for 3 h. TLC (MeOH/DCM=1/12, Rf=0.6) showed (4-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)phenyl)methanamine was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was directly purified with pre-TLC (MeOH/DCM=1/12) to afford *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-oxo-7-((4-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)benzyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 30**, 4.5mg, off-white solid). ESI-MS: 977.3[M+H]+.

Example S30

Synthesis N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-(4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)heptyl)piperazin-1-yl)benzamide (Compound 31)



[268] **Step 1:** To a mixture of 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine (35 mg, 0.14 mmol) and TEA (67 mg, 0.66 mmol) was added tert-butyl 4-(chlorosulfonyl)piperidine-1-carboxylate (61 mg, 0.22 mmol) in DCM (2mL) at RT for 3 hours. Then the mixture was concentrated in vacuo to give the crude product which was purified by P-TLC with PE/EA(1/1) to give tert-butyl 4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidine-1-carboxylate (25 mg,0.05mmol,35%) as white solid.

[269] **Step 2:** tert-butyl 4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidine-1-carboxylate (25 mg, 0.05 mmol) and TFA (2 mL) were dissolved in DCM (4 ml), and the reaction mixture was stirred at RT for 3 hours, and was then concentrated in vacuo to give the crude product 1-(piperidin-4-ylsulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine (15 mg, 0.04 mmol, 80%) as white solid.

[270] **Step 3:** To a mixture of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benzamide (50 mg, 0.11 mmol), 7-bromoheptan-1-ol (22 mg,

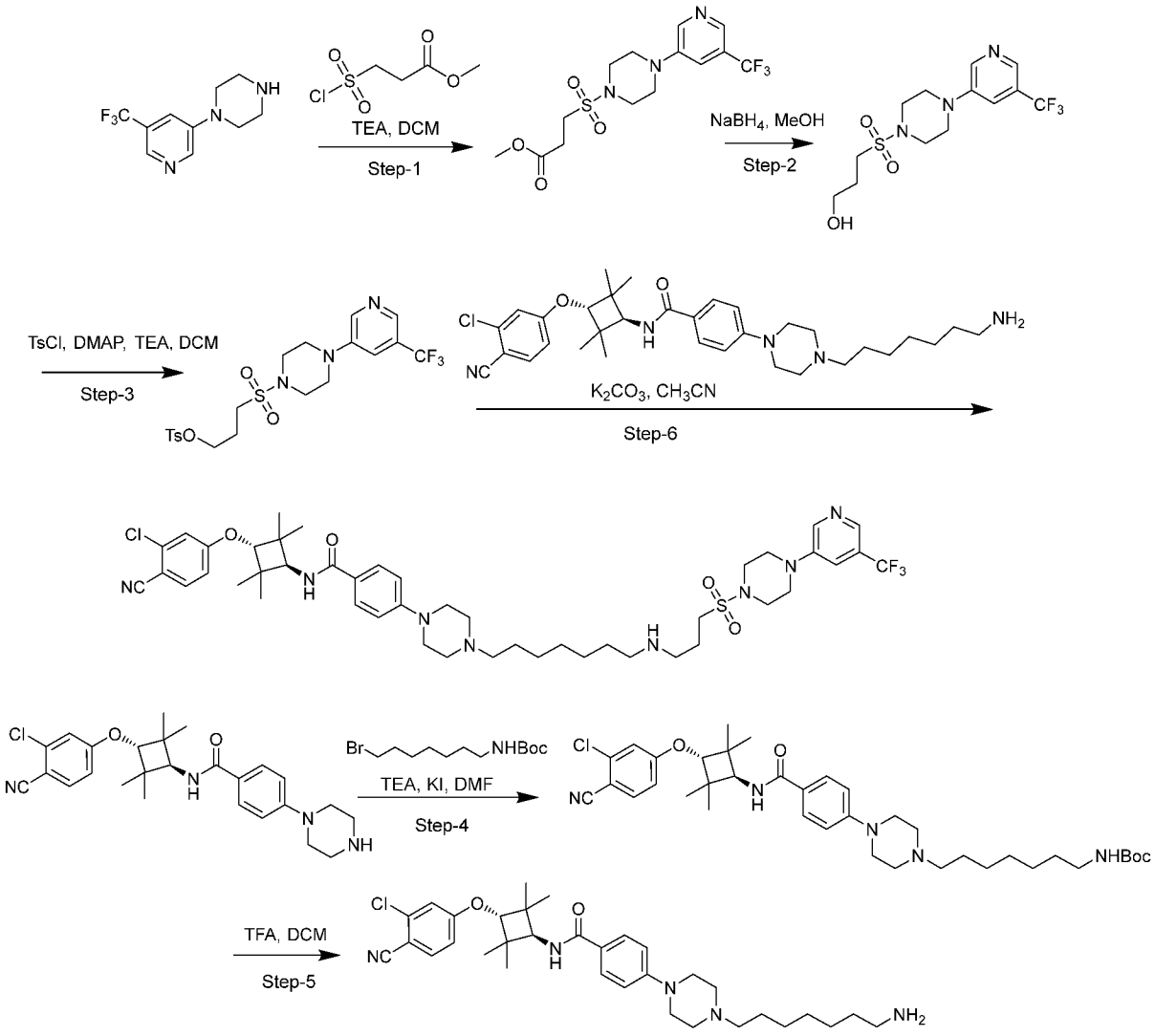
0.11 mmol), KI (20 mg, 0.11 mmol) in DMF (2 ml) was added TEA (56 mg, 0.55 mmol). The mixture was stirred at 70°C for 4 hours, and then concentrated in vacuo to give the crude product which was purified by P-TLC with DCM/MeOH (10/1) to give N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-hydroxyheptyl)piperazin-1-yl)benzamide (50 mg, 0.086 mmol, 78%) as solid.

[271] **Step 4:** To a mixture of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-hydroxyheptyl)piperazin-1-yl)benzamide (20 mg, 0.034 mmol), DMAP (6 mg, 0.049 mmol) and TEA (25 mg, 0.25 mmol) was added TsCl (6.6 mg, 0.034 mmol) in DCM (3 mL). The mixture stirred at RT overnight, and was concentrated in vacuo to give the crude product which was purified by P-TLC with DCM/MeOH=20/1) to give 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptyl 4-methylbenzenesulfonate (10 mg, 0.0136 mmol, 30%) as white solid.

[272] **Step 5:** To a mixture of 7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptyl 4-methylbenzenesulfonate (3.3 mg, 0.0045 mmol), 1-(piperidin-4-ylsulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine (3 mg, 0.008 mmol), and KI (7 mg 0.042 mmol) in DMF (1 ml) was added TEA (20 mg, 0.2 mmol). The mixture stirred at 70°C for 4 hours, and was then concentrated in vacuo to give the crude product which was purified by P-TLC with DCM/MeOH (10/1) to give *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-(4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)heptyl)piperazin-1-yl)benzamide (**Compound 31**, 2.6 mg, 0.0027 mmol, 60%) as white solid.

Example S31

Synthesis N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-((3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl)amino)heptyl)piperazin-1-yl)benzamide (Compound 32)



[273] **Step 1:** To a solution of 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine (150 mg, 1 eq) in DCM (3 mL) were added methyl 3-(chlorosulfonyl)propanoate (112 mg, 1 eq) and TEA (328 mg, 5 eq), and the reaction was stirred at room temperature for 6 hours. TLC showed new spot was observed, and no starting material as remained. The reaction mixture was diluted with water and extracted with DCM. The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, and the mixture was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=20:1) to afford methyl 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propanoate (30 mg).

[274] **Step 2:** To a solution of methyl 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propanoate (30 mg, 1 eq) in MeOH (2 mL) was added $NaBH_4$ (15 mg, 5 eq), the reaction mixture was stirred at room temperature for 3 hours under nitrogen atmosphere. TLC showed new spot was observed, and no starting material remained. The reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=10:1) to afford 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propan-1-ol (10 mg).

[275] **Step 3:** To a solution of 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propan-1-ol (10 mg, 1 eq) in DCM (2 mL) were added TsCl (11 mg, 2 eq), TEA (12 mg, 4 eq), and DMAP (4 mg, 1 eq), the reaction was stirred at room temperature for 16 hours. TLC showed new spot was observed, and no starting material remained. The reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=15:1) to afford 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl 4-methylbenzenesulfonate (5 mg). ESI-MS: 594.8 $[M+H]^+$.

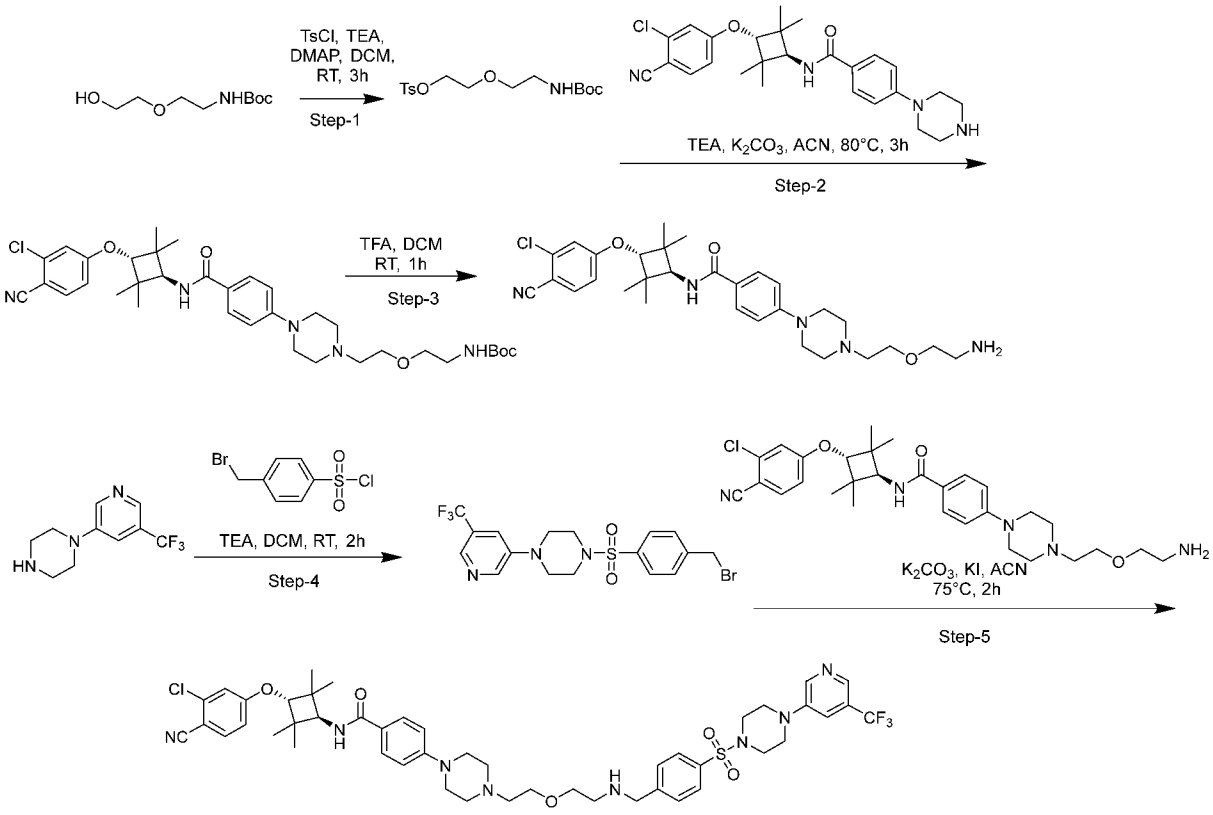
[276] **Step 4:** To a solution of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benzamide (15 mg, 1 eq) in DMF (2 mL) were added tert-butyl(7-bromoheptyl)carbamate (20 mg, 2 eq), TEA (17 mg, 5 eq), and KI (5 mg, 1 eq), and the reaction was stirred at 70 °C for 16 hours. TLC showed new spot was observed, and no starting material remained, The reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=15:1) to give tert-butyl (7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptyl)carbamate (5 mg). ESI-MS: 679.8 $[M+H]^+$.

[277] **Step 5:** To a solution of tert-butyl (7-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)heptyl)carbamate (5 mg, 1 eq) in DCM (2 mL) was added TFA (2 mL), and the reaction was stirred at room temperature for 16 hours. TLC showed new spot was observed, and no material was remained. The reaction mixture was concentrated in vacuo to give 4-(4-(7-aminoheptyl)piperazin-1-yl)-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)benzamide (4 mg). ESI-MS: 579.9 $[M+H]^+$.

[278] **Step 6:** To a solution of 4-(4-(7-aminoheptyl)piperazin-1-yl)-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)benzamide (4 mg, 1 eq) in CH_3CN (3 mL) were added 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl 4-methylbenzenesulfonate (5 mg, 1.43 eq) and K_2CO_3 (3 mg, 3 eq), and the reaction was stirred at 80 °C for 16 hours. TLC showed new spot was observed, and no starting material remained. The reaction mixture was diluted with water and extracted with DCM, The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, and the mixture was concentrated in vacuo. Th residue was purified by preparative TLC (DCM: MeOH=5:1) to afford N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-((3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl)amino)heptyl)piperazin-1-yl)benzamide (**Compound 32**, 2.1 mg). ESI-MS: 914.5 $[M+H]^+$.

Example S32

Synthesis N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(2-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)benzyl)amino)ethoxy)ethyl)piperazin-1-yl)benzamide (Compound 33)



[279] **Step 1:** To a mixture of tert-butyl (2-(2-hydroxyethoxy)ethyl)carbamate (109 mg, 0.53 mmol), DMAP (10 mg, 0.053 mmol) and TEA (169 mg, 1.6 mmol) in DCM (10 ml) was added 4-methylbenzenesulfonyl chloride (100 mg, 0.53 mmol). The reaction mixture was stirred at RT for 3 hours and then concentrated in vacuo to give the crude product which was purified by silica gel column chromatography eluting with PE/EA (3/1) to give 2-(2-((tert-butoxycarbonyl)amino)ethoxy)ethyl 4-methylbenzenesulfonate (126 mg, 0.35 mmol, 66%) as white solid.

[280] **Step 2:** To a mixture of 2-(2-((tert-butoxycarbonyl)amino)ethoxy)ethyl 4-methylbenzenesulfonate (20 mg, 0.056 mmol), K_2CO_3 (10 mg, 0.072 mmol), and N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benzamide (26 mg, 0.056 mmol) in ACN (2 ml) was added TEA (28 mg, 0.28 mmol). The mixture stirred at 80 °C for 3 hours and was concentrated in vacuo to give the crude product which was purified by P-TLC with DCM/MeOH (10/1) to give tert-butyl (2-(2-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)ethoxy)ethyl)carbamate (10 mg, 0.015 mmol, 27%) as white solid.

[281] **Step 3:** To a mixture of tert-butyl (2-(2-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)ethoxy)ethyl)carbamate (10 mg, 0.015 mmol) in DCM (2 mL) was added TFA (0.5 mL). The mixture stirred at RT for 1 hour, and was concentrated in

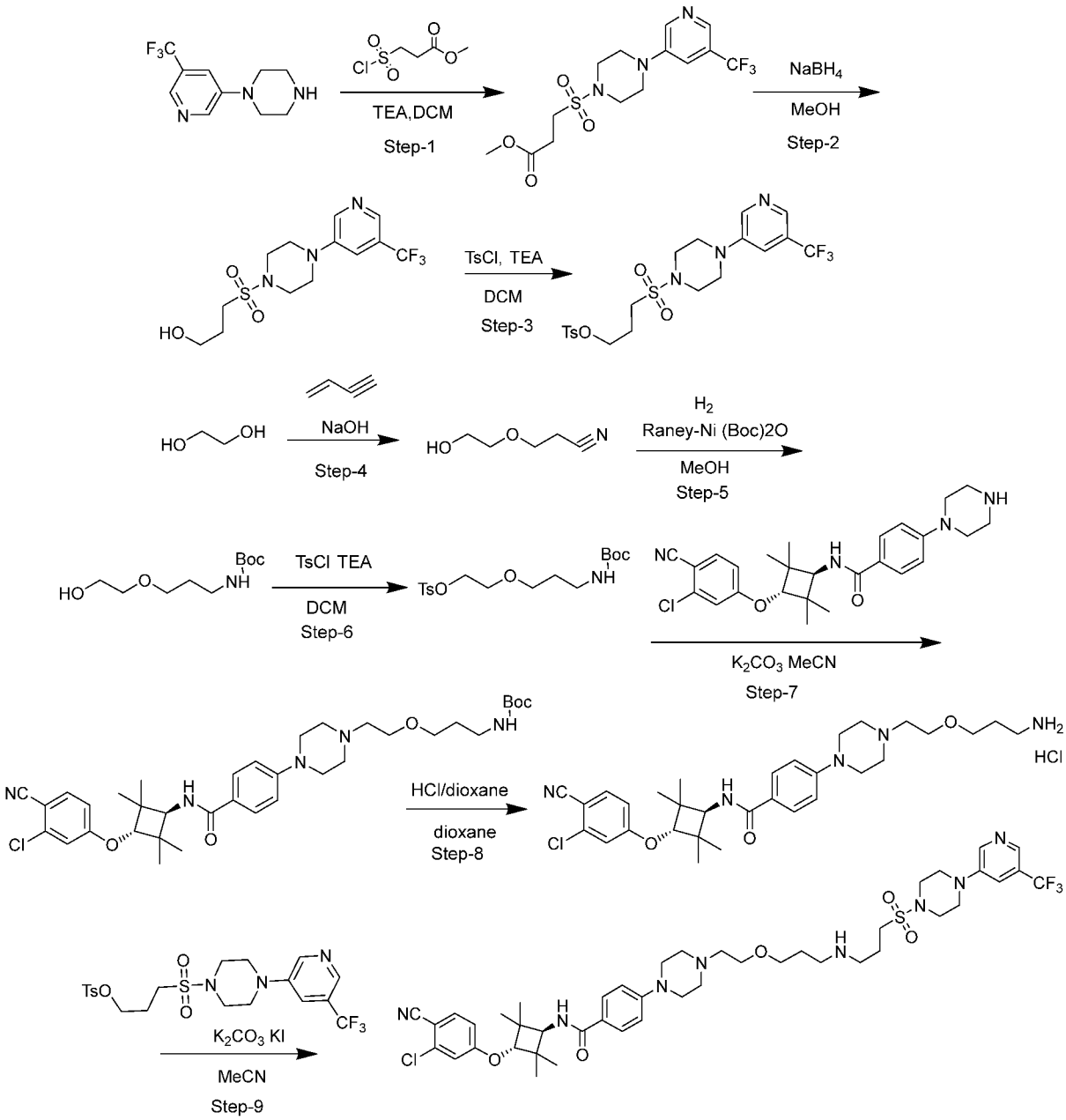
vacuo to give the crude product 4-(4-(2-(2-aminoethoxy)ethyl)piperazin-1-yl)-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)benzamide (8.4 mg, 0.15 mmol, 99%) as oil.

[282] **Step 4:** To a mixture of 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine (30mg, 0.13mmol) in DCM (2 mL) was added TEA (0.5 mL) and 4-(bromomethyl)benzenesulfonyl chloride (35 mg, 0.13 mmol). The mixture stirred at RT for 2 hours, and was concentrated in vacuo to give the crude product which was purified by P-TLC with PE/EA (2/1) to give 1-((4-(bromomethyl)phenyl)sulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine (20 mg, 0.043 mmol, 33%) as white solid.

[283] **Step 5:** A mixture of 1-((4-(bromomethyl)phenyl)sulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine (20 mg, 0.043 mmol), 4-(4-(2-(2-aminoethoxy)ethyl)piperazin-1-yl)-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)benzamide (8.4 mg, 0.015 mmol), K_2CO_3 (10 mg 0.072) and KI (2 mg, 0.0075 mmol) in ACN (2 ml) was stirred at 75°C for 2 hours, and was then concentrated in vacuo to give the crude product which was purified by P-TLC with DCM/MeOH (10/1) to give *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(2-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)benzyl)amino)ethoxy)ethyl)piperazin-1-yl)benzamide (**Compound 33**, 2.2 mg, 0.023 mmol, 54%) as white solid.

Example S33

Synthesis N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(3-((3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl)amino)propoxy)ethyl)piperazin-1-yl)benzamide (Compound 34)



[284] **Step 1:** To a solution of 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine (222 mg, 1.0e q.) in DCM (5 mL) was added methyl 3-(chlorosulfonyl)propanoate (155 mg, 1.0 eq.) and TEA (500 mg, 5.0 eq), and the yellow mixture was stirred at r.t. for 4 h. TLC (PE/EA=1/1, Rf=0.4) showed 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine was consumed, reaction had mainly a new spot. 5 mL of water were added to the reaction solution. The combined aqueous layers were extracted with DCM (4 mL×3) to remove neutral impurities. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was directly purified with pre-TLC (PE/EA=1/1) to afford methyl 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propanoate (180.0 mg, yellow liquid).

[285] **Step 2:** To a solution of methyl 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propanoate (20 mg, 1.0 eq.) in MeOH (1 mL) was added $NaBH_4$ (6.0 mg, 3.0 eq.), The yellow mixture was stirred at r.t. for 4 h. TLC (MeOH/DCM=1/20, Rf=0.2) showed methyl 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propanoate was consumed, reaction had mainly a new spot. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl. The combined aqueous layers were extracted with EtOAc (2 mL×4) to remove neutral impurities. The mixture was concentrated in vacuo to afford 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propan-1-ol (18.9 mg, white solid). ESI-MS: 354.1[M+H]+.

[286] **Step 3:** To a solution of 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propan-1-ol (18.4 mg, 1.0 eq.) in DCM (1 mL) was added TsCl (9.9 mg, 1.0 eq.) and TEA (500 mg, 1.5 eq), and the yellow mixture was stirred at r.t. for 14 h. TLC (MeOH/DCM=1/20, Rf=0.4) showed 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propan-1-ol was consumed, reaction had mainly a new spot. Added 2 mL of water to the reaction solution. The combined aqueous layers were extracted with DCM (2 mL×3) to remove neutral impurities. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was directly purified with pre-TLC (MeOH/DCM=1/20) to afford 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl 4-methylbenzenesulfonate (15.0 mg, Yellow solid).

[287] **Step 4:** To a solution of but-1-en-3-yne (0.4 g, 1.0 eq.) in ethane-1,2-diol (2.0g, 4.0eq.) was added NaOH (32 mg, 0.1 eq.). The yellow mixture was stirred at rt. for 14 h. TLC (EA=1, Rf=0.6) showed but-1-en-3-yne was consumed, reaction had mainly a new spot. The mixture was adjusted to pH 5 with 1M HCl. The combined aqueous layers were extracted with EtOAc (2 mL×4) to remove neutral impurities. The mixture was concentrated in vacuo, The crude product was purified by column chromatography on silica eleluted with (PE/EA=1/1) to give 3-(2-hydroxyethoxy)propanenitrile (360 mg) as a colourless liquid.

[288] **Step 5:** A mixture of 3-(2-hydroxyethoxy)propanenitrile (50 mg, 1.0 eq.) and Raney Ni (5 mg) in MeOH (2 mL) and $(Boc)_2O$ (50 mg, 1.0 eq.) was stirred under 1 atm of H_2 at room temperature for 1 hour. TLC (EA=1, Rf=0.6) showed 3-(2-hydroxyethoxy)propanenitrile was consumed, reaction had mainly a new spot. The reaction solution was filtered. The mixture was concentrated in vacuo, to afford tert-butyl (3-(2-hydroxyethoxy)propyl)carbamate (93.3 mg, colorless liquid). ESI-MS: 220.1[M+H]+.

[289] **Step 6:** To a solution of tert-butyl (3-(2-hydroxyethoxy)propyl)carbamate (93 mg, 1.0 eq.) in DCM (2 mL) was added TsCl (82 mg, 1.0 eq.) and TEA (66.4 mg, 1.5 eq), and the yellow mixture was stirred at rt. for 24 h. TLC (PE/EA=1/1, Rf=0.9) showed tert-butyl (3-(2-hydroxyethoxy)propyl)carbamate was consumed, reaction had mainly a new spot. 2 mL of water were added to the reaction solution. The combined aqueous layers were extracted with DCM (2 mL×3) to remove neutral impurities. The combined

organic layers were dried over $MgSO_4$ and concentrated. The residue was directly purified with pre-TLC (PE/EA=1/1) to afford 2-(3-((tert-butoxycarbonyl)amino)propoxy)ethyl 4-methylbenzenesulfonate (65 mg, colorless liquid) ESI-MS: 373.1[M+H]+.

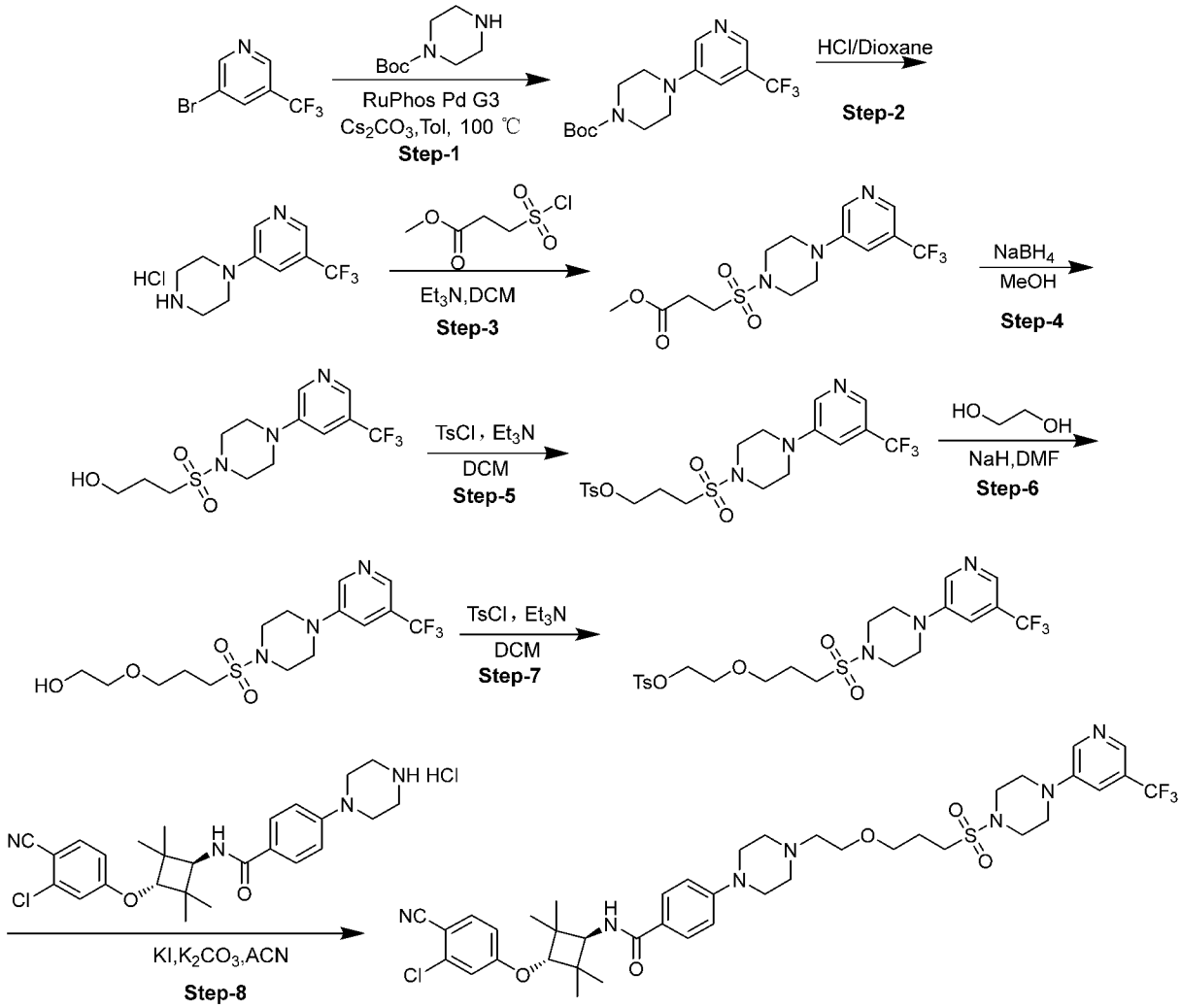
[290] **Step 7:** To a solution of 2-(3-((tert-butoxycarbonyl)amino)propoxy)ethyl 4-methylbenzenesulfonate (26 mg, 1.0 eq.) in MeCN (2 mL) was added N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benzamide (35 mg, 1.0 eq.) and K_2CO_3 (14.4 mg, 1. 5eq), and the yellow mixture was stirred at 80 °C for 24 h. TLC (MeOH/DCM=1/10) showed 2-(3-((tert-butoxycarbonyl)amino)propoxy)ethyl 4-methylbenzenesulfonate was consumed, reaction had mainly a new spot. The reaction solution was filtered. The mixture was concentrated in vacuo. The residue was directly purified with pre-TLC (MeOH/DCM=1/13) to afford tert-butyl (3-(2-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)ethoxy)propyl)carbamate (65 mg, colorless liquid), ESI-MS: 668.3[M+H]+.

[291] **Step 8:** To a solution of tert-butyl (3-(2-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)ethoxy)propyl)carbamate (2mg, 1.0eq.) in Dioxane (0.5 mL) was added 4M HCl/dioxane (0.5 mL). The yellow mixture was stirred at rt. for 3 h. TLC (MeOH/DCM=1/10, Rf=0.1) showed tert-butyl (3-(2-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)ethoxy)propyl)carbamate was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo to afford 4-(4-(2-(3-aminopropoxy)ethyl)piperazin-1-yl)-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)benzamide•HCl (93.3 mg, colourless liquid).

[292] **Step 9:** To a solution of 4-(4-(2-(3-aminopropoxy)ethyl)piperazin-1-yl)-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)benzamide•HCl (1.8 mg, 1.0 eq.) in MeOH (1 mL) was added 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl 4-methylbenzenesulfonate (1.5 mg, 1.0 eq.), K_2CO_3 (0.62 mg, 1.5 eq.), and KI (0.01 mg, 0.01 eq.) at 20 °C. The yellow mixture was stirred at 80 °C for 14 h. The reaction solution was filtered. The mixture was concentrated in vacuo. The residue was directly purified with pre-TLC (MeOH/DCM=1/12) to afford *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(3-((3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl)amino)propoxy)ethyl)piperazin-1-yl)benzamide (**Compound 34**, 1.2 mg, white solid) ESI-MS: 903.3[M+H]+.

Example S34

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(4-oxo-4-((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propyl)amino)butyl)piperazin-1-yl)benzamide (Compound 35)



[293] **Step 1:** To a stirred solution of 3-bromo-5-(trifluoromethyl)pyridine (500.0 mg, 2.212mmol) in toluene (10 ml) were added tert-butyl piperazine-1-carboxylate (618.1 mg, 3.319 mmol), RuPhos Pd G_3 (92.5 mg, 1.106 mmol) and Cs_2CO_3 (1441.7 mg, 4.424 mmol) and the reaction was stirred at 90°C for 3 h. The reaction was concentrated, diluted with DCM and H_2O. The organic layer was separated, washed with H_2O and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-carboxylate (585.0 mg, 84.40%).

[294] **Step 2:** Tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-carboxylate (585.0 mg, 1.766 mmol) was added to HCl/1,4-dioxane(4M, 8mL) and was stirred at 30 °C for 3 h. The reaction was concentrated and dried in vacuo to afford 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine hydrochloride (601.3 mg, 101.15%).

[295] **Step 3:** To a stirred solution of 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine hydrochloride (601.3 mg, 2.246mmol) in DCM (15 ml) were added methyl 3-(chlorosulfonyl)propanoate (419.2 mg, 2.246 mmol) and Et_3N (1136.5 mg, 11.231 mmol) and the reaction was stirred at room temperature for 3 h. The reaction was diluted with DCM and H_2O. The organic layer was separated, washed with saturated

NH_4Cl solution, H_2O, saturated $NaHCO_3$ solution, H_2O and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo and purified with column chromatography to afford methyl 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propanoate (223.8 mg, 26.12%).

[296] **Step 4:** To a stirred solution in MeOH (6 mL) of methyl 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propanoate (223.8 mg 0.587 mmol) was added $NaBH_4$ (222.0 mg, 5.868 mmol) slowly at 0 °C. After the addition, the reaction was stirred at room temperature for 16 h. The reaction was quenched with water and the resulting mixture was diluted with DCM and H_2O. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified with column chromatography to afford 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propan-1-ol (129.7 mg, 62.53%).

[297] **Step 5:** To a solution of 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propan-1-ol (38.8 mg, 0.110 mmol) in DCM (4 mL) were added TsCl (41.9 mg, 0.220 mmol), Et_3N (44.4 mg, 0.440 mmol), and DMAP (1.3 mg, 0.011 mmol), and the reaction was stirred at room temperature for 16 h. The reaction was diluted with DCM and water. The organic layer was separated, washed with saturated NH_4Cl solution, H_2O, saturated $NaHCO_3$ solution, H_2O and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl 4-methylbenzenesulfonate (54.8 mg, 98.18%).

[298] **Step 6:** To a solution of ethylene glycol (10.1 mg, 0.162 mmol) in DMF (0.5 mL) was added NaH (8.6 mg, 0.216 mmol) and the reaction was stirred at room temperature. After stirring for 30 minutes, to the reaction was added a solution in DMF(1.0 ml) of 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl 4-methylbenzenesulfonate (54.8 mg, 0.108 mmol), and the reaction was stirred at 75 °C for 3 hr. The reaction was quenched with saturated NH_4Cl solution, and extracted with DCM. The organic layer was washed with saturated $NaHCO_3$ solution three times. The organic layer was concentrated in vacuo, and purified by pre-TLC to afford 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethan-1-ol (35.5 mg, 82.7%).

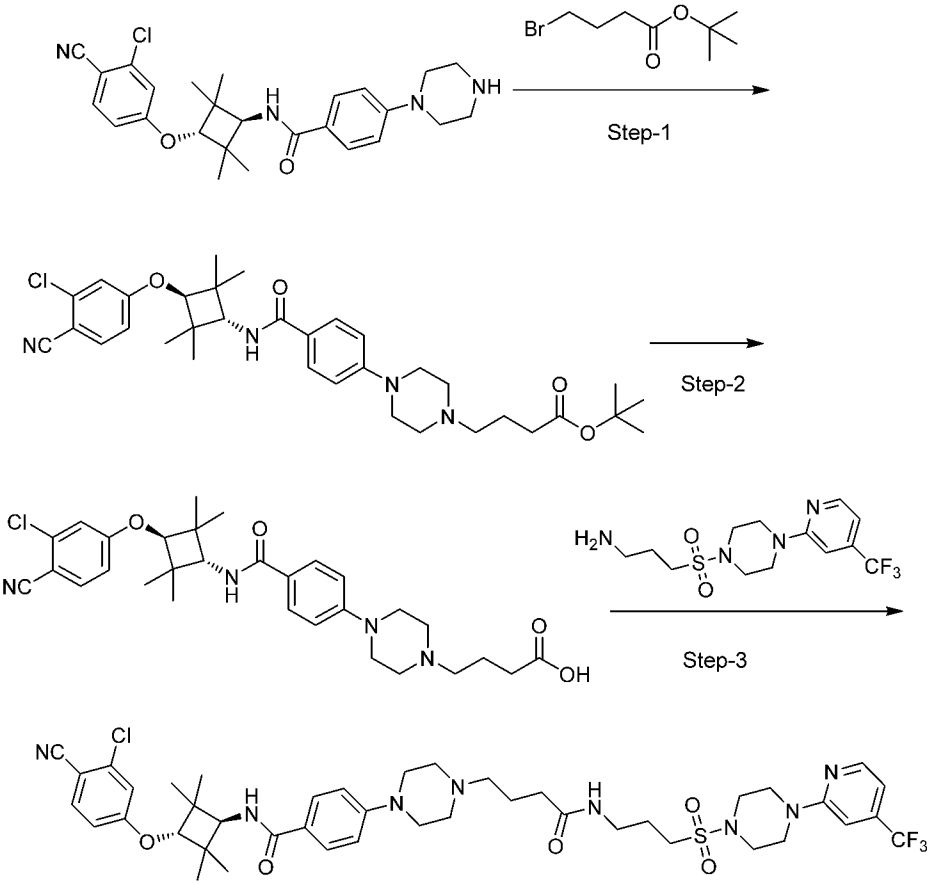
[299] **Step 7:** To a solution in DCM (3 mL) of 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethan-1-ol (35.5 mg, 0.089 mmol) were added TsCl (33.9 mg, 0.178 mmol), Et_3N (36.0 mg, 0.356 mmol), and DMAP (0.25 mg, 1.1 mmol), and the reaction was stirred at room temperature for 4 hr. The reaction was diluted with DCM and water. The organic layer was separated, washed with water, and concentrated in vacuo. The residue was purified by Pre-TLC to afford 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl 4-methylbenzenesulfonate (38.2 mg, 77.81%).

[300] **Step 8:** To a solution of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benzamide hydrochloride (16.1 mg, 0.032 mmol) in ACN (1 mL)

were added 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl 4-methylbenzenesulfonate (17.6 mg, 0.032 mmol), K_2CO_3 (11.0 mg, 0.080 mmol), and potassium iodide (1.0 mg, 0.007 mmol), and the reaction was stirred at 80 °C for 6 h. The reaction was concentrated in vacuo, and purified by pre-TLC to afford *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(4-oxo-4-((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propyl)amino)butyl)piperazin-1-yl)benzamide (**Compound 35**, 8.5 mg, 31.38%). ESI-MS: 843.7[M-H]$^-$, 846.6[M+H]$^+$.

Example S35

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(4-oxo-4-((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propyl)amino)butyl)piperazin-1-yl)benzamide (Compound 36)



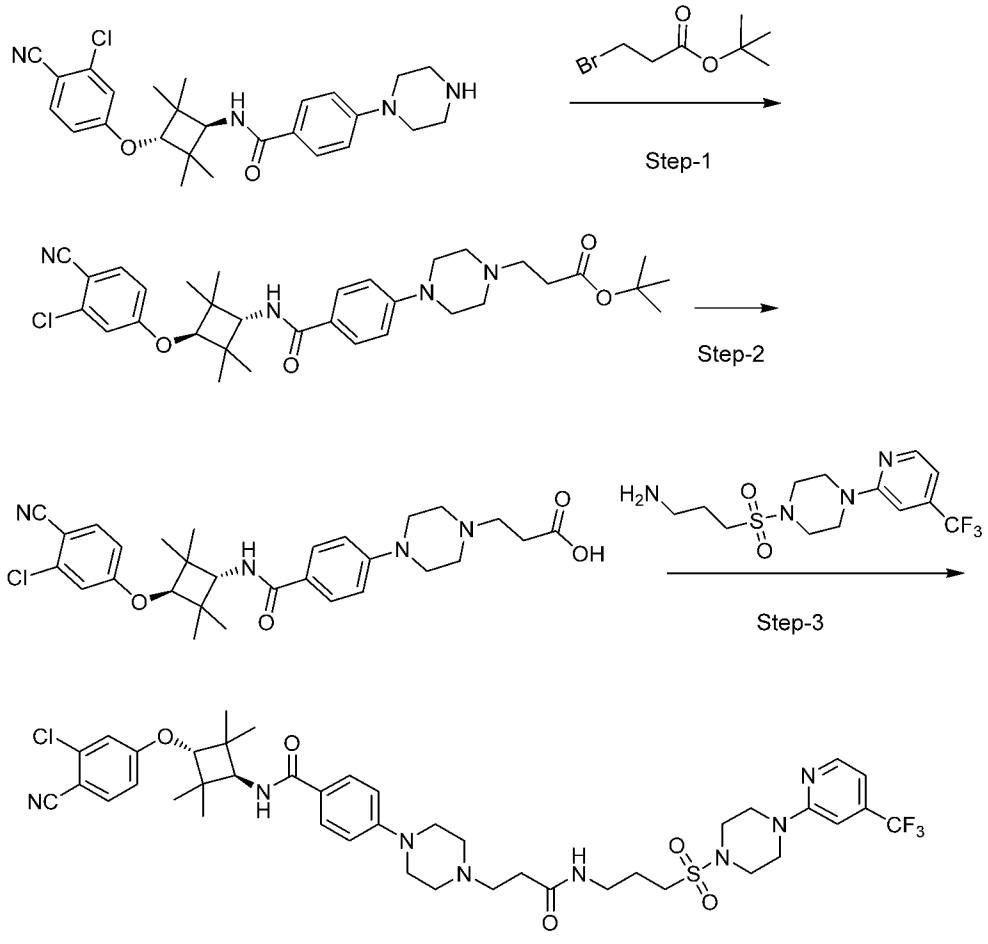
[301] **Step 1:** A solution of *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benzamide (10 mg, 1.0 eq), tert-butyl 4-bromobutanoate (6.7 mg, 1.5 eq), Et_3N (6 mg, 3.0 eq), and KI (1.7 mg, 0.5 eq) in DMF (1ml) was stirred at 90°C for 2.5h. The solvent was removed and the mixture was purified by pre-TLC (DCM:MeOH=20:1) to afford tert-butyl 4-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)butanoate (10 mg), ESI-MS: 609.3 [M+H]+.

[302] **Step 2:** To a solution of tert-butyl tert-butyl 4-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)butanoate (10 mg) in DCM (1 ml) was added TFA (0.5 ml). The reaction was stirred at RT for 1h. TLC showed complete reaction of starting materials. The solvent was removed to afford 4-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)butanoic acid (9 mg), ESI-MS: 553.3 [M+H]+.

[303] **Step 3:** To a solution of 4-(4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)butanoic acid (5.5 mg,1.0eq) in DMF (1 ml) was added HATU (5.7 mg, 1.5 eq), DIEA (4 mg, 3.0 eq) and 3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propan-1-amine (3.5 mg, 1.0 eq). The reaction was stirred at RT for 1 h. The solvent was removed and the mixture was purified by pre-TLC (DCM:MeOH=10:1) to afford the product *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(4-oxo-4-((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)propyl)amino)butyl)piperazin-1-yl)benzamide (**Compound 36**, 4 mg), ESI-MS: 887.4[M+H]+.

Example S36

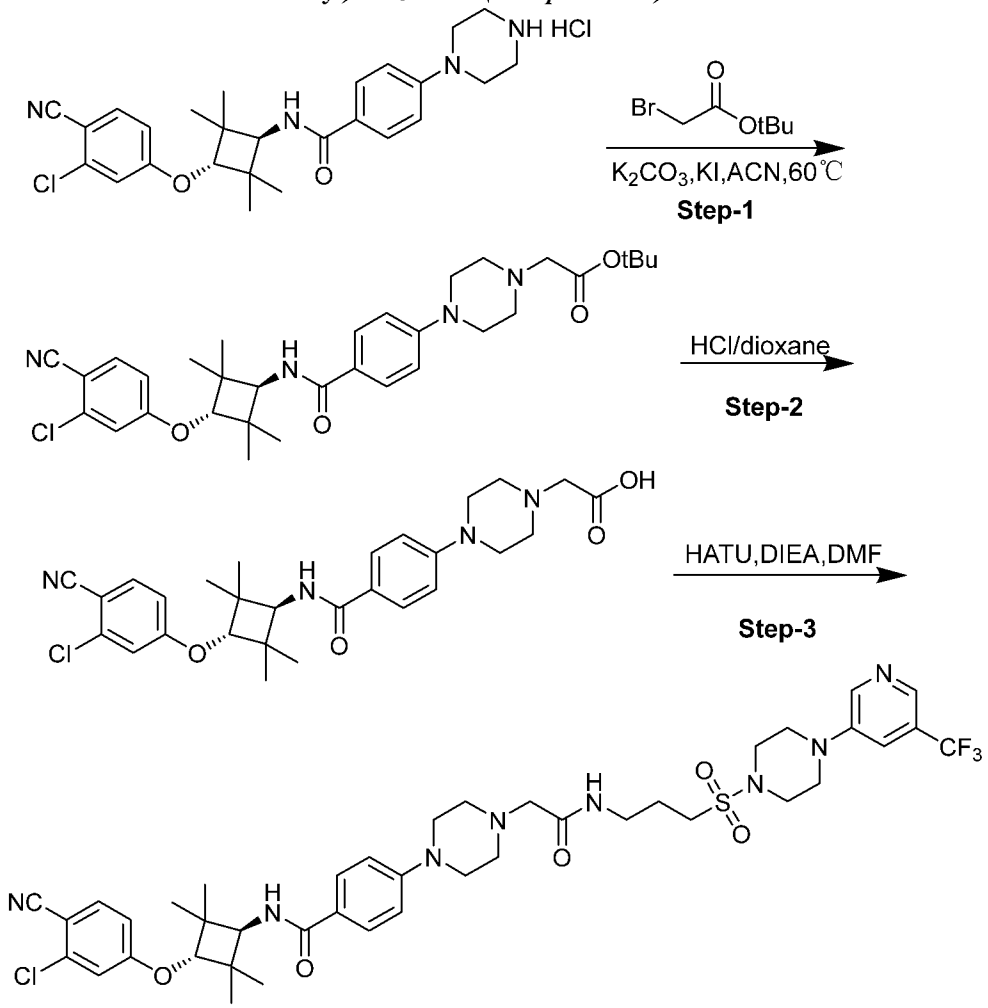
Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((1-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-4-yl)methyl)piperazin-1-yl)benzamide (Compound 37)



[304] N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((1-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-4-yl)methyl)piperazin-1-yl)benzamide (**Compound 37**, ESI-MS: 873.3 $[M+H]^+$) was synthesized in the same manner as **Compound 36**.

Example S37

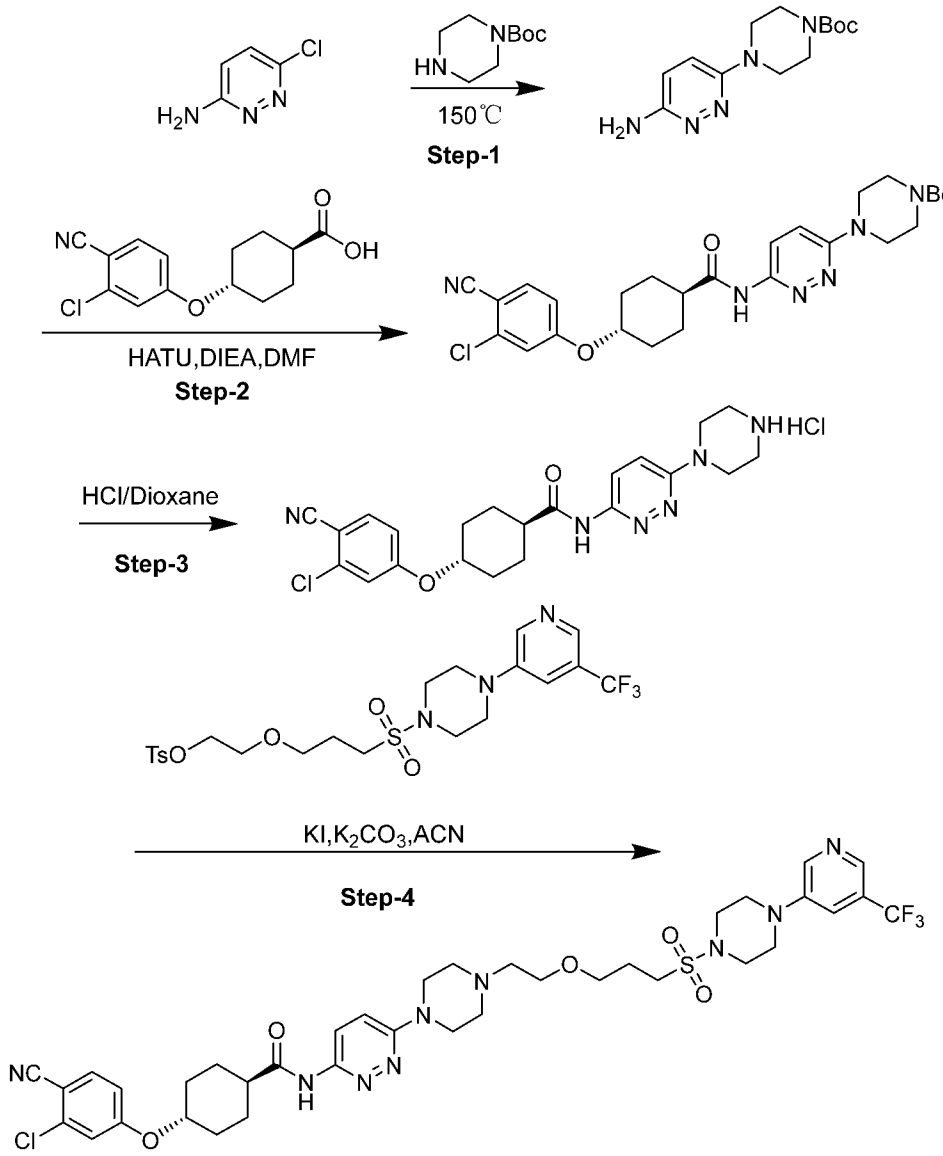
Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-oxo-2-((3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl)amino)ethyl)piperazin-1-yl)benzamide (Compound 38)



[305] N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-oxo-2-((3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl)amino)ethyl)piperazin-1-yl)benzamide (**Compound 38**, 6.2 mg, 63.13%, ESI-MS: 856.6, 858.7$[M-H]^-$; 860.5$[M+H]^+$).

Example S38

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 39)



[306] **Step 1:** To a flask containing 6-chloropyridazin-3-amine (200.0 mg, 1.544 mmol) was added tert-butyl piperazine-1-carboxylate (2287.5 mg, 1.544 mmol). The reaction mixture was stirred at 150 °C under N_2 atmosphere for 4 h. The reaction was cooled to room temperature and DCM/MeOH was added. After stirring for 15 minutes, the resulting mixture was filtered. The filtrate was concentrated in vacuo and purified by pre-TLC to afford tert-butyl 4-(6-aminopyridazin-3-yl)piperazine-1-carboxylate (122.9 mg, 28.46%).

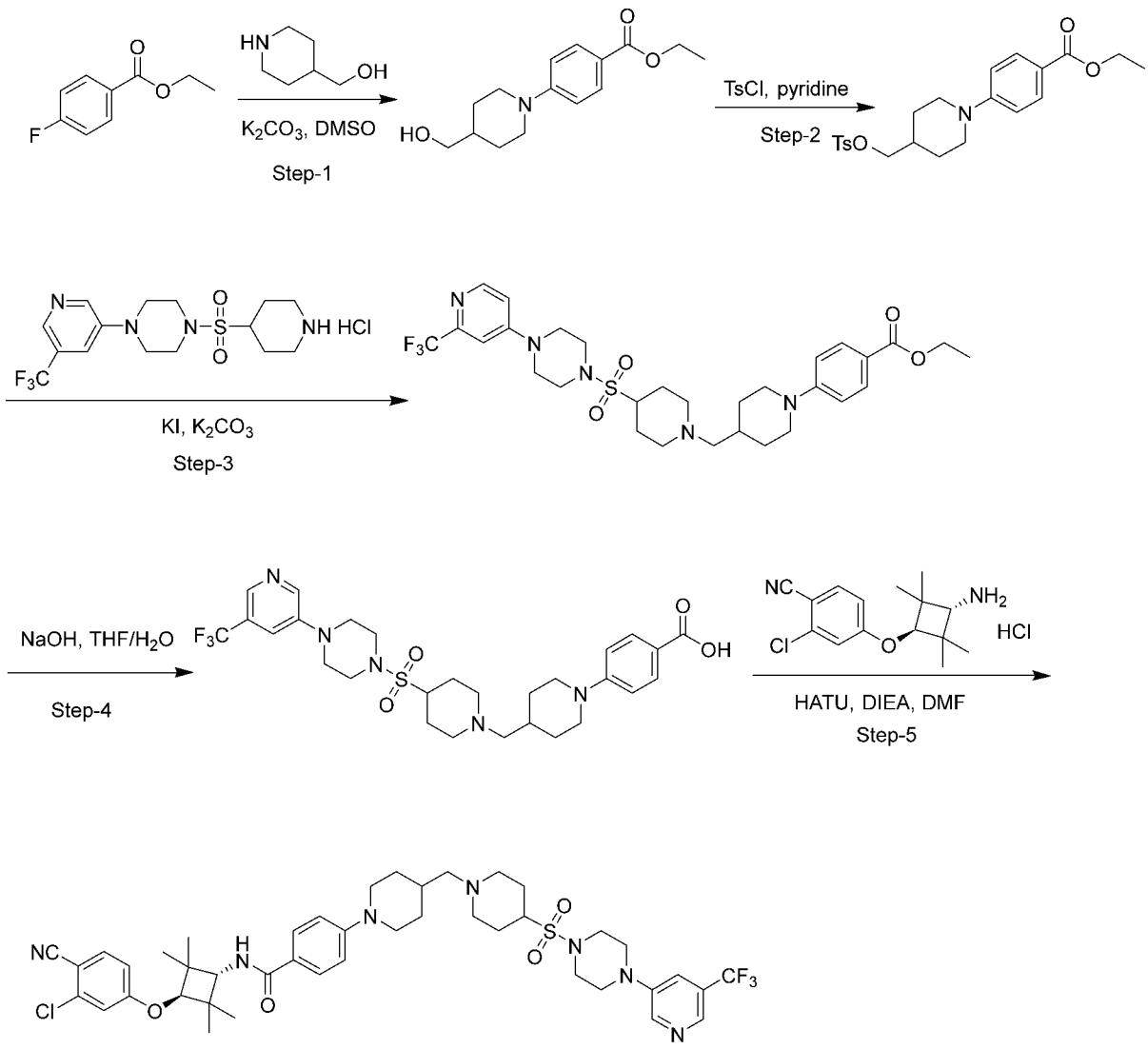
[307] **Step 2:** To a solution in DMF (1.5 mL) of (1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxylic acid (20.0 mg, 71.500 μmol) and HATU (40.8 mg, 107.25 mmol) was added Ethyldiisopropylamine (27.7 mg, 214.500 μmol) followed by tert-butyl 4-(6-aminopyridazin-3-yl)piperazine-1-carboxylate (20.0 mg, 71.500 μmol). The reaction was stirred at room temperature for 3 hr. The reaction was concentrated in vacuo, diluted with DCM and water. The organic layer was separated and concentrated in vacuo. The residue was purified by pre-TLC to afford tert-butyl 4-(6-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxamido)pyridazin-3-yl)piperazine-1-carboxylate (18.3 mg, 47.31%).

[308] **Step 3:** HCl/dioxane (4 M, 2.0 mL) was added to tert-butyl 4-(6-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxamido)pyridazin-3-yl)piperazine-1-carboxylate (18.3 mg, 33.823 μmol). The reaction was stirred at room temperature for 3 h. The reaction was concentrated in vacuo and dried to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide hydrochloride (16.1 mg, 33.823 μmol).

[309] **Step 4:** To a solution of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide hydrochloride (16.1 mg, 33.823 μmol) in ACN (1.5 mL) were added 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl 4-methylbenzenesulfonate (18.7 mg, 33.823 μmol), K_2CO_3 (14.0 mg, 101.469 μmol), and potassium iodide (1.2 mg, 6.765 μmol), and the reaction was stirred at 80 °C for 16 h. The reaction was concentrated in vacuo, and purified by pre-TLC to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-*N*-(6-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 39**, 6.2 mg, 22.35%). ESI-MS: 817.7, 818.6$[M-H]^-$; 817.5,820.5$[M+H]^+$.

Example S39

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((4-((4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzamide (Compound 40)



[310] **Step 1:** A mixture of ethyl 4-fluorobenzoate(1 g, 5.95 mmol), piperidin-4-ylmethanol(684.5 mg, 5.95 mmol), and K_2CO_3(2.46 g, 17.85 mmol) in DMSO (30 mL) was heated at 100°C overnight. Poured into H_2O, extracted with EA for 3 times, washed with H_2O, Na_2SO_4 dried over, filtered, concentrated and got the crude product ethyl 4-(4-(hydroxymethyl)piperidin-1-yl)benzoate(1.2 g).

[311] **Step 2:** A solution of ethyahydroxymethyl)piperidin-1-yl)benzoate(263 mg, 1 mmol) in pyridine was added TsCl (286 mg, 1.5 mmol) at 0°C. After addition, the reaction was stirred at RT for 3h. Poured into H_2O, a lot of solid seperated out, filtered, washed with H2O for 5 times, the solid was dried over under reduced vacuum and got ethyl 4-(4-((tosyloxy)methyl)piperidin-1-yl)benzoate(260 mg).

[312] **Step 3:** A mixture of ethyl 4-(4-((tosyloxy)methyl)piperidin-1-yl)benzoate (32 mg, 76.7μmol), 1-(piperidin-4-ylsulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine hydrochloride (24 mg, 57.8 μmol), KI (1 mg, 4.8 μmol) and K_2CO_3 (25.2 mg, 182.6 μmol) in DMF(2 mL) was heated at 90°C overnight. Concentrated, purified by pre-TLC eluting with DCM/MeOH=20/1 and got the product ethyl 4-

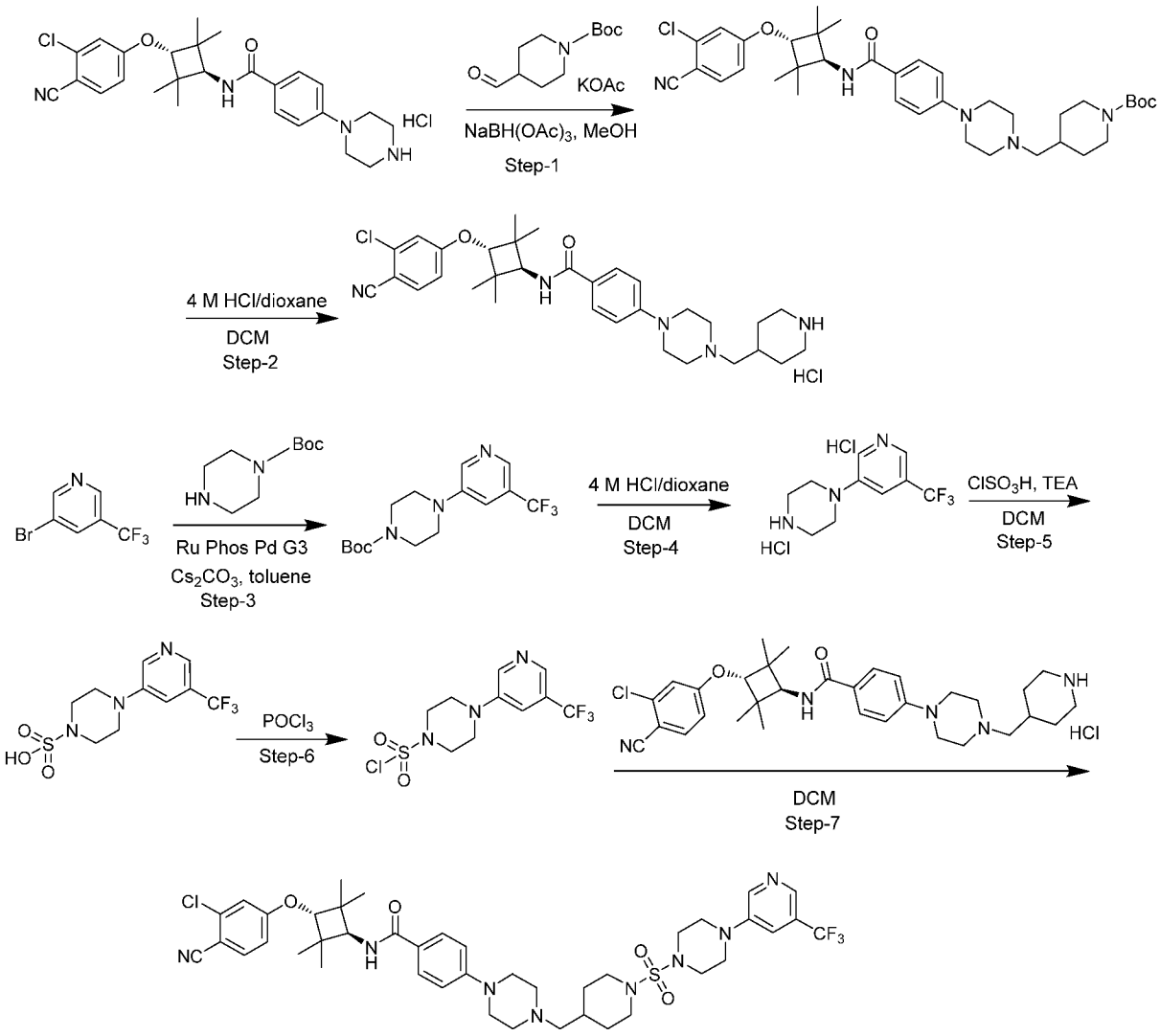
(4-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzoate(30 mg) as a solid.

[313] **Step 4**: ethyl4-(4-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzoate(20 mg, 33.6 μmol) was dissolved in THF/EtOH(1 mL/1 mL) was added NaOH(33.6 mg, 840.3 μmol) and H_2O(0.5 mL). Then the reaction was heated at 80oC for 2h. Concentrated, acedified with 1N HCl aqueous to pH=3-4, concentrated, extracted with DCM/MeOH, purified by pre-TLC eluting with DCM/MeOH=20/1 for 2 times and got the product 4-(4-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzoic acid(8 mg).

[314] **Step 5**: 4-(4-((4-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzoic acid(8 mg, 13.5 μmol), 4-((1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile hydrochloride(4.8 mg, 13.5 μmol) and HATU(7.7 mg, 20.2 μmol) in DMF(1 mL) was added DIEA(5.2 mg, 40.4 μmol) and stirred at RT for 1.5h. Concentrated, purified by pre-TLC eluting with DCM/MeOH=20/1 and got the product N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzamide(3.6 mg).

Example S40

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((1-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-4-yl)methyl)piperazin-1-yl)benzamide (Compound 41)



[315] **Step 1:** To a solution of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benzamide hydrochloride (60 mg, 1.0 eq.) in MeOH (1.5 mL) was added KOAc (35 mg, 3.0 eq.) at r.t., and the yellow mixture was stirred at r.t. for 0.5 h. Then tert-butyl 4-formylpiperidine-1-carboxylate (29.6 mg, 1.2 eq.) was added (in 0.3 mL MeOH) at r.t., and the yellow mixture was stirred at r.t. for 1.5 h. Then $NaBH(OAc)_3$ was added (130.2 mg, 5.0 eq.) at 0-5 ^0C, and the yellow mixture was stirred at r.t. for o/n. TLC (MeOH/DCM=1/10, Rf=0.7) showed N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benzamide hydrochloride was consumed, reaction had mainly a new spot. The mixture was adjusted pH ~ 7 with sat. $NaHCO_3$, extracted with DCM (10 mL×3), dried over Na_2SO_4, concentrated in vacuo. The residue was purified with pre-TLC (MeOH/DCM=1/30) to afford tert-butyl 4-((4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (65 mg, white solid).

[316] **Step 2:** Into a solution of tert-butyl 4-((4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (65 mg, 1.0 eq.) in DCM (1 mL) was dropped 4 M HCl/dioxane (1.5 mL) at 0-5 ^{0}C, and the light yellow mixture was stirred at r.t. for o/n. TLC (MeOH/DCM=1/20, Rf=0.05) showed tert-butyl 4-((4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazin-1-yl)methyl)piperidine-1-carboxylate consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo to afford N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(piperidin-4-ylmethyl)piperazin-1-yl)benzamide hydrochloride (55 mg, white solid, crude).

[317] **Step 3:** To a solution of 3-bromo-5-(trifluoromethyl)pyridine (1.2 g, 1.0 eq.) in toluene (15 mL) was added tert-butyl piperazine-1-carboxylate (1.185 mg, 1.2 eq.), Cs_2CO_3 (3.462 g, 2.0 eq.), and RuPhos Pd G3 (110 mg, 0.025 eq.) at r.t., and the yellow mixture was stirred at 100 ^{0}C for 6 h. TLC (EA/PE=1/5, Rf=0.1) showed 3-bromo-5-(trifluoromethyl)pyridine was consumed, reaction had mainly a new spot. To the mixture was added water (30 mL), and the mixture was extracted with EA (20 mL*2), dried over Na_2SO_4, concentrated in vacuo. The residue was purified with silica gel chromatography column eluted EA in PE 20% to afford tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-carboxylate (1.55 g, yellow semi-solid).

[318] **Step 4:** Into a solution of tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-carboxylate (1.55 g, 1.0 eq.) in DCM (5 mL) was dropped 4 M HCl/dioxane (16 mL) at 0-5 ^{0}C, and the yellow mixture was stirred at r.t. for o/n. TLC (MeOH/DCM=1/20, Rf=0.0) showed tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-carboxylate consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo to afford 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine dihydrochloride (1.45 g, yellow solid, crude).

[319] **Step 5:** Into a solution of 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine dihydrochloride (100 mg, 1.0 eq.) in DCM (3 mL) was dropped TEA (132.8 mg, 4.0 eq.), $ClSO_3H$ (42.2 mg, 1.1 eq.) at 0-5 ^{0}C, and the yellow mixture was stirred at r.t. for 2 h. TLC (MeOH/DCM=1/10, Rf=0.2) showed 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine dihydrochloride consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was purified with pre-TLC (MeOH/DCM=1/10) to afford 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-sulfonic acid (117 mg, yellow semi-solid).

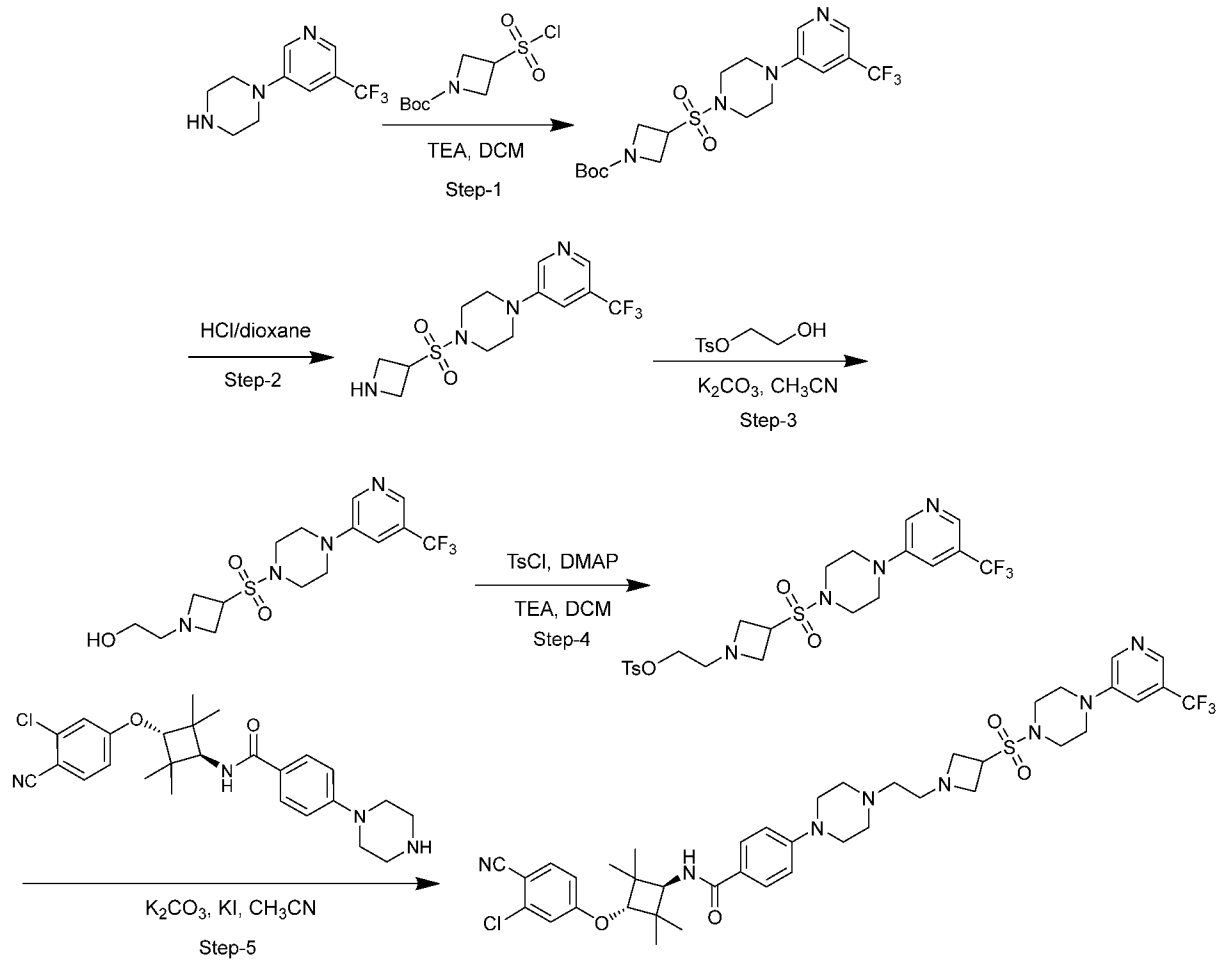
[320] **Step 6:** 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-sulfonic acid (100 mg, 1.0 eq.) in DCM (3 mL) was added into $POCl_3$ (0.5 mL) at r.t., and the yellow mixture was stirred at 80 ^{0}C for 3 h. TLC (MeOH/DCM=1/20, Rf=0.9) showed 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-sulfonic acid consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo to afford 82 mg of the crude product. Then 50 mg of the crude product was purified with pre-TLC (MeOH/DCM=1/20) to afford

4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-sulfonyl chloride (2.2 mg, light yellow oil). ESI-MS: 330.0 $[M+H]^+$.

[321] **Step 7:** Into a solution of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(piperidin-4-ylmethyl)piperazin-1-yl)benzamide (3 mg, 1.0 eq.) in DCM (0.5 mL) was dropped TEA (1.52 mg, 3.0 eq.) and 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-sulfonyl chloride (2.2 mg, 1.2 eq.) at 0-5 ^{0}C, and the yellow mixture was stirred at r.t. for 1 h. TLC (MeOH/DCM=1/15, Rf=0.6) showed N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(piperidin-4-ylmethyl)piperazin-1-yl)benzamide consumed and little 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-sulfonyl chloride remaining, reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was purified with pre-TLC (MeOH/DCM=1/25) to afford *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((1-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-4-yl)methyl)piperazin-1-yl)benzamide (**Compound 41**, 3 mg, yellow solid). ESI-MS: 857.3 $[M+H]^+$.

Example S41

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)azetidin-1-yl)ethyl)piperazin-1-yl)benzamide (Compound 42)



[322] **Step 1:** To a solution of 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine (50 mg, 1 eq) in DCM (3 mL) were added tert-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate (42 mg, 1 eq) and TEA (84 mg, 5 eq), and the reaction was stirred at room temperature for 3 hours. TLC showed new spot was observed, and no material was remained. The reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=20:1) to afford tert-butyl 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)azetidine-1-carboxylate (110 mg).

[323] **Step 2:** A solution of tert-butyl 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)azetidine-1-carboxylate(110 mg, 1 eq) in HCl/dioxane (10 mL) and dioxane (3 mL) was stirred at room temperature for 16 hours. TLC showed new spot was observed, and no material was remained. The reaction mixture was concentrated in vacuo to afford 1-(azetidin-3-ylsulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine (80 mg).

[324] **Step 3:** To a solution of 1-(azetidin-3-ylsulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine (40 mg, 1 eq) in CH_3CN (3 mL) were added 2-hydroxyethyl 4-methylbenzenesulfonate (28 mg, 1.1 eq), K_2CO_3 (48 mg, 3 eq), and KI (19 mg, 1 eq), the reaction was stirred at 100°C for 8 hours. TLC showed new spot was observed. The reaction mixture was diluted with water and extracted with DCM, the

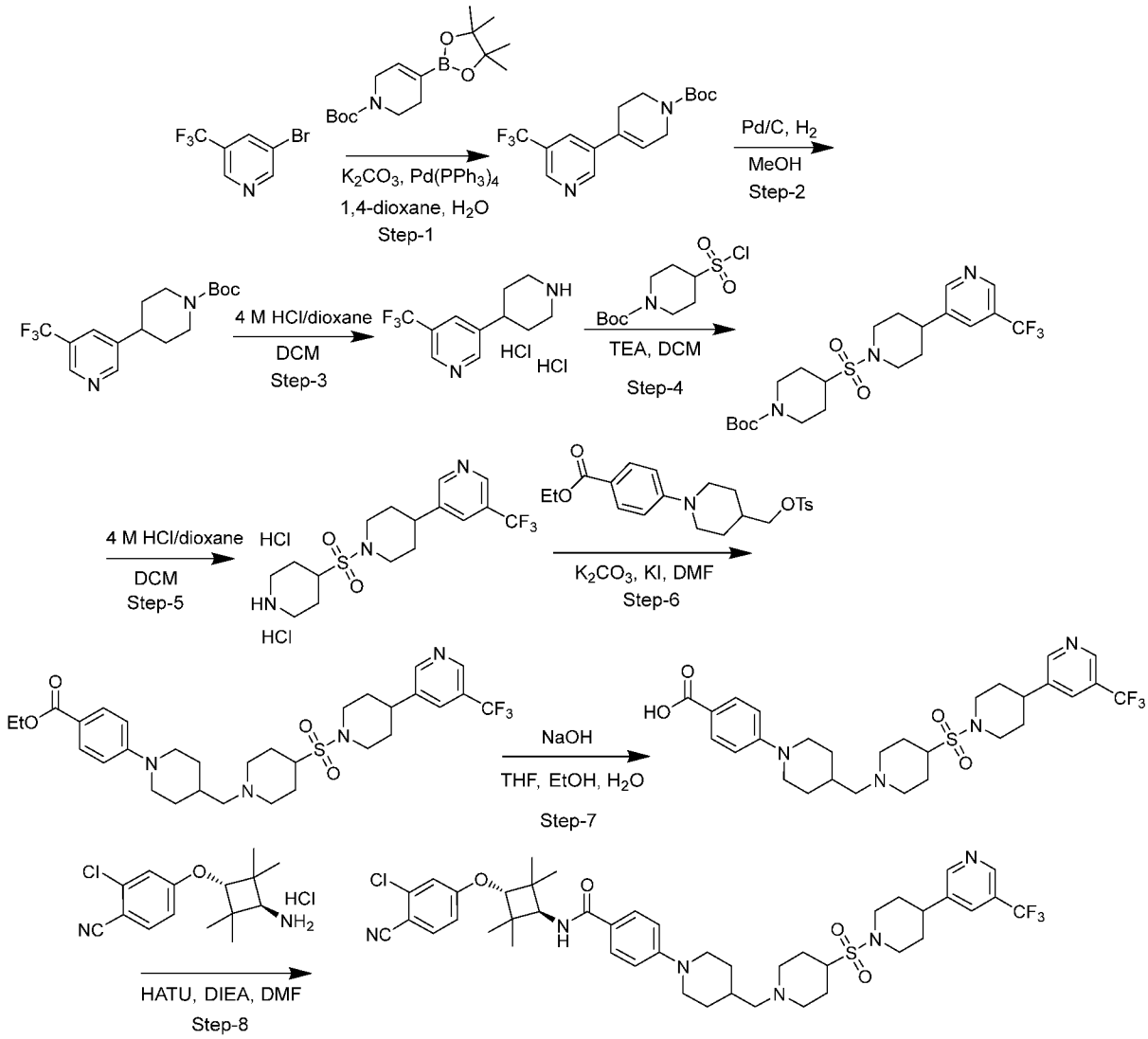
combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, and the mixture was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=10:1) to afford 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)azetidin-1-yl)ethan-1-ol (15 mg).

[325] **Step 4:** To a solution of 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)azetidin-1-yl)ethan-1-ol (15 mg, 1 eq) in DCM (5 mL) were added TsCl (15 mg, 2 eq), TEA (16 mg, 4 eq), and DMAP (5 mg, 1 eq), and the reaction was stirred at room temperature for 16 hours under nitrogen atmosphere. TLC showed new spot was observed, and no material was remained, the reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=10:1) to give 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)azetidin-1-yl)ethyl 4-methylbenzenesulfonate (5 mg).

[326] **Step 5:** To a solution of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benzamide (10 mg, 1 eq) in CH_3CN (3 mL) were added 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)azetidin-1-yl)ethyl 4-methylbenzenesulfonate (12 mg, 1 eq), Cs_2CO_3 (21 mg, 3 eq) and KI (4 mg, 1 eq), and the reaction was stirred at 100°C for 3 hours. TLC showed new spot was observed, and no material was remained, The reaction mixture concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=15:1) to afford *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)azetidin-1-yl)ethyl)piperazin-1-yl)benzamide (**Compound 42**, 5 mg) as a white solid. ESI-MS: 842.5 $[M+H]^+$.

Example S42

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzamide (Compound 43)



[327] **Step 1:** To a solution of 3-bromo-5-(trifluoromethyl)pyridine (300 mg, 1.0 eq.) in 1,4-dioxane (7 mL) was added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (615.2 mg, 1.5 eq.), K_2CO_3 (366 mg, 2.0 eq.), $Pd(PPh_3)_4$ (76.7 mg, 0.05 eq.), and H_2O (1.0 mL) at r.t., and the yellow mixture was stirred at 100 ^{0}C for 8 h. TLC (EA/PE=1/5, Rf=0.3) showed 3-bromo-5-(trifluoromethyl)pyridine was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo, added water (15 mL), extracted with EA (20 mL*2), dried over Na_2SO_4, concentrated in vacuo. The residue was purified with silica gel. Chromatography column eluted EA in PE 15~30% to afford tert-butyl 5-(trifluoromethyl)-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate (530 mg, light yellow oil).

[328] **Step 2:** To a solution of tert-butyl 5-(trifluoromethyl)-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate (200 mg, 1.0 eq.) in MeOH (10 mL) was added Pd/C (10%) (50 mg) at r.t., the atmosphere of the black reaction mixture was exchanged with H_2 3 times and stirred at r.t. o/n under H_2 atmosphere. TLC (EA/PE=1/5, Rf=0.2) showed tert-butyl 5-(trifluoromethyl)-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-

carboxylate consumed, reaction had mainly a new spot. The mixture was filtered and concentrated in vacuo to afford tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate (190 mg, colorless oil).

[329] **Step 3:** Into a solution of tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate (140 mg, 1.0 eq.) in DCM (2 mL) was dropped 4 M HCl/dioxane (2 mL) at 0-5 ^{0}C, and the yellow mixture was stirred at r.t. o/n. TLC (EA/PE=1/5, Rf=0.0) showed tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo to afford 3-(piperidin-4-yl)-5-(trifluoromethyl)pyridine dihydrogen chloride (140 mg, light yellow solid, crude).

[330] **Step 4:** To a solution of 3-(piperidin-4-yl)-5-(trifluoromethyl)pyridine dihydrogen chloride (39.7 mg, 1.0 eq.) in DCM (2 mL) was added TEA (40 mg, 3.0 eq.) and tert-butyl 4-(chlorosulfonyl)piperidine-1-carboxylate (30 mg, 0.8 eq.) at 0-5 ^{0}C, and the yellow mixture was stirred at r.t. for 1 h. TLC (EA/PE=1/1, Rf=0.2) showed 3-(piperidin-4-yl)-5-(trifluoromethyl)pyridine dihydrogen chloride remained, reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was purified with pre-TLC (EA/PE=3/1) to afford tert-butyl 4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)piperidine-1-carboxylate (14 mg, white solid).

[331] **Step 5:** Into a solution of tert-butyl 4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)piperidine-1-carboxylate (14 mg, 1.0 eq.) in DCM (0.5 mL) was dropped 4 M HCl/dioxane (1 mL) at 0-5 ^{0}C, and the yellow mixture was stirred at r.t. o/n. TLC (EA/PE=1/1, Rf=0.0) showed tert-butyl 4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)piperidine-1-carboxylate consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo to afford 3-(1-(piperidin-4-ylsulfonyl)piperidin-4-yl)-5-(trifluoromethyl)pyridine dihydrogen chloride (16 mg, white solid, crude).

[332] **Step 6:** Into a solution of 3-(1-(piperidin-4-ylsulfonyl)piperidin-4-yl)-5-(trifluoromethyl)pyridine dihydrogen chloride (14 mg, 1.0 eq.) in DMF (1 mL) was dropped ethyl 4-(4-((tosyloxy)methyl)piperidin-1-yl)benzoate (38 mg, crude, 2.0 eq.), K_2CO_3 (37.7 mg, 6.0 eq.), and KI (0.7 mg, 0.1 eq.) at r.t., and the yellow mixture was stirred at 80 ^{0}C o/n. TLC (MeOH/DCM=1/20, Rf=0.7) showed 3-(1-(piperidin-4-ylsulfonyl)piperidin-4-yl)-5-(trifluoromethyl)pyridine dihydrogen chloride was consumed, reaction had three new spots. The mixture was filtered and washed with DCM (5 mL*2), and the organic layer was concentrated in vacuo. The residue was purified with pre-TLC (MeOH/DCM=1/30) to afford ethyl 4-(4-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzoate (15 mg, yellow oil).

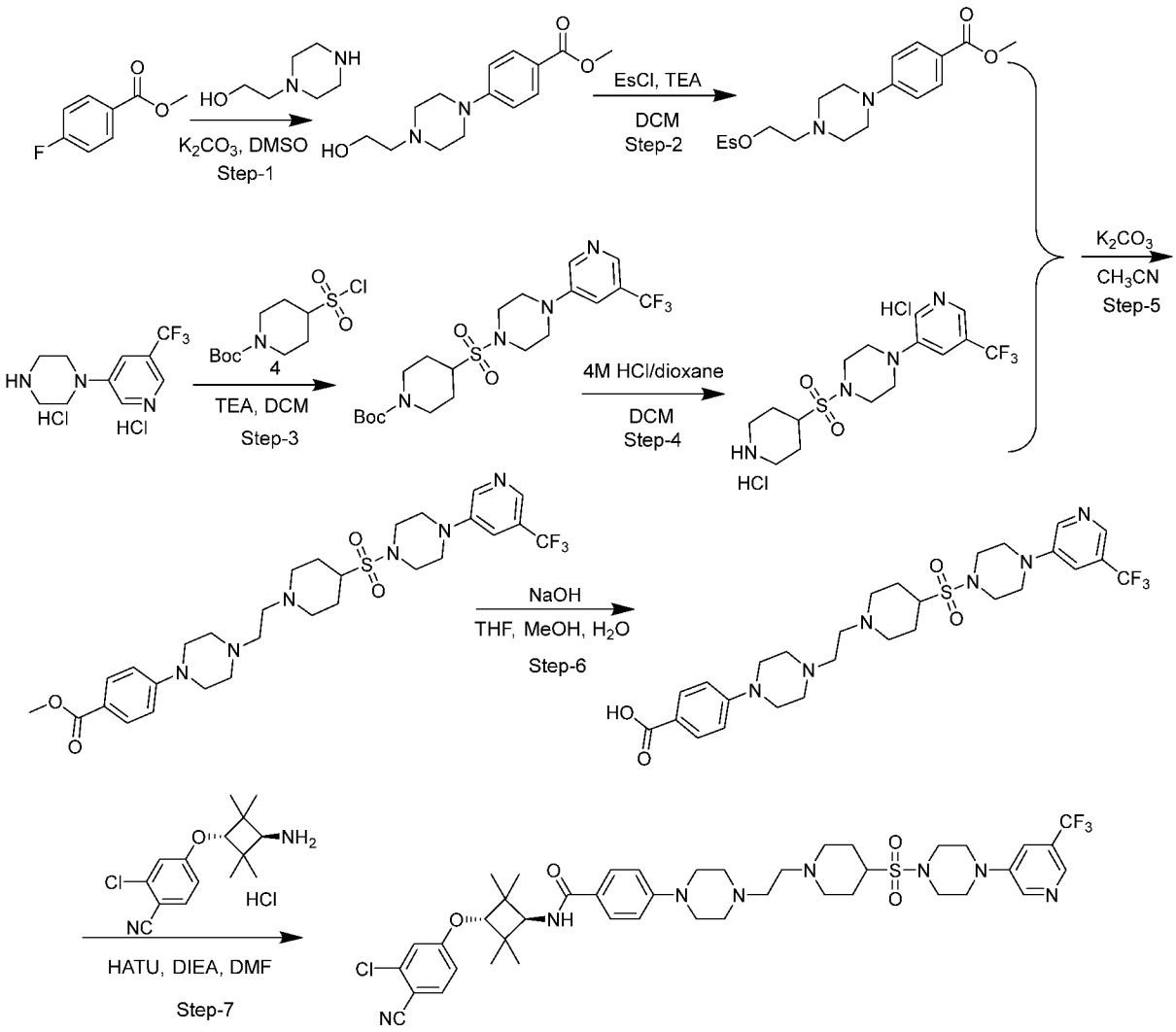
[333] **Step 7:** Into a solution of ethyl 4-(4-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzoate (64 mg, 1.0 eq.) in EtOH (0.5 mL) and THF (0.5 mL) was added NaOH (24 mg, 25 eq.), H_2O (0.5 mL) at 0-5 ^{0}C, and the yellow mixture was stirred at 80

^{0}C for o/n. TLC (MeOH/DCM=1/20, Rf=0.15) showed ethyl 4-(4-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzoate was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo, then water was added (2 mL), the pH adjusted to ~4 with 1 M HCl, and the mixture was extracted with DCM (10 mL×2), dried over Na_2SO_4, and concentrated in vacuo to afford 4-(4-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzoic acid (13 mg, yellow solid, crude).

[334] **Step 8:** To a solution of 4-(4-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzoic acid (13 mg, 1.0 eq.) in DMF (0.5 mL) was added 4-((1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile (6.8 mg, 1.0 eq.), HATU (10 mg, 1.2 eq.), and DIEA (8.5 mg, 3.0 eq.) at 0-5 ^{0}C, and the yellow mixture was stirred at r.t. for 3 h. TLC (MeOH/DCM=1/20, Rf=0.45) showed 4-(4-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzoic acid was consumed, reaction had mainly a new spot. The mixture was quenched with water (5 mL), extracted with DCM (10 mL*2), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with pre-TLC (MeOH/DCM=1/20) to afford *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)piperidin-1-yl)methyl)piperidin-1-yl)benzamide (**Compound 43**, 5.0 mg, white solid). ESI-MS: 854.36 $[M+H]^+$.

Example S43

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)ethyl)piperazin-1-yl)benzamide (Compound 44)



[335] **Step 1:** To a solution of methyl 4-fluorobenzoate (500 mg, 1.0 eq.) in DMSO (8 mL) was added 2-(piperazin-1-yl)ethan-1-ol (419.1 mg, 1.0 eq.) and K_2CO_3 (896.6 mg, 2.0 eq.) at r.t., and the yellow mixture was stirred at 100 ^{0}C for o/n. TLC (MeOH/DCM=1/15, Rf=0.15) showed methyl 4-fluorobenzoate consumed, reaction had mainly a new spot. The mixture was quenched with water (15 mL), extracted with EA (15 mL×3), washed with brine (15 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with silica gel. Chromatography column eluted MeOH in DCM 5% to afford methyl 4-(4-(2-hydroxyethyl)piperazin-1-yl)benzoate(460 mg, yellow solid).

[336] **Step 2:** To a solution of methyl 4-(4-(2-hydroxyethyl)piperazin-1-yl)benzoate(132 mg, 1.0 eq.) in DCM (3 mL) was added TEA (126.3 mg, 2.5 eq.) and EsCl (64 mg, 1.0 eq.) at 0~5 ^{0}C, and the yellow mixture was stirred at r.t. for 0.5 h. TLC (MeOH/DCM=1/20, Rf=0.8) showed methyl 4-(4-(2-hydroxyethyl)piperazin-1-yl)benzoate was consumed, and two new spots were present. The mixture was concentrated in vacuo to afford (2-(4-(4-(methoxycarbonyl)phenyl)piperazin-1-yl)ethoxy)einsteinium (330 mg, white semi-solid, crude).

[337] **Step 3:** To a solution of 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine dihydrochoride (150 mg, 1.0 eq.) in DCM (5 mL) was added TEA (199 mg, 4.0 eq.) and tert-butyl 4-(chlorosulfonyl)piperidine-1-carboxylate (168 mg, 1.2 eq.) at 0~5 ^{0}C, and the yellow mixture was stirred at r.t. for 3 h. TLC (MeOH/DCM=1/30, Rf=0.8) showed 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine dihydrochoride still remained, reaction had mainly a new spot. The mixture was concentrated in vacuo and purified with pre-TLC (MeOH/DCM=1/30) to afford tert-butyl 4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidine-1-carboxylate (130 mg, white solid).

[338] **Step 4:** Into a solution of tert-butyl 4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidine-1-carboxylate (130 mg, 1.0 eq.) in DCM (2 mL) was dropped 4 M HCl/dioxane (2 mL) at 0-5 ^{0}C, the yellow mixture was stirred at r.t. o/n. TLC (MeOH/DCM=1/30, Rf=0.0) showed tert-butyl 4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidine-1-carboxylate consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo to afford 1-(piperidin-4-ylsulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine dihydrochloride (110 mg, yellow solid, crude).

[339] **Step 5:** To a solution of 1-(piperidin-4-ylsulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine dihydrochloride (70 mg, 1.0 eq.) in CH_3CN (5 mL) was added (2-(4-(4-(methoxycarbonyl)phenyl)piperazin-1-yl)ethoxy)einsteinium (330 mg, 30% purity, 1.8 eq.), and K_2CO_3 (85.7 mg, 4.0 eq.) at r.t., and the yellow mixture was stirred at 70 ^{0}C for 0.5 h. TLC (MeOH/DCM=1/20, Rf=0.4) showed 1-(piperidin-4-ylsulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine dihydrochloride still remained, but (2-(4-(4-(methoxycarbonyl)phenyl)piperazin-1-yl)ethoxy)einsteinium was consumed and many new spots were present. The mixture was quenched with water (15 mL), extracted with DCM (15 mL*3), dried over Na_2SO_4, concentrated in vacuo, and purified with pre-TLC (MeOH/DCM=1/15) to afford methyl 4-(4-(2-(4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)ethyl)piperazin-1-yl)benzoate (39 mg, white solid). ESI-MS: 624.7 $[M+H]^+$.

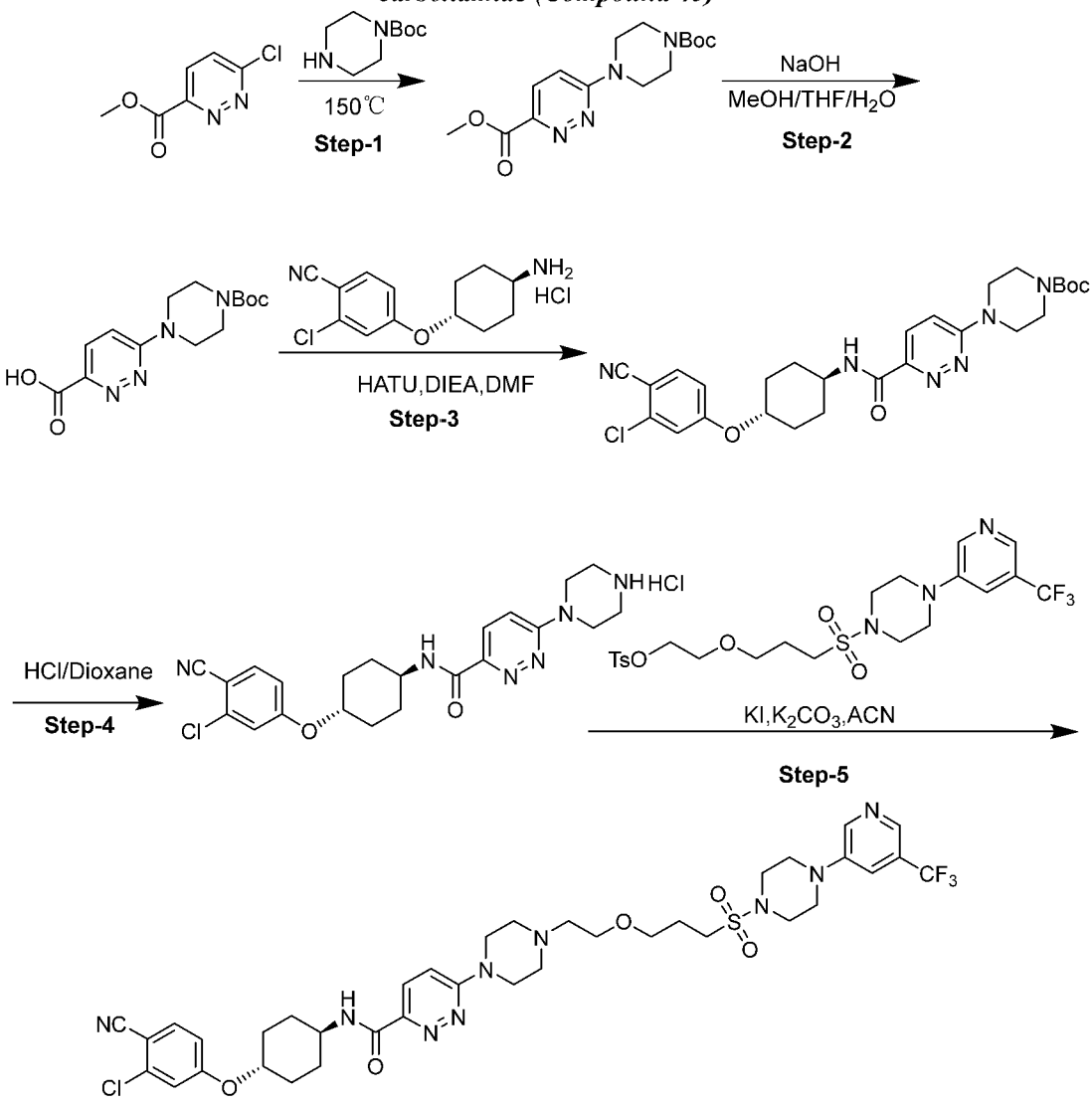
[340] **Step 6:** To a solution of methyl 4-(4-(2-(4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)ethyl)piperazin-1-yl)benzoate (20 mg, 1.0 eq.) in MeOH (0.5 mL) and THF (0.5 mL) was added NaOH (32 mg, 25 eq.) and H_2O (0.5 mL) at 0-5 ^{0}C, and the yellow mixture was stirred at 80 ^{0}C for 3 h. TLC (MeOH/DCM=1/15, Rf=0.1) showed methyl 4-(4-(2-(4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)ethyl)piperazin-1-yl)benzoate was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo, then water was added (1 mL), the pH was adjusted to ~4 with 1 M HCl, and the mixture was extracted with DCM (10 mL*3), dried over Na_2SO_4, concentrated in vacuo to afford methyl 4-(4-(2-(4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)ethyl)piperazin-1-yl)benzoate (16 mg, white solid, crude).

[341] **Step 7:** To a solution of methyl 4-(4-(2-(4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)ethyl)piperazin-1-yl)benzoate (13 mg, 1.0 eq.) in DMF (0.5 mL) was added 4-

((1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile (8 mg, 1.0 eq.), HATU (12 mg, 1.2 eq.), and DIEA (10 mg, 3.0 eq.) at 0-5 ^{0}C, and the yellow mixture was stirred at r.t. for o/n. TLC (MeOH/DCM=1/20, Rf=0.55) showed methyl 4-(4-(2-(4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)ethyl)piperazin-1-yl)benzoate was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo and oil pump. The residue was purified with pre-TLC (MeOH/DCM=1/17) to afford *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(4-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)piperidin-1-yl)ethyl)piperazin-1-yl)benzamide (**Compound 44**, 11 mg, light yellow solid). ESI-MS: 871.3 $[M+H]^+$.

Example S44

Synthesis of N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)pyridazine-3-carboxamide (Compound 45)



[342] **Step 1:** To a flask containing methyl 6-chloropyridazine-3-carboxylate (200.0 mg, 1.159 mmol) was added tert-butyl piperazine-1-carboxylate (215.85 mg, 1.159 mmol). The reaction mixture waw

stirred at 150°C under N_2 atmosphere for 2.0 h. The reaction was cooled to room temperature and DCM was added. After stirring for 15 minutes, the resulting mixture was filtered. The filtration was concentrated in vacuo and purified by pre-TLC to afford methyl 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridazine-3-carboxylate (62.4 mg, 0.194 mmol, 16.70%).

[343] **Step 2:** To a solution of methyl 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridazine-3-carboxylate (62.4 mg, 0.194 mmol) in MeOH (1.0 mL)/ THF (1.0 mL)/H2O (0.5 mL) was added NaOH (38.71 mg, 0.968 mmol), and the reaction was stirred at room temperature overnight. The reaction was acidified to pH 3-4 with HCl solution (1.0 M), diluted with EA and water. The organic layer was separated, washed with water. The organic layer was collected, concentrated in vacuo, and dried to afford 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridazine-3-carboxylic acid (37.5 mg, 62.84%).

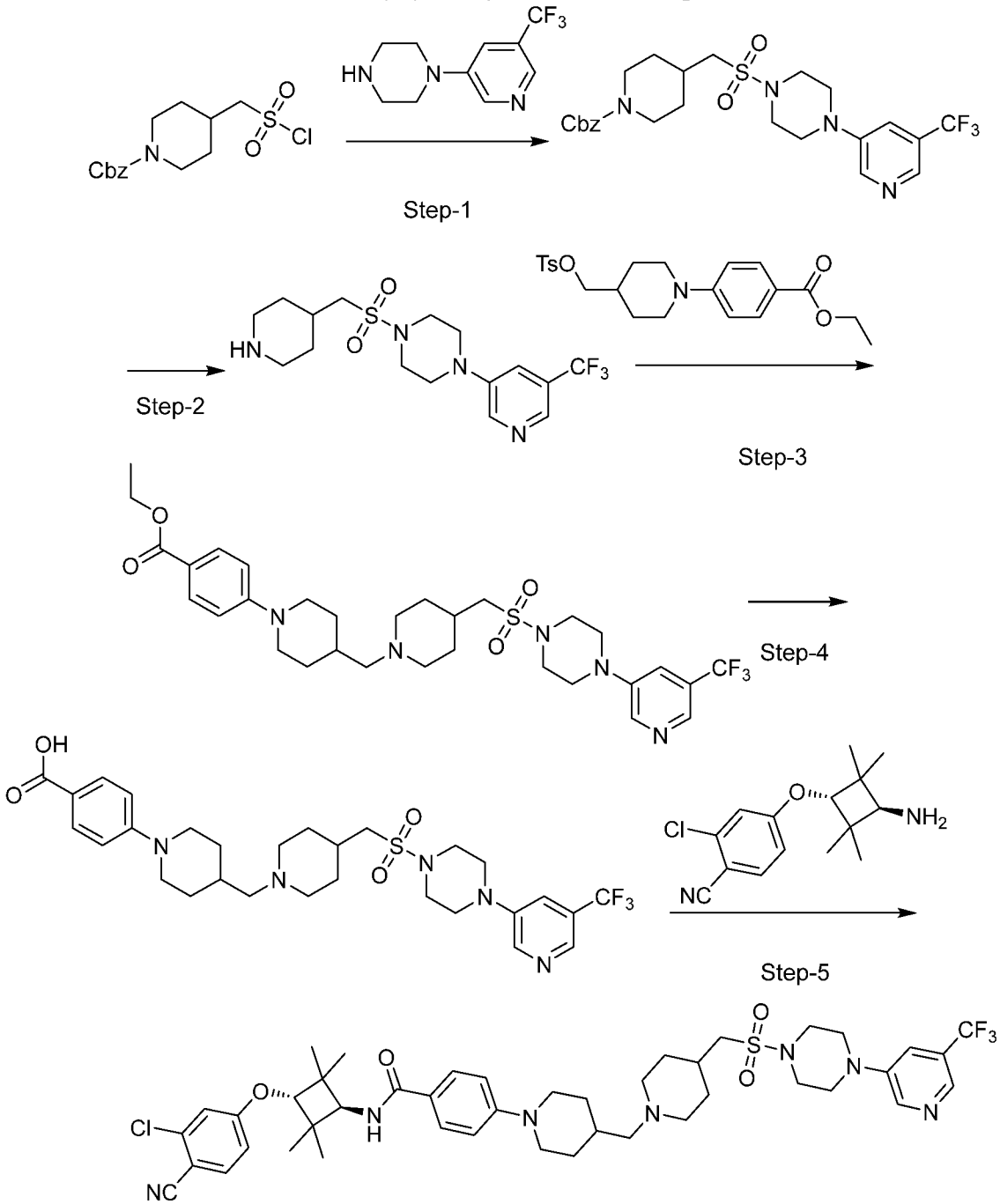
[344] **Step 3:** To a solution of 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridazine-3-carboxylic acid (37.5 mg, 0.122 mmol) in DMF (1.5 mL) were added HATU (69.37 mg, 0.182 mmol), Ethyldiisopropylamine (47.16 mg, 0.365mmol), and 4-(((1r,4r)-4-aminocyclohexyl)oxy)-2-chlorobenzonitrile hydrochloride (36.67 mg, 0.128 mmol), and the reaction was stirred at room temperature for 2 hr. The reaction was diluted with EA and water. The organic layer was separated. The aqueous layer was back extracted with EtOAc. The EtOAc layers were combined and washed with saturated $NaHCO_3$ solution and water. The EtOAc layer was concentrated in vacuo. The residue was purified by Pre-TLC to afford tert-butyl 4-(6-(((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)carbamoyl)pyridazin-3-yl)piperazine-1-carboxylate (45.1 mg, 68.54%).

[345] **Step 4:** To tert-butyl 4-(6-(((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)carbamoyl)pyridazin-3-yl)piperazine-1-carboxylate (45.1 mg, 0.083 mmol) was added HCl/dioxane (2.5 mL), and the reaction was stirred at room temperature for 3 hr. The reaction was concentrated in vacuo and dried to afford N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(piperazin-1-yl)pyridazine-3-carboxamide (47.4 mg, 0.083 mmol).

[346] **Step 5:** To a solution of 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl 4-methylbenzenesulfonate (11.0 mg, 0.020 mmol) in ACN (1.5 mL) were added N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(piperazin-1-yl)pyridazine-3-carboxamide (10.47 mg, 0.022 mmol), K_2CO_3 (6.91 mg, 0.050 mmol), and potassium iodide (1.66 mg, 0.010 mmol), and the reaction was stirred at 80°C for 6 h. The reaction was concentrated in vacuo and purified by pre-TLC to afford N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)pyridazine-3-carboxamide (**Compound 45**, 4.9 mg, 29.95%). ESI-MS: 820.2, 821.2, 824.2$[M+H]^+$.

Example S45

Synthesis of 4-(4-{4-[2-(dioxo{4-[5-(trifluoromethyl)pyridin-3-yl]piperazin-1-yl}-λ⁶-sulfanyl)ethyl]piperazin-1-yl}hexahydropyridin-1-yl)-N-[(1r,3r)-3-[(3-chloro-4-cyanophenyl)oxy]-2,2,4,4-tetramethylcyclobutyl]benzamide (Compound 46)



[347] **Step 1:** A solution of benzyl 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine (41 mg, 1.0 eq), benzyl 4-((chlorosulfonyl)methyl)piperidine-1-carboxylate (50 mg, 1.0 eq), and Et_3N (46 mg, 3.0 eq) in DCM (1.5ml) was stirred at RT for 3h. The solvent was removed and the mixture was purified by pre-TLC (PE:EA=1:1) to afford benzyl 4-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)piperidine-1-carboxylate (50 mg, 1.0 eq), ESI-MS: 527.2[M+H]+.

[348] **Step 2:** To a solution of benzyl 4-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)piperidine-1-carboxylate (50 mg, 1.0 eq) in MeOH/THF (2ml/1ml) was added 10%Pd/C (10 mg). The reaction was stirred under H_2 at RT for 1h. TLC showed complete reaction of starting materials. The mixture was filtered, and the filtrate was concentrated to give 1-((piperidin-4-ylmethyl)sulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine (19 mg), ESI-MS: 393.2[M+H]+.

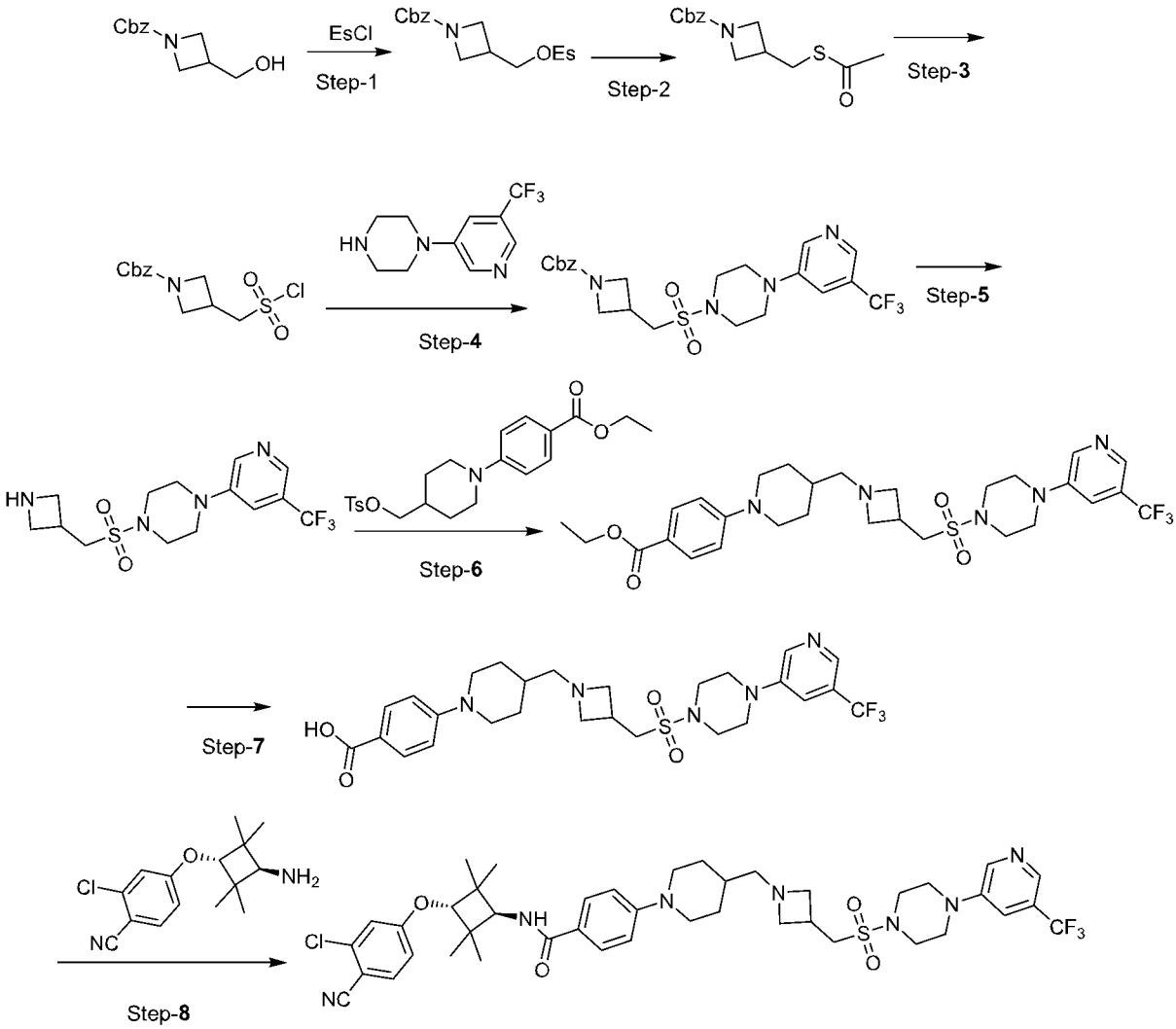
[349] **Step 3:** A solution of ethyl 4-(4-((tosyloxy)methyl)piperidin-1-yl)benzoate (22.2 mg, 1.1 eq), 1-((piperidin-4-ylmethyl)sulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine (19 mg, 1.0 eq), K_2CO_3 (13.4 mg, 2.0 eq) and KI (0.8 mg, 0.1 eq) in DMF (1.5 ml) was stirred at 90 °C overnight. DCM and H_2O were added, and then the organic layers was washed with NaCl aqueous solution, dried over $MgSO_4$ and concentrated. The crude product was purified by pre-TLC (DCM:MeOH=15:1) to afford ethyl 4-(4-((4-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)piperidin-1-yl)methyl)piperidin-1-yl)benzoate (14 mg), ESI-MS: 638.3[M+H]+.

[350] **Step 4:** To a solution of ethyl 4-(4-((4-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)piperidin-1-yl)methyl)piperidin-1-yl)benzoate (14 mg, 1.0 eq) in EtOH/THF/H2O (1ml/1ml/0.5ml) was added NaOH (18 mg, 20 eq). The reaction was stirred at 80°C for 3 h. The solvent was removed and added 1M HCl aqueous solution to adjust to aqueous pH=3, concentrated and the mixture was purified by pre-TLC (DCM:MeOH=15:1) to afford 4-(4-((4-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)piperidin-1-yl)methyl)piperidin-1-yl)benzoic acid (5 mg), ESI-MS: 610.3[M+H]+.

[351] **Step 5:** To a solution of 4-(4-((4-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)piperidin-1-yl)methyl)piperidin-1-yl)benzoic acid (5 mg, 1.0 eq) in DMF (1ml) was added HATU (4.7 mg, 1.5 eq), DIEA (3.2 mg, 3.0 eq) and 4-((1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile (2.6 mg, 1.0 eq). The reaction was stirred at RT for 40 min. The solvent was removed and the mixture was purified by pre-TLC (DCM:MeOH=15:1) to afford the product 4-(4-{4-[2-(dioxo{4-[5-(trifluoromethyl)pyridin-3-yl]piperazin-1-yl}-λ^6-sulfanyl)ethyl]piperazin-1-yl}hexahydropyridin-1-yl)-*N*-[(1r,3r)-3-[(3-chloro-4-cyanophenyl)oxy]-2,2,4,4-tetramethylcyclobutyl]benzamide (**Compound 46**, 4 mg), ESI-MS: 870.4 [M+H]+.

Example S46

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)azetidin-1-yl)methyl)piperidin-1-yl)benzamide (Compound 47)



[352] **Step 1:** A solution of benzyl 3-(hydroxymethyl)azetidine-1-carboxylate (500 mg, 1.0 eq), Et_3N (297 mg, 1.3 eq) in DCM (5ml) was added EsCl (321 mg, 1.1 eq) at 0-10°C. The reaction was stirred at RT for 1h. TLC showed complete reaction of raw materials. The reaction mixture was quenched by the addition of H_2O and extracted with DCM. The organic layers was washed with NaCl aqueous solution for 3 times, then dried over Na_2SO_4 and concentrated to afford crude product benzyl ((1-((benzyloxy)carbonyl)azetidin-3-yl)methoxy)einsteinium (689 mg), ESI-MS: 314.1[M+H]+.

[353] **Step 2:** To a solution of AcSK (371 mg, 1.5 eq) in DMF (4ml) was added the solution of ((1-((benzyloxy)carbonyl)azetidin-3-yl)methoxy)einsteinium (680 mg, 1.0 eq) in DMF (3ml) at 50°C. The reaction was stirred at 70°C for 4h. The reaction mixture was quenched by the addition of H_2O (10ml) and extracted with EA. The organic layers was dried over Na_2SO_4 and concentrated to afford crude product benzyl 3-((acetylthio)methyl)azetidine-1-carboxylate (600 mg), ESI-MS: 280.1[M+H]+.

[354] **Step 3:** To a solution of benzyl 3-((acetylthio)methyl)azetidine-1-carboxylate (600 mg, 1.0 eq) in CH_3CN (8 ml) was added 2M HCl (1 ml), NCS (1148 mg, 4.0 eq) at 10°C. The reaction was stirred

at RT for 2h. The solvent was removed and added DCM and H_2O, the organic layers was washed with NaCl aqueous solution, dried over Na_2SO_4 and concentrated to afford crude product benzyl 3-((chlorosulfonyl)methyl)azetidine-1-carboxylate (650 mg), ESI-MS: 304[M+H]+.

[355] **Step 4:** A solution of 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine (210 mg, 0.6 eq), benzyl 3-((chlorosulfonyl)methyl)azetidine-1-carboxylate (400 mg, 1.0 eq), Et_3N(398 mg, 3.0 eq) in DCM (3ml) was stirred at RT for 2h. The solvent was removed and the mixture was purified by column chromatography on silica gel eluted with (PE:EA=2:1-1:2) to afford benzyl 3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)azetidine-1-carboxylate (84 mg), ESI-MS: 499.1[M+H]+.

[356] **Step 5:** To a solution of benzyl 3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)azetidine-1-carboxylate (84 mg) in MeOH/THF (2ml/1ml) was added 10%Pd/C (40 mg). The reaction was stirred under H_2 at RT for 2h. TLC showed complete reaction of raw materials. The mixture was filtered, and the filtrate was concentrated to give 1-((azetidin-3-ylmethyl)sulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine (46 mg), ESI-MS: 365.1[M+H]+.

[357] **Step 6:** A solution of ethyl 4-(4-((tosyloxy)methyl)piperidin-1-yl)benzoate (58 mg, 1.1 eq), 1-((azetidin-3-ylmethyl)sulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine (46 mg, 1.0 eq), K_2CO_3 (35 mg, 2.0 eq) and KI (2.1 mg, 0.1 eq) in DMF (2 ml) was stirred at 90°C for 2h. Added DCM and H_2O, the organic layers was washed with NaCl aqueous solution, dried over Na_2SO_4 and concentrated. The crude product was purified by pre-TLC (DCM:MeOH=15:1) to afford ethyl 4-(4-((3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)azetidin-1-yl)methyl)piperidin-1-yl)benzoate, ESI-MS: 610.2[M+H]+.

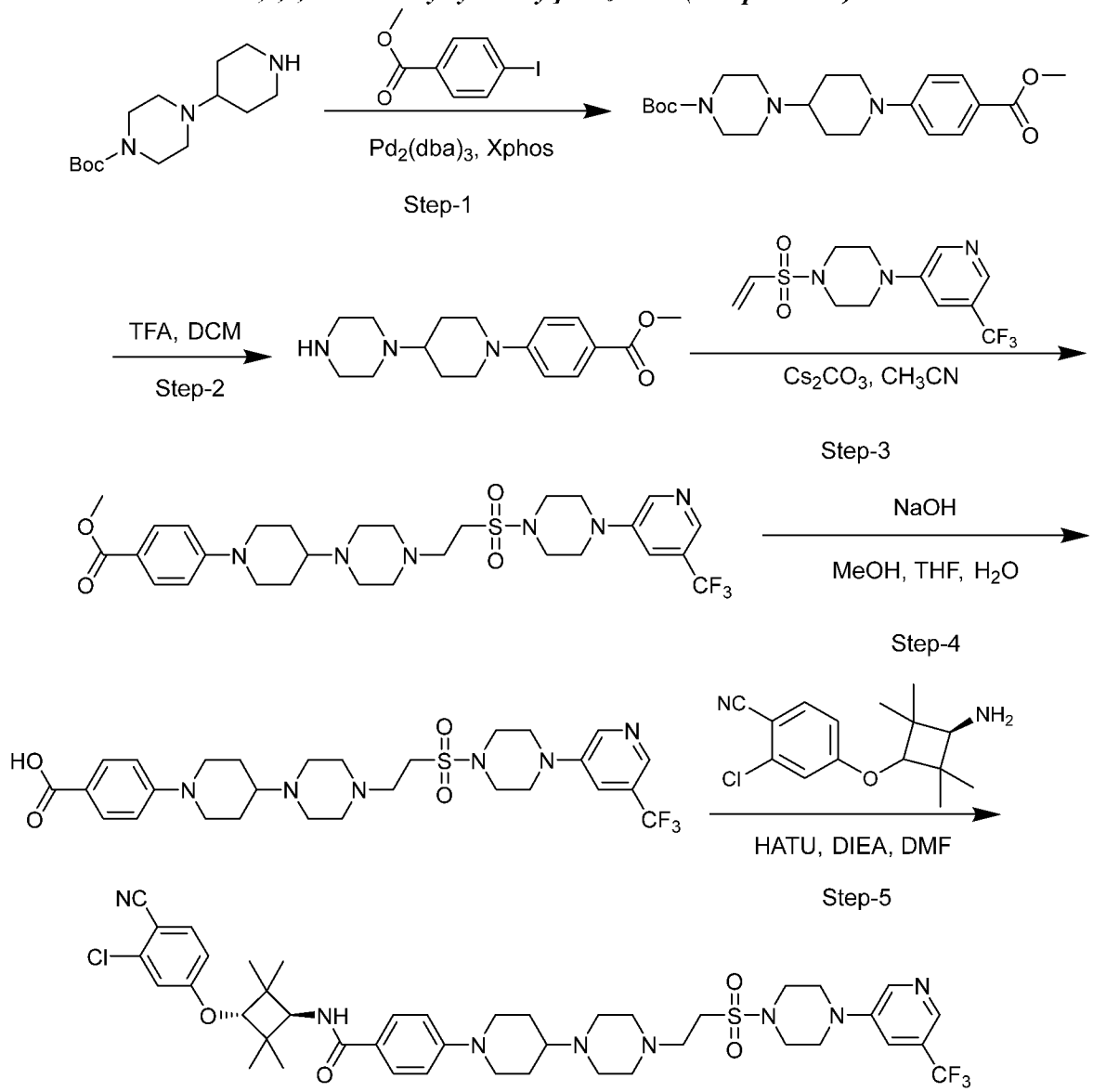
[358] **Step 7:** To a solution of ethyl 4-(4-((3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)azetidin-1-yl)methyl)piperidin-1-yl)benzoate (23 mg, 1.0 eq) in EtOH/THF/H2O (1.5ml/1.5ml/0.5ml) was added NaOH (30.2 mg, 20 eq). The reaction was stirred at 80°C for 3h. The solvent was removed and added 1M HCl aqueous solution to adjust to aqueous PH=3, concentrated and the mixture was purified by pre-TLC (DCM:MeOH=15:1) to afford 4-(4-((3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)azetidin-1-yl)methyl)piperidin-1-yl)benzoic acid (6 mg), ESI-MS: 582.2[M+H]+.

[359] **Step 8:** A solution of 4-(4-((3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)azetidin-1-yl)methyl)piperidin-1-yl)benzoic acid (6 mg, 1.0 eq) in DMF （1ml） was added HATU (5.9 mg, 1.5 eq), DIEA (4 mg, 3.0 eq) and 4-((1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile (3.3 mg, 1.0 eq). The reaction was stirred at RT for 40min. The solvent was removed and the mixture was purified by pre-TLC (DCM:MeOH=10:1) to afford the product N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((3-(((4-(5-

(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)azetidin-1-yl)methyl)piperidin-1-yl)benzamide (**Compound 47**, 5 mg), ESI-MS: 842.3[M+H]+.

Example S47

Synthesis of 4-(4-{4-[2-(dioxo{4-[5-(trifluoromethyl)pyridin-3-yl]piperazin-1-yl}-λ⁶-sulfanyl)ethyl]piperazin-1-yl}hexahydropyridin-1-yl)-N-[(1r,3r)-3-[(3-chloro-4-cyanophenyl)oxy]-2,2,4,4-tetramethylcyclobutyl]benzamide (Compound 48)



[360] **Step 1:** To a solution of tert-butyl 4-(piperidin-4-yl)piperazine-1-carboxylate (100 mg, 0.371 mmol) in dioxane (3 mL) were added methyl 4-iodobenzoate (116.73 mg, 0.026 mmol), Cs_2CO_3 (302.37 mg, 0.928 mmol), XPHOS (35.39 mg, 0.074 mmol) and $Pd_2(dba)_3$ (33.99 mg, 0.037 mmol), and the reaction was stirred at for 90 °C for 3 hours. The reaction was complete as detected by TLC (DCM: MeOH= 25:1) to afford tert-butyl 4-(1-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)piperazine-1-carboxylate (40 mg, 0.099 mmol, 26.70%). ESI-MS: 403.9 $[M+H]^+$.

[361] **Step 2:** To a solution of tert-butyl 4-(1-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)piperazine-1-carboxylate (40 mg, 0.099 mmol) in DCM (10 mL) was added TFA (5 mL, 65.296 mmol) and the reaction was stirred at room temperature for 18 hours. The reaction was complete as detected by TLC (DCM: MeOH= 10:1). The reaction was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=10:1) to afford methyl 4-(4-(piperazin-1-yl)piperidin-1-yl)benzoate (40 mg, 0.096 mmol, 96.79%). ESI-MS: 303.9 $[M+H]^+$.

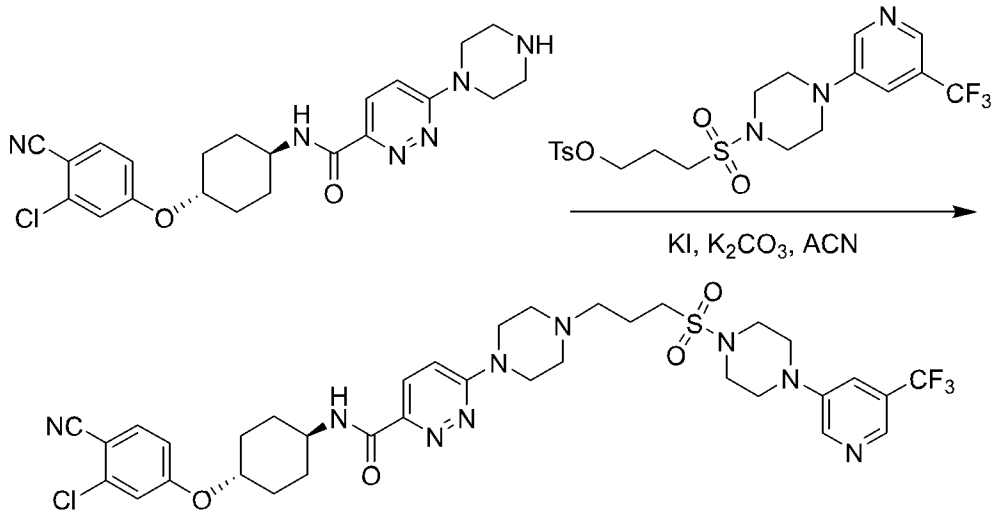
[362] **Step 3:** To a solution of methyl 4-(4-(piperazin-1-yl)piperidin-1-yl)benzoate (10 mg, 0.024 mmol) in CH_3CN (3 mL) were added Cs_2CO_3 (23.46 mg, 0.072 mmol) and 1-[dioxo(vinyl)-λ6-sulfanyl]-4-[5-(trifluoromethyl)pyridin-3-yl]piperazine (7.70 mg, 0.024 mmol), and the reaction was stirred at 100 °C for 3 hours. TLC showed new spot was observed, and no material remained. The reaction was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=20:1) to afford methyl 4-(4-(4-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethyl)piperazin-1-yl)piperidin-1-yl)benzoate (14 mg, 0.022 mmol, 93.52%) as a yellow solid.

[363] **Step 4:** To a solution of methyl methyl 4-(4-(4-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethyl)piperazin-1-yl)piperidin-1-yl)benzoate (14 mg, 0.022 mmol) in MeOH (2 mL), THF (2 mL), H_2O (0.5 mL) was added NaOH (4.48 mg, 0.112 mmol), and the reaction was stirred at room temperature for 16 hours. TLC showed major material was remained, and trace product was observed, the mixture was stirred at 40 °C for 3 hours. TLC showed product was observed, and no material remained. The reaction was diluted with water and adjusted to pH=2 with conc. HCl, then extracted with DCM (20 mL × 10), The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo to afford 4-(4-(4-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethyl)piperazin-1-yl)piperidin-1-yl)benzoic acid (13 mg, 0.021 mmol, 93.25%) as a yellow solid.

[364] **Step 5:** To a solution of 4-(4-{4-[2-(dioxo{4-[5-(trifluoromethyl)pyridin-3-yl]piperazin-1-yl}-λ^6-sulfanyl)ethyl]piperazin-1-yl}hexahydropyridin-1-yl)benzoic acid (8 mg, 0.013 mmol) in DMF (2 mL) were added DIEA (8.47 mg, 0.065 mmol), HATU (12.45 mg, 0.033 mmol), and 4-(4-(4-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethyl)piperazin-1-yl)piperidin-1-yl)benzoic acid (3.65 mg, 0.013 mmol), and the reaction was stirred at room temperature for 3 hours. The reaction was complete detected by TLC (DCM: MeOH= 10:1). The reaction was concentrated in vacuo. The residue was purified by preparative TLC (DCM:MeOH=20:1) to afford 4-(4-{4-[2-(dioxo{4-[5-(trifluoromethyl)pyridin-3-yl]piperazin-1-yl}-λ^6-sulfanyl)ethyl]piperazin-1-yl}hexahydropyridin-1-yl)-N-[(1r,3r)-3-[(3-chloro-4-cyanophenyl)oxy]-2,2,4,4-tetramethylcyclobutyl]benzamide (**Compound 48**, 4 mg, 0.005 mmol, 35.03%). ESI-MS: 871.3 $[M+H]^+$.

Example S48

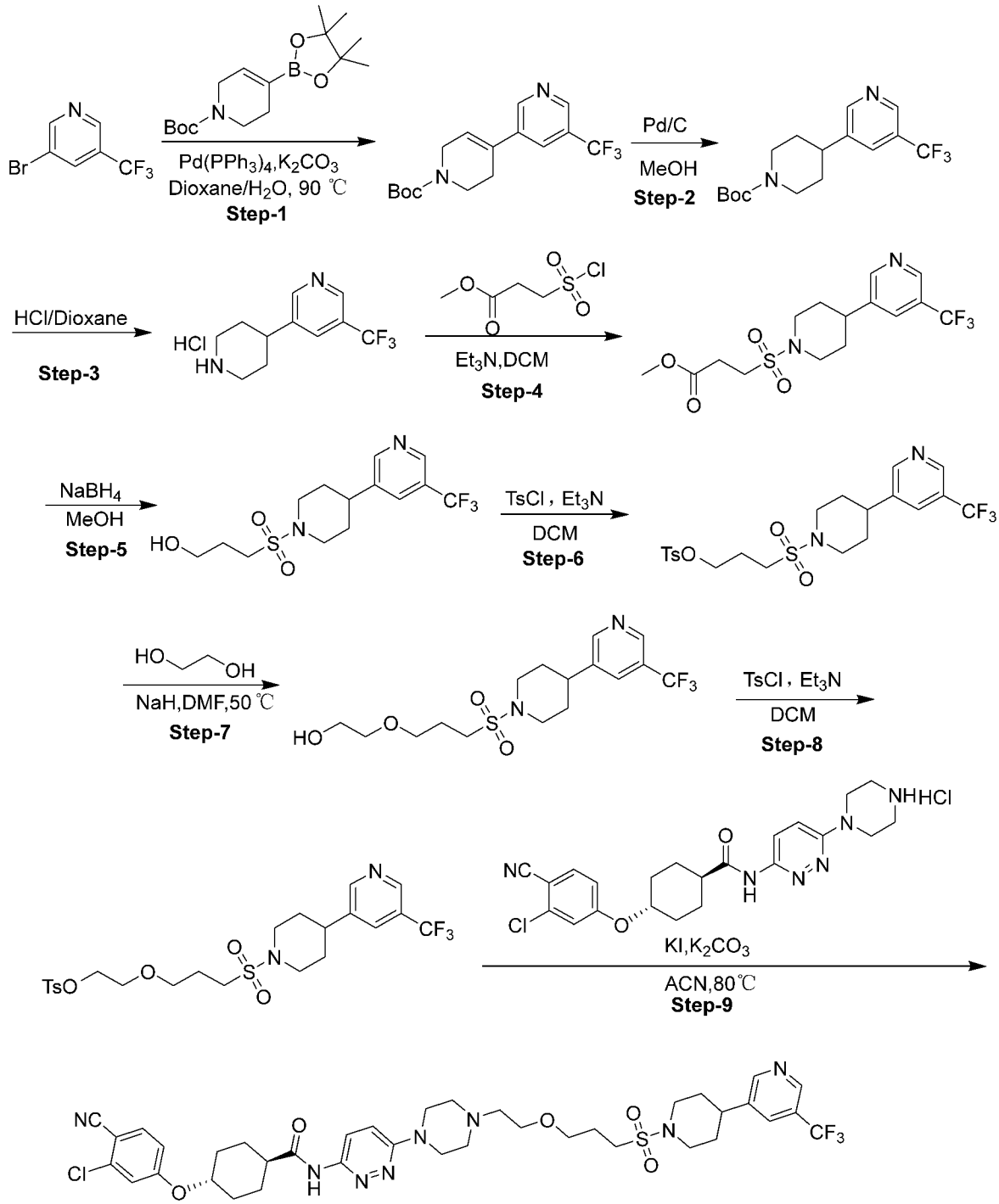
Synthesis of N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl)piperazin-1-yl)pyridazine-3-carboxamide (Compound 49)



[365] To a solution of 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl 4-methylbenzenesulfonate (10.2 mg, 0.020 mmol) in ACN (1.5 mL) were added N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(piperazin-1-yl)pyridazine-3-carboxamide hydrochloride (10.47 mg, 0.022 mmol), K_2CO_3 (6.91 mg, 0.050 mmol), and potassium iodide (1.66 mg, 0.010 mmol), and the reaction was stirred at 80°C for 6 h. The reaction was concentrated in vacuo, and purified by pre-TLC to afford *N*-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl)piperazin-1-yl)pyridazine-3-carboxamide (**Compound 49**, 4.2 mg, 27.05%). ESI-MS: 776.2,777.2,779.2$[M+H]^+$.

Example S49

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(6-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)hexyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 50)



[366] **Step 1:** To a solution of 3-bromo-5-(trifluoromethyl)pyridine (109.63 mg, 0.485 mmol) in dioxane-water (2.0 mL) were added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (150.00 mg, 0.485 mmol), $Pd(PPh_3)_4$ (11.21 mg, 0.010 mmol), and K_2CO_3 (201.13 mg, 1.455 mmol), and the reaction was stirred at 100 °C for 4.5 h. The reaction mixture was concentrated in vacuo. The residue was diluted with DCM and water. The organic layer was separated, washed with further water, and concentrated in vacuo. The residue was purified using silica gel column chromatography eluting with ethyl acetate in petroleum ether to afford tert-butyl 5-(trifluoromethyl)-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate (159.2 mg, 99.95%).

[367] **Step 2:** To a solution of tert-butyl 5-(trifluoromethyl)-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate (159.2 mg, 0.485 mmol) in MeOH (8.0 mL) was added Pd/C 10% (32.0 mg, 0.301 mmol), and the reaction was purged 4 times with H_2 and stirred at room temperature under H_2 for 2 h. The reaction mixture was filtered through Buchner funnel. The filtrate was concentrated and dried to afford tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate (155.7 mg, 97.18%).

[368] **Step 3:** HCl/dioxane (2.0 mL) was added to tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate (155.7 mg, 0.471 mmol). The reaction was stirred at room temperature for 3 h. The reaction was concentrated in vacuo, and dried to afford 3-(piperidin-4-yl)-5-(trifluoromethyl)pyridine hydrochloride (125.7 mg, 100.00%).

[369] **Step 4:** To a solution of 3-(piperidin-4-yl)-5-(trifluoromethyl)pyridine hydrochloride (125.7 mg, 0.471 mmol) in DCM (5.0 mL) were added methyl 3-(chlorosulfonyl)propanoate (105.55 mg, 0.566 mmol) and Et_3N (0.328 mL, 2.357 mmol), and the reaction was stirred at room temperature for 4 h. The reaction was diluted with DCM and water. The organic layer was separated, washed with water, and concentrated in vacuo. The residue was purified using silica gel column chromatography eluting with methanol in DCM. The organic layer was collected, concentrated in vacuo, and dried to afford methyl 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)propanoate (49.9 mg, 27.83%).

[370] **Step 5:** To a solution of methyl 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)propanoate (49.9 mg, 0.131 mmol) in MeOH (2.0 mL) was added $NaBH_4$ (24.81 mg, 0.656 mmol) in portions and the reaction was stirred at room temperature overnight. The reaction was concentrated in vacuo and diluted with DCM and water. The organic layer was separated and washed with water. The organic layer was collected, concentrated in vacuo, and dried to afford 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)propan-1-ol (45.8 mg, 99.07%).

[371] **Step 6:** To a solution of 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)propan-1-ol (45.8 mg, 0.130 mmol) in DCM (2.0 mL) were added TsCl (24.78 mg, 0.130 mmol), Et_3N (0.072 mL, 0.520 mmol), and DMAP (1.59 mg, 0.013 mmol), and the reaction was stirred at room temperature overnight. The reaction was diluted with DCM and water. The organic layer was separated, washed with water, and concentrated in vacuo. The residue was purified by pre-TLC to afford 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)propyl 4-methylbenzenesulfonate (48.4 mg, 73.51%).

[372] **Step 7:** To ethylene glycol (1.5 mL) was added NaH (60%, 4.59 mg, 0.115 mmol) and the reaction was stirred at room temperature. After stirring for 30 minutes, to the reaction was added 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)propyl 4-methylbenzenesulfonate (48.4 mg, 0.096 mmol), and the reaction was stirred at 50 °C for 3 hr. The reaction was quenched with saturated NH_4Cl solution and extracted with DCM. The organic layer was washed with saturated $NaHCO_3$ solution three

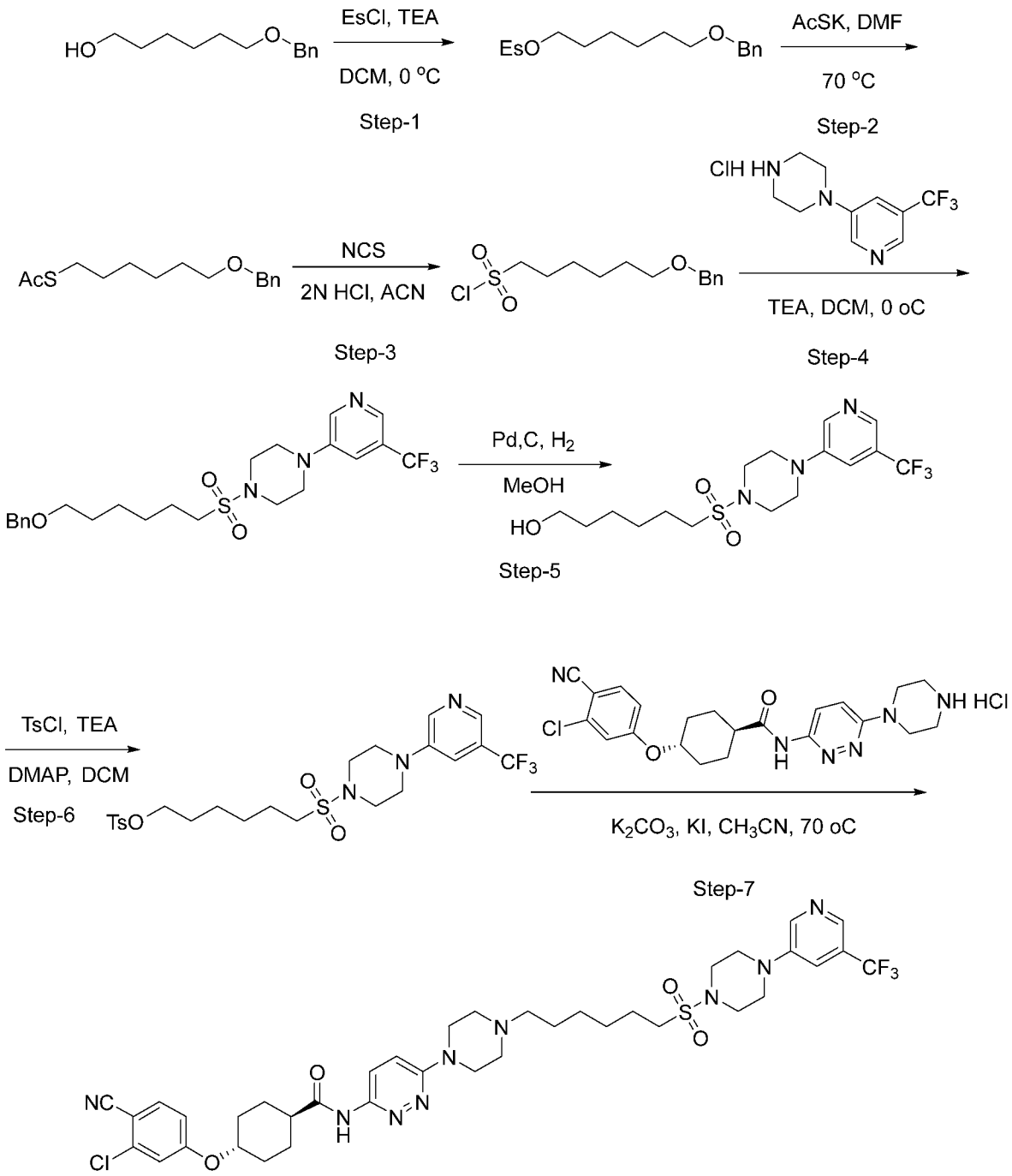
times. The organic layer was concentrated in vacuo and purified by pre-TLC to afford 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)propoxy)ethan-1-ol (27.2 mg, 71.81%). LCMS: 397.1$[M+H]^+$.

[373] **Step 8:** To a solution of 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)propoxy)ethan-1-ol (11.4 mg, 0.029 mmol) in DCM (1.5 mL) were added TsCl (10.96 mg, 0.058 mmol), Et_3N (0.016 mL, 0.115 mmol) and DMAP (0.35 mg, 0.003 mmol), and the reaction was stirred at room temperature for 5 h. The reaction was concentrated in vacuo. The residue was purified by pre-TLC to afford 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)propoxy)ethyl 4-methylbenzenesulfonate (11.5 mg, 72.65%).

[374] **Step 9:** To a solution of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide hydrochloride (10.97 mg, 0.023 mmol) in ACN (1.5 mL) were added 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperidin-1-yl)sulfonyl)propoxy)ethyl 4-methylbenzenesulfonate (11.5 mg, 0.021 mmol), K_2CO_3 (7.26 mg, 0.052 mmol), and potassium iodide (1.74 mg, 0.011 mmol), and the reaction was stirred at 80 °C for 6 h. The reaction was concentrated in vacuo, and purified to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(6-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)hexyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 50**, 8.2 mg, 47.93%).

Example S50

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(6-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)hexyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 51)



[375] **Step 1:** 6-(benzyloxy)hexan-1-ol (296 mg, 1.421 mmol) and triethylamine (0.593 mL, 4.263 mmol) were dissolved in 3 mL of DCM, and ethanesulfonyl chloride (365.40 mg, 2.842 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 1h, TLC show 6-(benzyloxy)hexan-1-ol (296 mg, 1.421 mmol) was consumed, the solvent was washed sat $NaHCO_3$ solvent and brine, dried over Na_2SO_4, filtered and concentrated to give ((6-(benzyloxy)hexyl)oxy)einsteinium (560 mg, 1.219 mmol, 85.80%) without purification and get next step.

[376] **Step 2:** Potassium(1+) thioacetic S-acid (280.94 mg, 2.439 mmol) was dissolved in 2 mL of DMF, and a solution of ((6-(benzyloxy)hexyl)oxy)einsteinium (560 mg, 1.219 mmol) in 1 mL DMF was

added at 50 °C. The reaction mixture was stirred at 70 °C for 3 h, TLC showed that ((6-(benzyloxy)hexyl)oxy)einsteinium was consumed. Then the mixture was diluted by 10 mL of sat $NaHCO_3$, extracted with EtOAc (5 mL x 3), then the organic solvent was washed by brine and dried over Na_2SO_4, filtered and concentrated to give the crude product, which was purified by chromatography, eluting with PE/EtOAc(20:1) to give *S*-(6-(benzyloxy)hexyl) ethanethioate (270 mg, 1.014 mmol, 83.12%) as brown oil. ESI-MS: 266.9$[M+H]^+$.

[377] **Step 3:** *S*-(6-(benzyloxy)hexyl) ethanethioate (270 mg, 1.014 mmol) was dissolved in 2 mL ACN and 0.5 mL HCl (2N), NCS (541.34 mg, 4.054 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. TLC showed *S*-(6-(benzyloxy)hexyl) ethanethioate was consumed, at which point the reaction was diluted with H_2O (10 mL) and extracted with EtOAc (5 mL x 3), and the organic layers were dried over Na_2SO_4, filtered and concentrated to give 6-(benzyloxy)hexane-1-sulfonyl chloride (250 mg, 0.860 mmol, 84.82%) as a white solid.

[378] **Step 4:** 1-[5-(trifluoromethyl)pyridin-3-yl]piperazine hydrochloride (150 mg, 0.560 mmol) and triethylamine (0.156 mL, 1.121 mmol) were dissolved in 2 mL of DCM, and the solution of 6-(benzyloxy)hexane-1-sulfonyl chloride (244.43 mg, 0.841 mmol) in 1 mL of DCM was added at 0 °C. The reaction mixture was stirred at room temperature for 1 h, diluted with 5 mL H_2O, extracted by DCM (5 mL x 3), washed with brine, dried over Na_2SO_4, filtered and concentrated, and the residue was purified by Prep-TLC to give 1-((6-(benzyloxy)hexyl)sulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine (128 mg, 0.264 mmol, 47.04%) as colorless solid. ESI-MS:485.7$[M+H]^+$.

[379] **Step 5:** 1-((6-(benzyloxy)hexyl)sulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine (128 mg, 0.264 mmol) and palladium(0) (10 mg, 0.094 mmol) were dissolved in 1 mL MeOH, and the reaction mixture was stirred at room temperature for 3 h. TLC showed that 1-((6-(benzyloxy)hexyl)sulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine was consumed, and then the reaction was filtered and concentrated to give 6-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)hexan-1-ol (96 mg, 0.243 mmol, 92.10%), as a colorless solid.

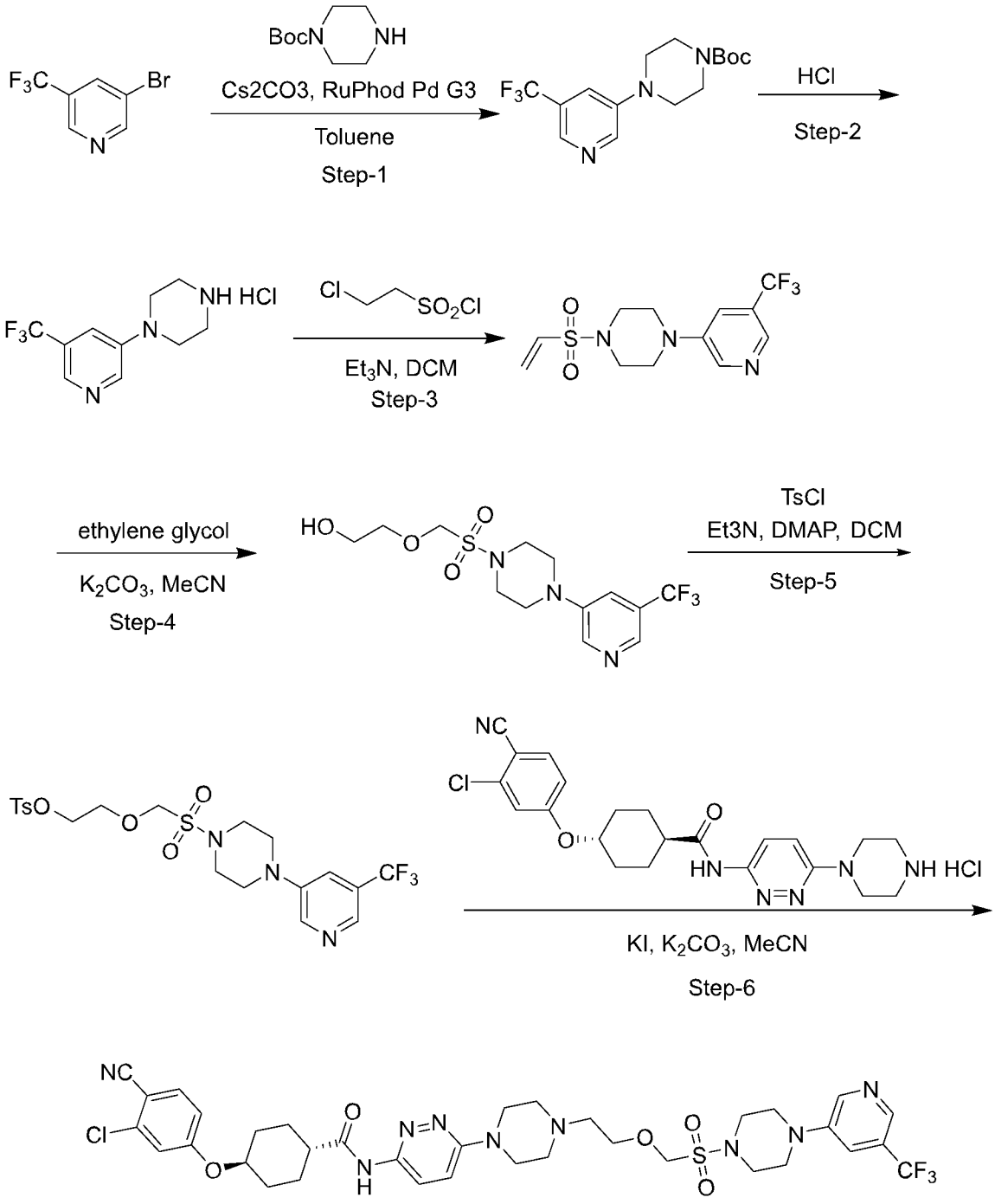
[380] **Step 6:** 6-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)hexan-1-ol (36 mg, 0.091 mmol), 4-(dimethylamino)pyridine (2.22 mg, 0.018 mmol) and triethylamine (0.063 mL, 0.455 mmol) were dissolved in 2 mL DCM, TsCl (52.07 mg, 0.273 mmol) was added, and the reaction mixture was stirred at room temperature for 4 h, and concentrated to give a residue which was purified by Prep-TLC (PE/EA=1:1) to give 6-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)hexyl 4-methylbenzenesulfonate (28 mg, 0.051 mmol, 55.96%).

[381] **Step 7:** 6-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)hexyl 4-methylbenzenesulfonate (28 mg, 0.051 mmol), (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(piperazin-1-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide hydrochloride (26.78 mg, 0.056 mmol), potassium

carbonate (14.08 mg, 0.102 mmol) and potassium iodide (0.85 mg, 0.005 mmol) were dissolved in CH_3CN (2 mL), and the reaction mixture was stirred at 80 °C for 3 h. TLC detected the reaction was complete, and it was then filtered and concentrated, and the residue was purified by Prep-TLC to give (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(6-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)hexyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 51**, 23.4 mg, 0.029 mmol, 56.13%) as a white solid. ESI-MS:818.2 $[M+H]^+$.

Example S51

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 52)



[382] **Step 1:** A solution of 5-bromo-3-(trifluoromethyl)pyridine (10 g, 44.248 mmol), 2-methylpropan-2-yl piperazine-1-carboxylate (9.89 g, 53.097 mmol), Cs_2CO_3 (28.83 g, 88.496 mmol) and RuPhos Pd G3 (0.07 g, 0.080 mmol) in toluene (140 mL) was replaced with N_2 for 1 min. Then the reaction was heated at 100 °C for 2h. Concentrated, purified by column chromatography on silica gel eluting with PE to PE/EA=3:1 to afford the product tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-carboxylate (6.546 g).

[383] **Step 2:** To a solution of tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-carboxylate (6.546 g, 19.756 mmol) in DCM (25 mL) was added HCl/dioxane (25 mL) over an ice-bath. After

addition, the reaction was stirred at RT for 3 h. Then the reaction was concentrated, and then purified by column chromatography on silica gel eluting with PE to PE/EA=5/1 to afford the product 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine hydrochloride (5.5 g) as a white solid.

[384] **Step 3:** To a solution of 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine hydrochloride (3 g, 11.207 mmol) in DCM (60 mL) was added Et_3N (7.789 mL, 56.037 mmol) and 2-chloroethane-1-sulfonyl chloride (2.74 g, 16.811 mmol) in an ice-bath. After addition, the reaction was stirred at rt for 2 h and purified by column chromatography on silica gel eluting with PE to PE/EA=4/1,3/1 and 2/1, to afford 1-(5-(trifluoromethyl)pyridin-3-yl)-4-(vinylsulfonyl)piperazine (2.08 g) as a solid.

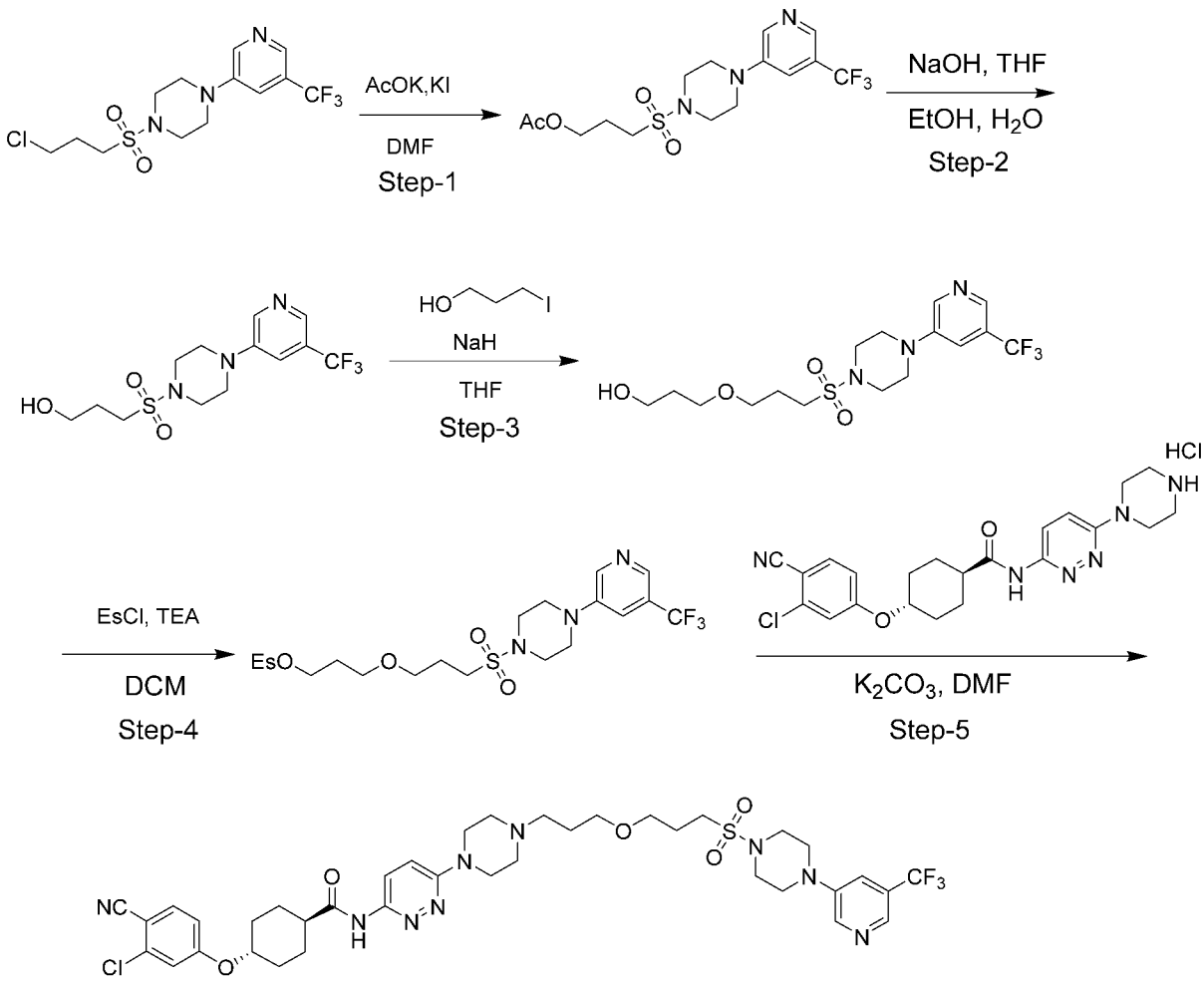
[385] **Step 4:** A solution of 1-(5-(trifluoromethyl)pyridin-3-yl)-4-(vinylsulfonyl)piperazine (500 mg, 1.556 mmol), ethylene glycol (0.868 mL, 15.561 mmol) and Cs_2CO_3 (1014.00 mg, 3.112 mmol) in MeCN (30 mL) was heated at 50 °C for 16 h. The reaction was purified by pre-TLC eluting with DCM/MeOH=20:1 to afford the product 2-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methoxy)ethan-1-ol (536 mg) for next step.

[386] **Step 5:** To a solution of 2-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methoxy)ethan-1-ol (133 mg, 0.347 mmol), Et_3N (0.145 mL, 1.041 mmol) and DMAP (4.24 mg, 0.035 mmol) in DCM (6 mL) was added TsCl (99.20 mg, 0.520 mmol) at ice-bath. After addition, the reaction was stirred at RT for 18h.TLC indicated it was completed. Purified by pre-TLC eluting with DCM/MeOH=20:1 to afford 2-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methoxy)ethyl 4-methylbenzenesulfonate (141 mg).

[387] **Step 6:** 4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(piperazin-1-yl)-1,2-diazin-3-yl]cyclohexanecarboxamide hydrochloride (125.22 mg, 0.262 mmol), 2-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methoxy)ethyl 4-methylbenzenesulfonate (141 mg, 0.262 mmol), KI (43.54 mg, 0.262 mmol) and K_2CO_3 (72.50 mg, 0.525 mmol) in MeCN was heated at reflux for 3 h. The reaction was purified by pre-TLC eluting with DCM/MeOH=15:1 and 10:1 to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 52**, 96 mg), ESI-MS: 806.2$[M+1]^+$.

Example S52

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(3-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)propyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 53)



[388] **Step 1:** To a solution of 1-((3-chloropropyl)sulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine (200 mg, 1.0 eq.) in DMF (5 mL) was added KI (8.9 mg, 0.1 eq.) and AcOK (79.2 mg, 1.5 eq.) at r.t., and the yellow mixture was stirred at 90 ^{0}C for 2 h. TLC (MeOH/DCM=1/40, Rf=0.35) showed 1-((3-chloropropyl)sulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine consumed, reaction had mainly a new spot. The mixture was quenched with water (15 mL), extracted with EA (15 mL×3), dried over Na_2SO_4, and concentrated in vacuo to afford 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl acetate (300 mg, yellow oil, crude).

[389] **Step 2:** To a solution of 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl acetate (300 mg, 1.0 eq.) in EtOH (1 mL) and THF (3 mL) was added NaOH (91 mg, 3 eq.), H_2O (2 mL) at 0-5 ^{0}C, and the yellow mixture was stirred at r.t. for 2 h. TLC (MeOH/DCM=1/10, Rf=0.5) showed 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propyl acetate was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo, then added water (15 mL), extracted with DCM (15 mL×3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with silica gel. Chromatography column eluted MeOH in DCM 5% to afford 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propan-1-ol (210 mg, yellow solid).

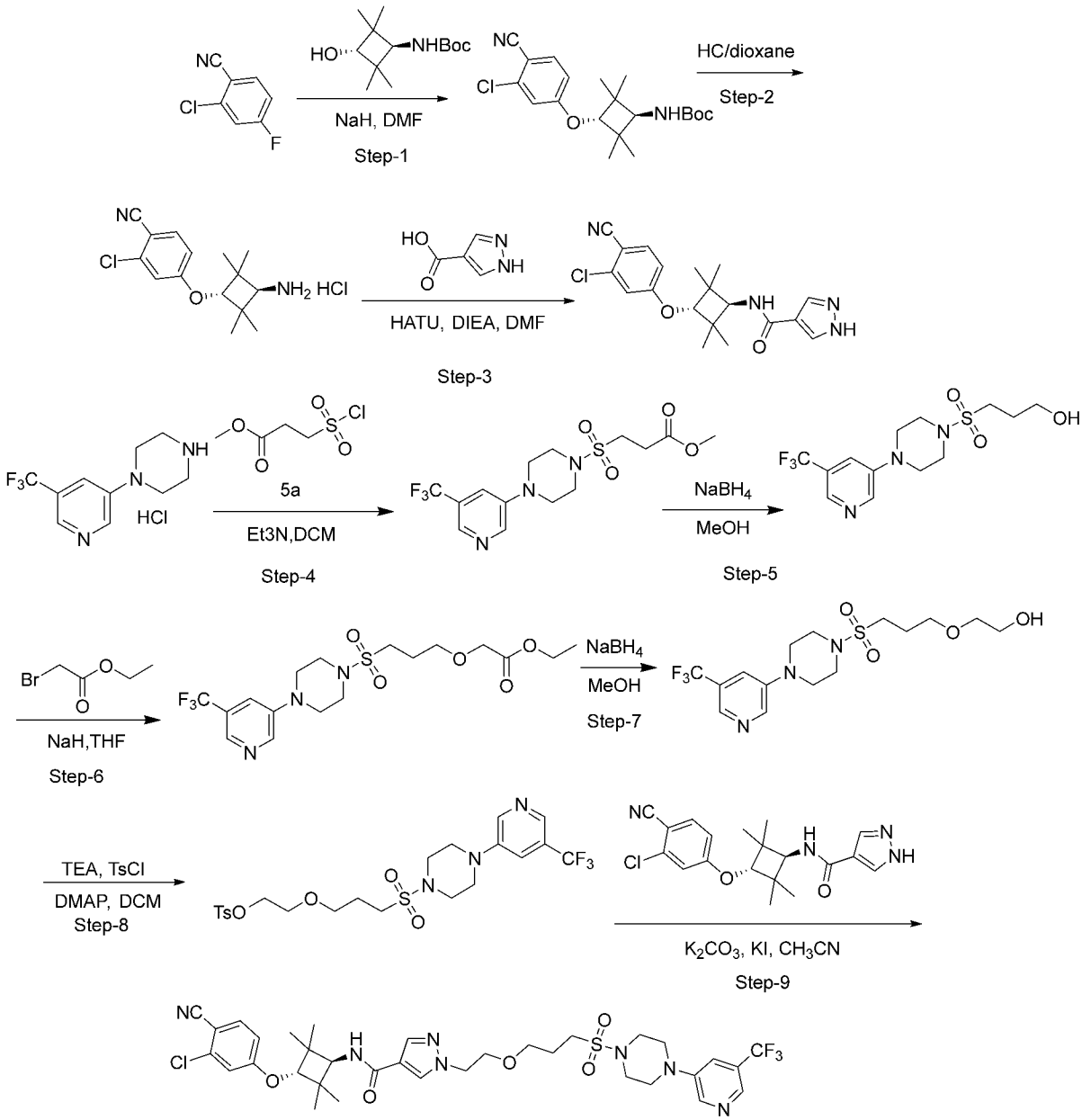
[390] **Step 3:** To a solution of 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propan-1-ol (50 mg, 1.0 eq.) in THF (0.5 mL) was added NaH (6.8 mg, 60% purity, 1.2 eq.) at 0-5 ^{0}C, and the yellow mixture was stirred at 0-5 ^{0}C for 15 minutes. Then 3-iodopropan-1-ol (105.3 mg, 4.0 eq.) was added at 0-5 ^{0}C, the yellow mixture was stirred at r.t. for 0.5 h, and then the temperature was raised to 50 ^{0}C for 3 h. TLC (MeOH/DCM=1/15, Rf=0.5) showed reaction had mainly a new spot. The mixture was quenched with sat. NH_4Cl (5 mL), extracted with EA (10 mL×2), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with pre-TLC (MeOH/DCM=1/15) several times to afford 3-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)propan-1-ol (8 mg, white solid).

[391] **Step 4:** To a solution of 3-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)propan-1-ol (8 mg, 1.0 eq.) in DCM (0.5 mL) was added TEA (4 mg, 2.0 eq.) and EsCl (2.5 mg, 1.0 eq.) at 0-5 ^{0}C, and the yellow mixture was stirred at r.t. for 15 minutes. TLC (MeOH/DCM=1/40, Rf=0.7) showed little starting material remained, reaction had mainly a new spot. The mixture was concentrated in vacuo to afford (3-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)propoxy)einsteinium (25 mg, about 30% purity, light yellow semi-solid).

[392] **Step 5:** To a solution of (3-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)propoxy)einsteinium (25 mg, 30% purity, 1.0 eq.) in DMF (0.5 mL) was added (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (7.1 mg, 1.0 eq.) and K_2CO_3 (2.5 mg, 4.0 eq.) at r.t., and the yellow mixture was stirred at 70 ^{0}C for 2 h. TLC (MeOH/DCM=1/15, Rf=0.3) showed (3-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)propoxy)einsteinium was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was purified with pre-TLC (MeOH/DCM=1/15) to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(3-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)propyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 53**, 2.1 mg, light yellow solid). ESI-MS: 834.2 $[M+H]^+$.

Example S53

Synthesis of 1-(2-{[3-(dioxo{1-[5-(trifluoromethyl)pyridin-3-yl]hexahydropyridin-4-yl}-λ^6-sulfanyl)propyl]oxy}ethyl)-N-[(1r,3r)-3-[(3-chloro-4-cyanophenyl)oxy]-2,2,4,4-tetramethylcyclobutyl]pyrazole-4-carboxamide (Compound 54)



[393] **Step 1:** 2-methylpropan-2-yl{[(1r,3r)-3-hydroxy-2,2,4,4-tetramethylcyclobutyl]amino}methanoate (2000 mg, 8.219 mmol) was dissolved in 15 mL of DMF, sodium hydride (657.52 mg, 16.438 mmol) was added dropwise, and the mixture was stirred at 0 °C for 0.5 h. Then a solution of 2-chloro-4-fluorobenzene-1-carbonitrile (1534.19 mg, 9.862 mmol) in 5 mL of DMF was added dropwise and the mixture continued stirring at 0 °C for 3 h. TLC showed starting material was consumed and the mixture was quenched by ice water (60 mL), and filtered to give tert-butyl ((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamate (900 mg, 2.375 mmol, 28.90%) as a white solid.

[394] **Step 2:** tert-butyl ((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamate (900 mg, 2.375 mmol) was dissolved in HCl/dioxane (5 mL) and the reaction mixture was stirred at room temperature for 3 h. TLC showed that tert-butyl ((1r,3r)-3-(3-chloro-

4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamate was consumed, the reaction was concentrated and the residue was washed by tert-Butyl methyl ether (10 mLto give 4-((1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile hydrochloride (620 mg, 1.967 mmol, 82.81%) as a white solid. ESI-MS:278.8$(M+H)^+$.

[395] **Step 3:** 4-((1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile hydrochloride (40 mg, 0.127 mmol), 1H-pyrazole-4-carboxylic acid (15.65 mg, 0.140 mmol) and HATU (53.07 mg, 0.140 mmol) were dissolved in 2 mL of DMF, Ethyldiisopropylamine (32.80 mg, 0.254 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, and ESI-MS show that 4-((1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile hydrochloride was consumed. The mixture was diluted with sat NH_4Cl solvent, extracted with DCM (5 mL x 3), and the organic solvent was washed by sat $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated to give N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-1H-pyrazole-4-carboxamide (40 mg, 0.107 mmol, 84.55%)(crude) as a white solid. ESI-MS:372.8$[M+H]^+$.

[396] **Step 4:** 1-[5-(trifluoromethyl)pyridin-3-yl]piperazine hydrochloride (105 mg, 0.392 mmol) and triethylamine (0.109 mL, 0.785 mmol) were dissolved in 2 mL of DCM, methyl 3-(chlorodioxo-λ6-sulfanyl)propanoate (109.80 mg, 0.588 mmol) was added at 0 °C, and the reaction mixture was stirred at room temperature for 1 h, diluted with sat $NaHCO_3$ solution, dried over Na_2SO_4, filtered and concentrated to give methyl 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propanoate (130 mg, 0.344 mmol, 87.81%) as a colorless solid without purification and get next step.

[397] **Step 5:** methyl 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propanoate (130 mg, 0.341 mmol) was dissolved in 3 mL of MeOH, sodium boranuide (128.95 mg, 3.409 mmol) in three portions. the reaction mixture was stirred at room temperature for 12 h. TLC show that starting material was consumed, concentrated and the residue was purified by CC, eluting with DCM/MeOH=20:1 to give 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propan-1-ol (86.5 mg, 0.245 mmol, 71.81%) as a yellow solid.

[398] **Step 6:** 3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propan-1-ol (73.9 mg, 0.209 mmol) was dissolved in 3 mL THF, was added sodium hydride (10.03 mg, 0.418 mmol), the reaction mixture was stirred at 0 °C for 30 min, and then was added ethyl bromoacetate (349.03 mg, 2.090 mmol), the mixture was continued stirring at room temperature for 3 h, quenched by sat NH_4Cl solution, extracted with EA (5 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated the residue was purified by Prep-TLC to give ethyl 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)acetate (30 mg, 0.068 mmol, 32.64%) as colorless solid.

[399] **Step 7:** ethyl 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)acetate (61 mg, 0.139 mmol) was dissolved in MeOH (3 mL), sodium borohydride

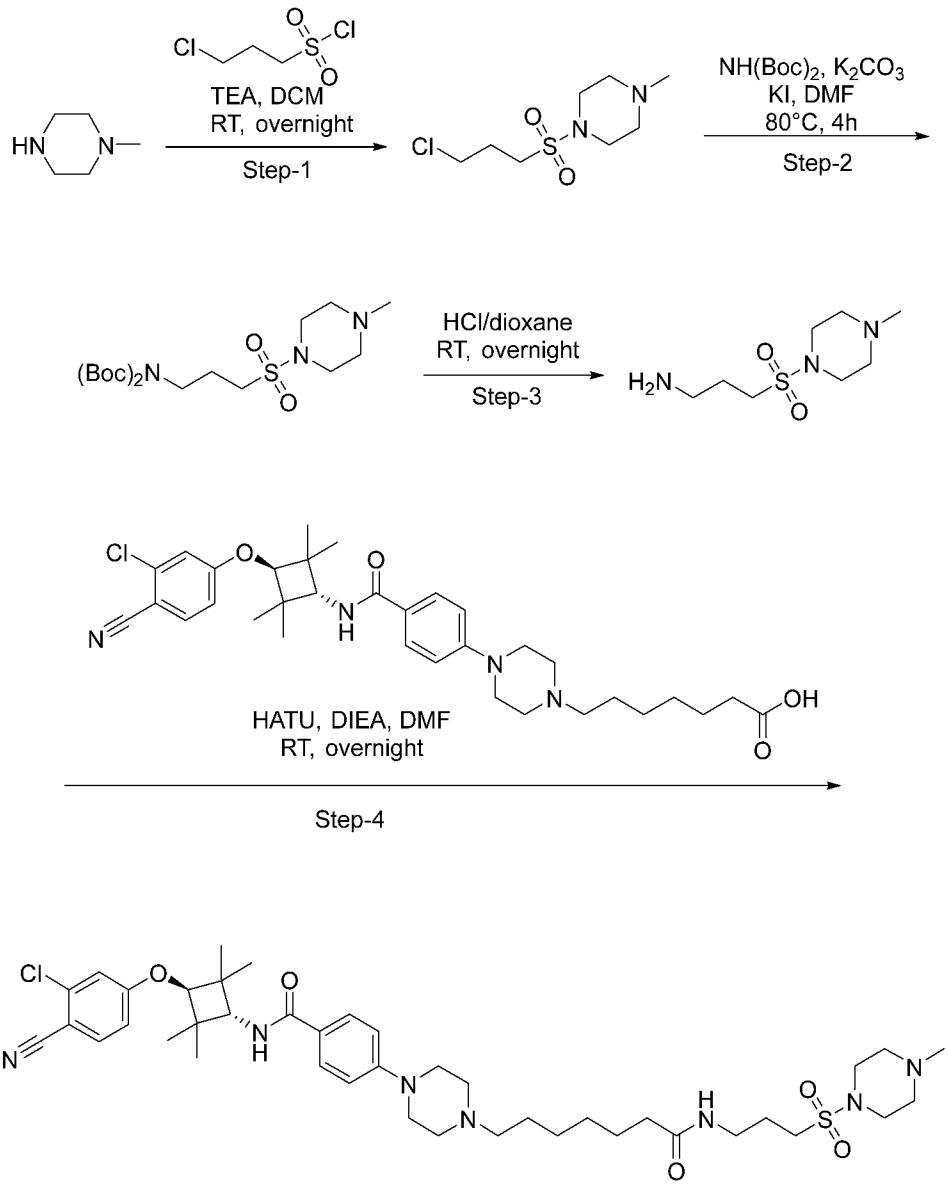
(52.51 mg, 1.388 mmol) was added, the reaction mixture was stirred at room temperature for 5 h, and the reaction was concentrated and the residue was purified by Prep-TLC to give 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethan-1-ol (25 mg, 0.063 mmol, 45.32%) as colorless solid. ESI-MS:396.0(M-H)-.

[400] **Step 8:** 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethan-1-ol (25 mg, 0.063 mmol) and triethylamine (0.026 mL, 0.189 mmol) were dissolved in DCM (2 mL), 4-methylbenzenesulfonyl chloride (35.98 mg, 0.189 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. TLC detected that the reaction was complete, and the the mixture was concentrated and the residue was purified by Prep-TLC to give 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl 4-methylbenzenesulfonate (4 mg, 0.007 mmol, 11.53%) as a colorless solid.

[401] **Step 9:** 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl 4-methylbenzenesulfonate (4 mg, 0.007 mmol), N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-1H-pyrazole-4-carboxamide (2.98 mg, 0.008 mmol), Cesium carbonate (4.73 mg, 0.015 mmol) and potassium iodide (0.60 mg, 0.004 mmol) were dissolved in CH_3CN (2 mL), and the reaction mixture was stirred at 70 °C for 12 h, filtered and concentrated, and the residue was purified by Prep-TLC to give 1-(2-{[3-(dioxo{1-[5-(trifluoromethyl)pyridin-3-yl]hexahydropyridin-4-yl}-λ^6-sulfanyl)propyl]oxy}ethyl)-N-[(1r,3r)-3-[(3-chloro-4-cyanophenyl)oxy]-2,2,4,4-tetramethylcyclobutyl]pyrazole-4-carboxamide (**Compound 54**, 2.1 mg, 0.003 mmol, 38.46%) as a white solid. ESI-MS:751.5[M+H]+.

Example S54

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-((3-((4-methylpiperazin-1-yl)sulfonyl)propyl)amino)-7-oxoheptyl)piperazin-1-yl)benzamide (Compound 55)



[402] **Step 1:** To a mixture of 1-methylpiperazine (510 mg, 5 mmol) and TEA (1100 mg, 10.8 mmol) in DCM (10 ml) was added 3-chloropropane-1-sulfonyl chloride (900 mg, 5.084 mmol), and the reaction mixture was stirred at RT overnight, and concentrated in vacuo to give the crude product 1-((3-chloropropyl)sulfonyl)-4-methylpiperazine (904 mg, 3.379 mmol, 67%) as oil.

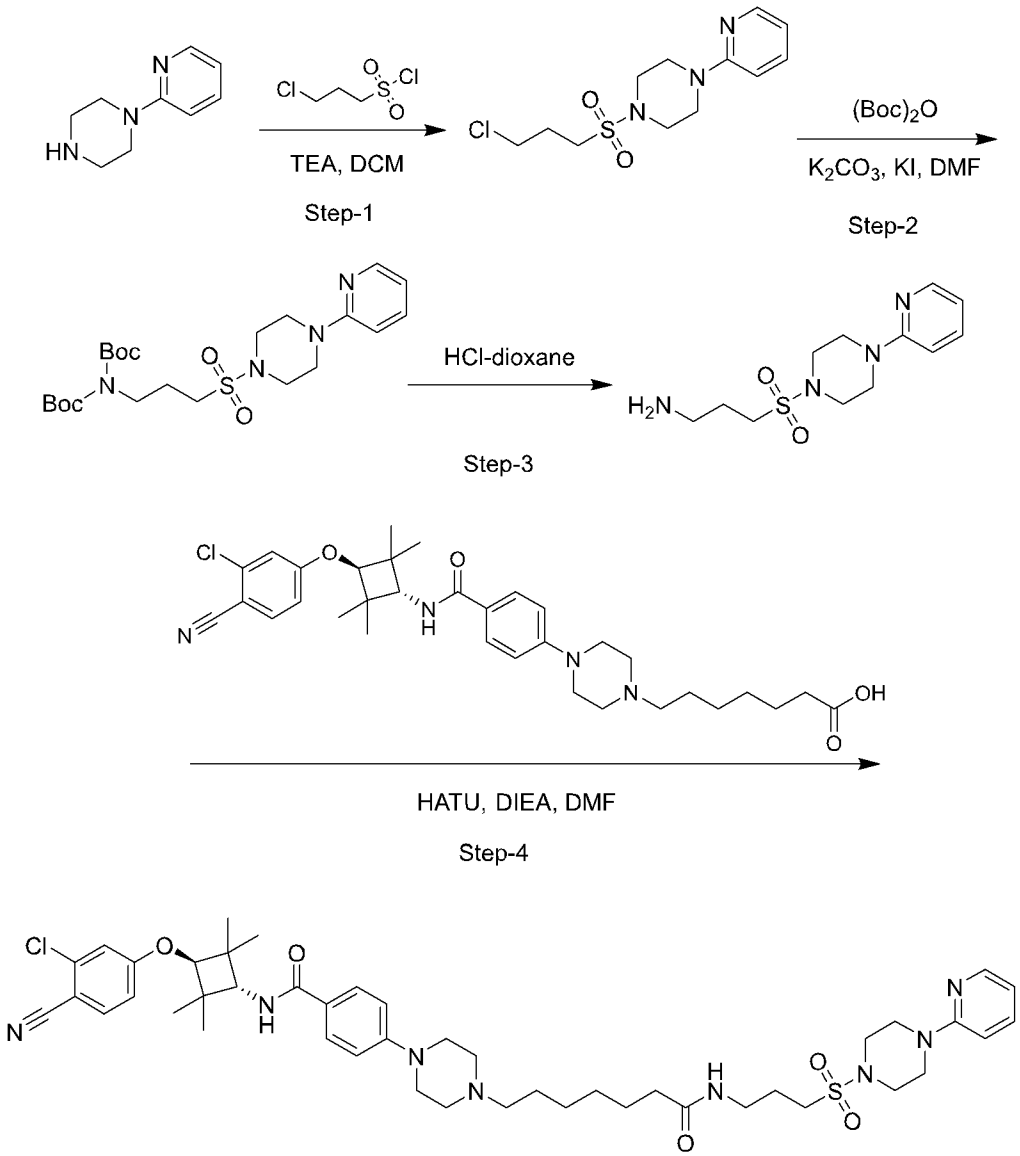
[403] **Step 2:** A mixture of 1-((3-chloropropyl)sulfonyl)-4-methylpiperazine (904 mg, 3.379 mmol), 2-methylpropan-2-yl ({[(2-methylprop-2-yl)oxy]carbonyl}amino)methanoate (734.22 mg, 3.379 mmol), K_2CO_3 (1400.93 mg, 10.137 mmol) and KI (560.91 mg, 3.379 mmol) in DMF (8 ml) was stirred at 80 °C for 4 hours, 10 mL of a saturated NaCl solution was then added, and the product extracted with EtOAc (3×10 mL).The organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford di-tert-butyl (3-((4-methylpiperazin-1-yl)sulfonyl)propyl)iminodicarbonate (1500 mg, 3.025 mmol, 90%) as a white solid.

[404] **Step 3:** To the mixture of di-tert-butyl (3-((4-methylpiperazin-1-yl)sulfonyl)propyl)iminodicarbonate (1500 mg, 3.025 mmol) was added HCl/dioxane (8 mL) at RT overnight, and the reaction was concentrated in vacuo to give the crude product 3-((4-methylpiperazin-1-yl)sulfonyl)propan-1-amine (900 mg, 2.84 mmol, 94%) as white solid.

[405] **Step 4:** To the mixture of HATU (6.46 mg, 0.017 mmol), 7-{4-[4-({[(1r,3r)-3-[(3-chloro-4-cyanophenyl)oxy]-2,2,4,4-tetramethylcyclobutyl]amino}carbonyl)phenyl]piperazin-1-yl}heptanoic acid (10 mg, 0.017 mmol) in DMF (1 mL) was added 3-((4-methylpiperazin-1-yl)sulfonyl)propan-1-amine (4.76 mg, 0.018 mmol) and DIEA (6.51 mg, 0.050 mmol). After 1 hour the reaction was completed. 2 mL of a saturated NaCl solution was then added and the product extracted with EtOAc (3×2 mL). The organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude product which was purified by P-TLC with DCM/MeOH (10/1) to give *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(7-((3-((4-methylpiperazin-1-yl)sulfonyl)propyl)amino)-7-oxoheptyl)piperazin-1-yl)benzamide (**Compound 55**, 3 mg, 0.004 mol, 23%) as a white solid.

Example S55

Synthesis of 4-(4-{7-[(3-{dioxo[4-(pyridin-2-yl)piperazin-1-yl]-λ⁶-sulfanyl}propyl)amino]-7-oxoheptyl}piperazin-1-yl)-N-[(1r,3r)-3-[(3-chloro-4-cyanophenyl)oxy]-2,2,4,4-tetramethylcyclobutyl]benzamide (Compound 56)



[406] **Step 1:** To a solution of 1-(pyridin-2-yl)piperazine (100 mg, 0.613 mmol) in DCM (3 mL) were added TEA (0.341 mL, 2.451 mmol) and 3-chloropropane-1-sulfonyl chloride (130.16 mg, 0.735 mmol), and the reaction was stirred at room temperature for 3 hours. The reaction was complete as detected by TLC (DCM: MeOH= 20:1). The reaction was diluted with water and extracted with ethyl acetate (10 mL × 4). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=30:1) to afford 1-((3-chloropropyl)sulfonyl)-4-(pyridin-2-yl)piperazine (160 mg, 0.527 mmol, 85.96%).

[407] **Step 2:** To a solution of 1-((3-chloropropyl)sulfonyl)-4-(pyridin-2-yl)piperazine (55 mg, 0.181 mmol) in DMF (2 mL) were added K_2CO_3 (75.06 mg, 0.543 mmol), potassium iodide (30.05 mg, 0.181 mmol), and $(Boc)_2O$ (59.00 mg, 0.272 mmol), and the reaction was stirred at 80 °C for 4 hours. TLC showed new spot was observed, the reaction was concentrated in vacuo. The residue was purified by

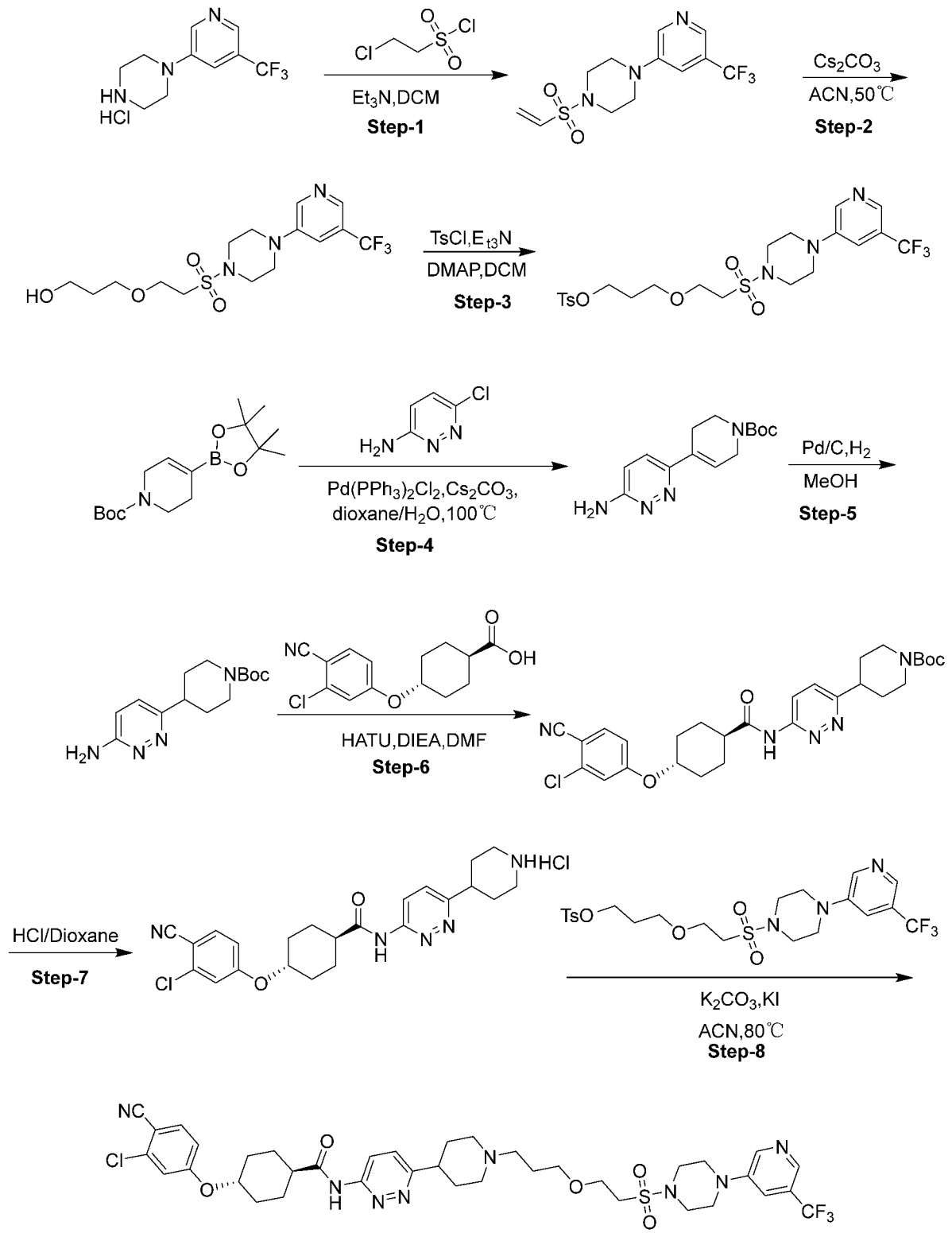
preparative TLC (PE:EA = 2:1) to afford tert-butyl (tert-butoxycarbonyl)(3-((4-(pyridin-2-yl)piperazin-1-yl)sulfonyl)propyl)carbamate (40 mg, 0.083 mmol, 45.60%) as a white solid.

[408] **Step 3:** A solution of tert-butyl (tert-butoxycarbonyl)(3-((4-(pyridin-2-yl)piperazin-1-yl)sulfonyl)propyl)carbamate (40 mg, 0.083 mmol) in HCl/dioxane (3 mL) was stirred at room temperature for 2 hours. TLC showed no starting material remained, and a new spot was observed, and the reaction was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=10:1) to afford 3-((4-(pyridin-2-yl)piperazin-1-yl)sulfonyl)propan-1-amine (38 mg, 0.118 mmol, 142.70%) as a yellow solid.

[409] **Step 4:** To a solution of 7-{4-[4-({[(1r,3r)-3-[(3-chloro-4-cyanophenyl)oxy]-2,2,4,4-tetramethylcyclobutyl]amino}carbonyl)phenyl]piperazin-1-yl}heptanoic acid (5 mg, 0.008 mmol) in DMF (2 mL) were added DIEA (5.43 mg, 0.042 mmol), HATU (7.99 mg, 0.021 mmol), and 3-((4-(pyridin-2-yl)piperazin-1-yl)sulfonyl)propan-1-amine (3.58 mg, 0.013 mmol), and the reaction was stirred at room temperature for 3 hours. The reaction was complete as detected by TLC (DCM: MeOH= 10:1). The reaction was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH= 20:1) to afford 4-(4-{7-[(3-{dioxo[4-(pyridin-2-yl)piperazin-1-yl]-λ^6-sulfanyl}propyl)amino]-7-oxoheptyl}piperazin-1-yl)-N-[(1r,3r)-3-[(3-chloro-4-cyanophenyl)oxy]-2,2,4,4-tetramethylcyclobutyl]benzamide (**Compound 56**, 2.7 mg, 0.003 mmol, 37.29%). ESI-MS: 861.3 $[M+H]^+$.

Example S56

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(3-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 57)



[410] **Step 1:** To the mixture of 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (6.78 g, 23.302 mmol)and TEA(34.341 mL, 247.060 mmol) in DCM(50ml) was added 2-chloroethane-1-sulfonyl chloride (15 g, 92.019 mmol), the reaction mixture was stirred at RT overnight ,The residue was purified by preparative TLC (PE: EA=3:1) to afford 1-(4-(trifluoromethyl)pyridin-2-yl)-4-(vinylsulfonyl)piperazine (4.4 g, 13.694 mmol, 58%) as white solid.

[411] **Step 2:** To a solution of 1-(5-(trifluoromethyl)pyridin-3-yl)-4-(vinylsulfonyl)piperazine (50.0 mg, 0.156 mmol) in ACN (2.0 mL) were added propane-1,3-diol (0.022 mL, 0.311 mmol) and Cs_2CO_3 (101.40 mg, 0.311 mmol), and the reaction was stirred at 50 °C for 3.5 h. The reaction was concentrated in vacuo, and the residue was diluted with DCM and water. The organic layer was separated, washed with water, and concentrated in vacuo. The residue was purified by pre-TLC to afford 3-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propan-1-ol (48.0 mg, 77.62%).

[412] **Step 3:** To a solution of 3-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propan-1-ol (30.0 mg, 0.075 mmol) in DCM (2.0 mL) were added TsCl (28.78 mg, 0.151 mmol), Et_3N (0.042 mL, 0.302 mmol), and DMAP (0.92 mg, 0.008 mmol), and the reaction was stirred at room temperature for 5 h. The reaction was diluted with DCM and water. The organic layer was separated, washed with water, and concentrated in vacuo. The residue was purified by pre-TLC to afford 3-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propyl 4-methylbenzenesulfonate (29.8 mg, 0.054 mmol, 71.57%).

[413] **Step 4:** To a solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (50.0 mg, 0.162 mmol) in dioxane-water (1.0 mL) were added 6-chloro-1,2-diazin-3-amine (20.95 mg, 0.162 mmol), dichlorobis(triphenylphosphine)palladium(II) (11.35 mg, 0.016 mmol), and Cs_2CO_3 (158.06 mg, 0.485 mmol), and the reaction was stirred at 100 °C for 7 h. The reaction mixture was concentrated in vacuo. The residue was purified by pre-TLC to afford tert-butyl 4-(6-aminopyridazin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (42.2 mg, 93.82%).

[414] **Step 5:** To a solution of tert-butyl 4-(6-aminopyridazin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (42.2 mg, 0.153 mmol) in MeOH (5.0 mL) was added Pd/C 10% (9.0 mg, 0.085 mmol), and the reaction was purged 4 times with H_2 and stirred at room temperature under H_2 for 16 h. The reaction mixture was filtered. The filtrate was collected, concentrated in vacuo, and dried to afford tert-butyl 4-(6-aminopyridazin-3-yl)piperidine-1-carboxylate (40.7 mg, 95.74%).

[415] **Step 6:** To a solution of (1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxylic acid (40.90 mg, 0.146 mmol) in DMF (2.5 mL) were added HATU (83.39 mg, 0.219 mmol), Ethyldiisopropylamine (56.69 mg, 0.439 mmol), and tert-butyl 4-(6-aminopyridazin-3-yl)piperidine-1-carboxylate (40.7 mg, 0.146 mmol), and the reaction was stirred at room temperature for 3 h. The reaction was concentrated in vacuo. The residue was diluted with DCM and water. The organic layer was separated, washed with water, and concentrated in vacuo. The residue was purified by pre-TLC to afford tert-butyl 4-(6-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxamido)pyridazin-3-yl)piperidine-1-carboxylate (38.2 mg, 48.38%).

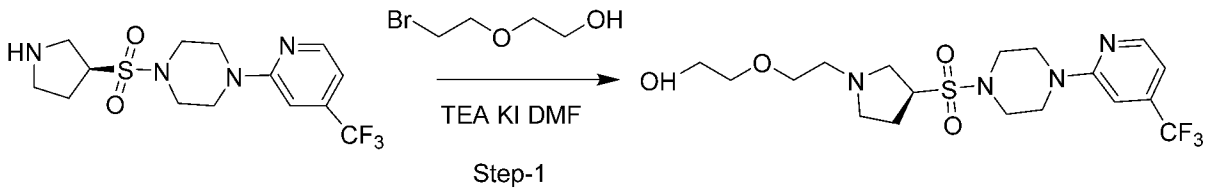
[416] **Step 7:** HCl/1,4-dioxane (2.5 mL) was added to tert-butyl 4-(6-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxamido)pyridazin-3-yl)piperidine-1-carboxylate (38.2 mg, 0.071

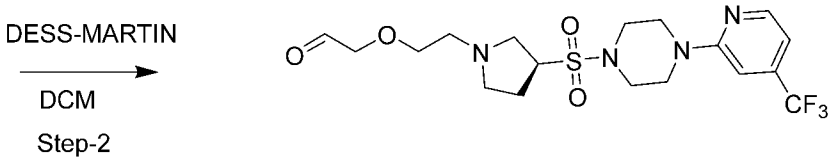
mmol). The reaction was stirred at room temperature for 3 hr. The reaction was concentrated in vacuo and dried to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (40.5 mg, 0.071 mmol).

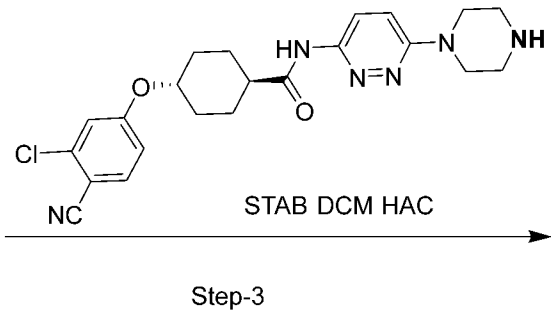
[417] **Step 8:** To a solution of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (27.02 mg, 0.057 mmol) in ACN (2.5 mL) were added 3-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propyl 4-methylbenzenesulfonate (29.8 mg, 0.054 mmol), K_2CO_3(18.66 mg, 0.135 mmol) and potassium iodide (4.48 mg, 0.027 mmol), and the reaction was purged 4 times with N_2 and stirred at 80 °C under N_2 for 5 h. The reaction was concentrated in vacuo. The residue was diluted with DCM and water. The organic layer was separated, washed with further water, and concentrated in vacuo. The residue was purified by pre-TLC to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(3-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 57**, 20.8 mg, 47.00%).

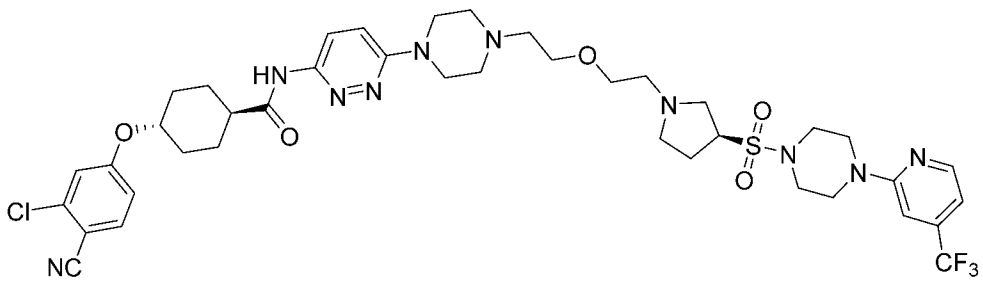
Example S57

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(2-((S)-3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 58)









[418] **Step 1:** To a solution of (S)-1-(pyrrolidin-3-ylsulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazine (50 mg, 1.0 eq) in DMF (1 mL) was added TEA (41.6 mg, 3.0 eq), potassium iodide (2.28 mg, 0.1 eq), and 2-(2-bromoethoxy)ethan-1-ol (25 mg, 1.1 eq.) at 90 ^{0}C, and the yellow mixture was stirred for 4 h. TLC (DCM/MeOH=15/1, Rf=0.56) showed (S)-1-(pyrrolidin-3-ylsulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazine was consumed, reaction had mainly a new spot. The mixture was concentrated in vacuo. The residue was directly purified with pre-TLC (DCM/MeOH=15/1) to afford (S)-2-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)ethan-1-ol (32.0 mg, light yellow solid). ESI-MS: 453.4 $[M+H]^+$.

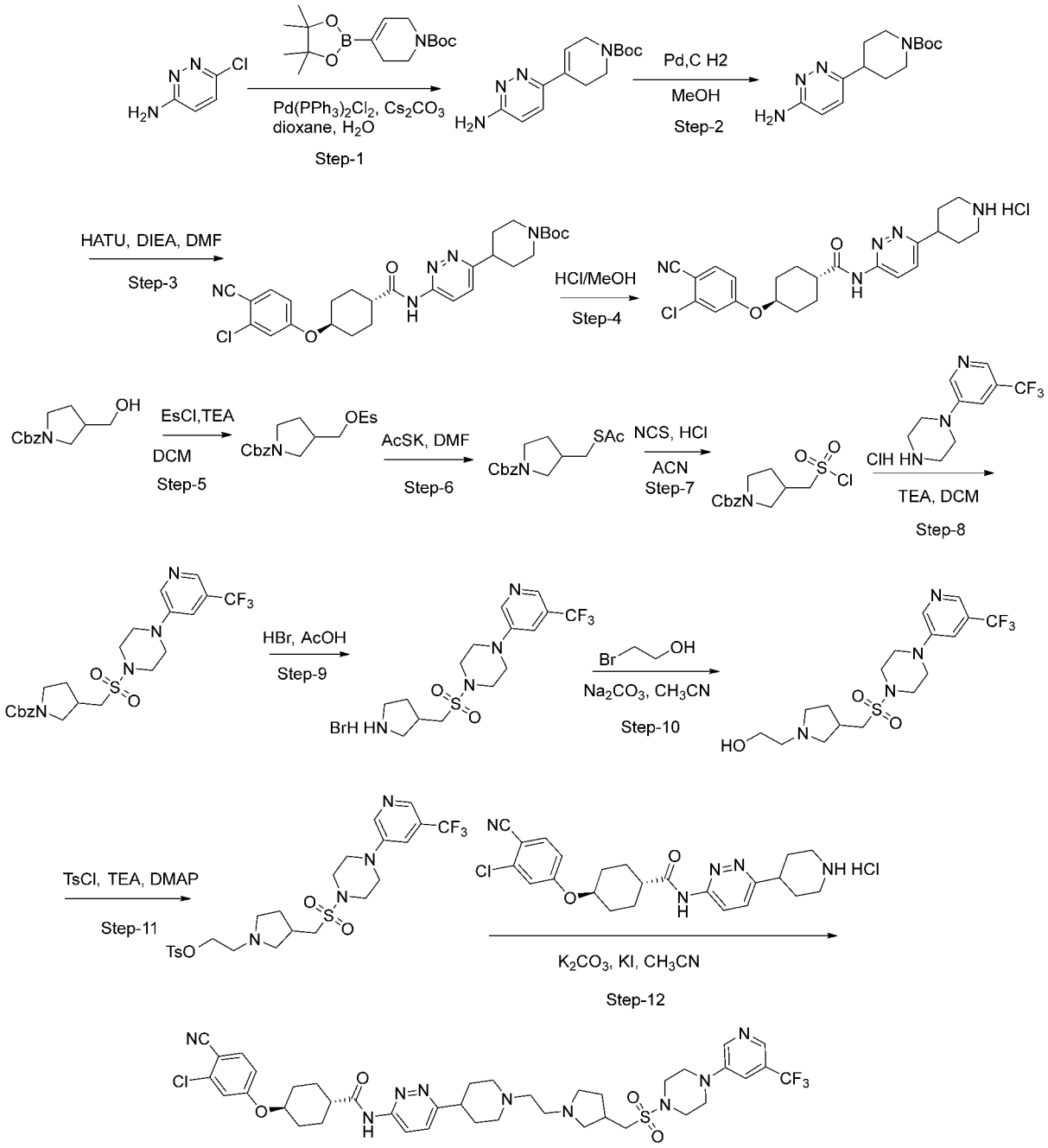
[419] **Step 2:** To a solution of (S)-2-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)ethan-1-ol (15 mg, 1.0 eq.) in DCM (1 mL) was added Dess-Martin (42

mg, 3.0 eq.), at 0-5 ^{0}C, and the yellow mixture was stirred at r.t. for 4 h. TLC (DCM/MeOH=15/1, Rf=0.70) showed (S)-2-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)ethan-1-ol was consumed, reaction had mainly a new spot. $NaHCO_3$ aqueous solution was added, then extracted with DCM 5ml×3. The mixture was concentrated in vacuo. The residue was directly purified with pre-TLC (DCM/MeOH=15/1) to afford (S)-2-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)acetaldehyde (6.0 mg, white solid). ESI-MS: 451.4[M+H]+.

[420] **Step 3:** (1r,4r)-N-(6-(4l2-piperazin-1-yl)pyridazin-3-yl)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxamide (6.89 mg, 1.0 eq) and HAC (4.25 mg, 3.0 eq) were mixed with MeOH (1.5 mL) and stirred for 0.5 h at room temperature. (S)-2-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)acetaldehyde (6.5 mg, 1.0 eq) was added and the reaction was stirred for 0.5h at room temperature, and STAB (4.53 mg, 5.0 eq) was added at 0-5 ^{0}C for reaction at room temperature for 5 h. TLC (DCM/MeOH=15/1, Rf=0.47) showed (S)-2-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)acetaldehyde was consumed, reaction had mainly a new spot. $NaHCO_3$ aqueous solution was added, then extracted with DCM 5ml×3, dried over Na_2SO_4. The mixture was concentrated in vacuo. The residue was directly purified with pre-TLC (DCM/MeOH=15/1) to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(2-((S)-3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 58**, 2.25 mg, white solid). ESI-MS: 876.4[M+H]+.

Example S58

Synthesis of (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-{6-[1-(2-{3-[(dioxo{4-[5-(trifluoromethyl)pyridin-3-yl]piperazin-1-yl}-λ^6-sulfanyl)methyl]tetrahydro-1H-pyrrol-1-yl}ethyl)hexahydropyridin-4-yl]-1,2-diazin-3-yl}(1r,4r)-cyclohexanecarboxamide (Compound 59)



[421] **Step 1:** 6-chloropyridazin-3-amine (417 mg, 3.219 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (995.30 mg, 3.219 mmol), palladium chloride bis(triphenylphosphane) (225.93 mg, 0.322 mmol) and cesium carbonate (3146.28 mg, 9.657 mmol) were dissolved in dioxane (5 mL) and water (0.5 mL), and the reaction mixture was stirred at 100 °C for 12 h under N_2 atmosphere. TLC detected 6-chloro-1,2-diazin-3-amine (417 mg, 3.219 mmol) was consumed, and then the reaction was concentrated and the residue was purified by chromatography to give tert-butyl 4-(6-aminopyridazin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (550 mg, 1.990 mmol, 61.83%) as a colorless solid.

[422] **Step 2:** Tert-butyl 4-(6-aminopyridazin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (580 mg, 2.099 mmol) was dissolved in MeOH (6 mL), 10% Pd/C (89.35 mg, 0.840 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. TLC detected tert-butyl 4-(6-aminopyridazin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate was consumed, the reaction was filtered and concentrated to give tert-butyl 4-(6-aminopyridazin-3-yl)piperidine-1-carboxylate (560 mg, 2.012 mmol, 95.85%) as a yellow solid.

[423] **Step 3:** Tert-butyl 4-(6-aminopyridazin-3-yl)piperidine-1-carboxylate (520 mg, 1.868 mmol), (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]cyclohexane-1-carboxylic acid (574.79 mg, 2.055 mmol) and HATU (781.35 mg, 2.055 mmol) were dissolved in DMF (2 mL), DIEA (482.90 mg, 3.736 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. TLC detected tert-butyl 4-(6-aminopyridazin-3-yl)piperidine-1-carboxylate (520 mg, 1.868 mmol) was consumed, then the reaction was diluted with water (8 mL) and extracted with DCM (5 mL x 3), and the organic layers were washed with saturated NH_4Cl, $NaHCO_3$ solution, and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give tert-butyl 4-(6-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxamido)pyridazin-3-yl)piperidine-1-carboxylate (600 mg, 1.111 mmol, 59.47%) as a colorless solid.

[424] **Step 4:** Tert-butyl 4-(6-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxamido)pyridazin-3-yl)piperidine-1-carboxylate (370 mg, 0.685 mmol) was dissolved in 4 mL HCl/dioxane, and the reaction mixture was stirred at room temperature for 1 h. The reaction was concentrated and the residue was washed by Et_2O to give (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide hydrochloride (350 mg, 0.624 mmol, 91.15%). ESI-MS:440.1$(M+H)^+$.

[425] **Step 5:** Benzyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (1000 mg, 4.250 mmol) and triethylamine (1.772 mL, 12.751 mmol) were dissolved in DCM (12 mL), ethanesulfonyl chloride (1092.91 mg, 8.501 mmol) was added, the reaction mixture was stirred at 0 °C for 2 h. TLC detected the reaction was complete, then the reaction was diluted with sat NH4Cl solution, extracted with DCM (10 mL x 3), dried over anhydrous Na2SO4, filtered and concentrated to give ((1-((benzyloxy)carbonyl)pyrrolidin-3-yl)methoxy)einsteinium (1300 mg, 2.780 mmol, 65.40%) as a brown oil.

[426] **Step 6:** Potassium(1+) thioacetic S-acid (640.47 mg, 5.559 mmol) was dissolved in 12 mL of CH_3CN, was added the solution of ((1-((benzyloxy)carbonyl)pyrrolidin-3-yl)methoxy)einsteinium (1300 mg, 2.780 mmol) in 4 mL CH_3CN, and the reaction mixture was stirred at 70 °C for 5 h. Then the reaction was diluted with H_2O (15 mL), extracted with EA (15 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated to give benzyl 3-((acetylthio)methyl)pyrrolidine-1-carboxylate (900 mg, 2.147 mmol, 77.26%) as a brown oil.

[427] **Step 7:** Benzyl 3-((acetylthio)methyl)pyrrolidine-1-carboxylate (900 mg, 2.147 mmol) was dissolved in CH_3CN (12 mL) and hydrogen chloride (6 mL), 1-chlorotetrahydropyrrole-2,5-dione (1146.96 mg, 8.590 mmol) was added, and the reaction mixture was stirred at room temperature for 3 h. TLC detected the reaction was complete, and then the reaction was diluted with H_2O (10 mL), extracted by DCM (10 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated to give benzyl 3-((chlorosulfonyl)methyl)pyrrolidine-1-carboxylate (500 mg, 1.259 mmol, 58.62%) as a brown oil.

[428] **Step 8:** 1-[5-(trifluoromethyl)pyridin-3-yl]piperazine hydrochloride (190 mg, 0.710 mmol) and triethylamine (0.296 mL, 2.129 mmol) were dissolved in DCM (10 mL). benzyl 3-((chlorosulfonyl)methyl)pyrrolidine-1-carboxylate (451.12 mg, 1.420 mmol) was added, and the reaction mixture was stirred at room temperature for 3 h, diluted with sat $NaHCO_3$ solution, extracted with DCM (10 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated, and the residue was purified by chromatography, eluting with PE/EA=1:1 to give benzyl 3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)pyrrolidine-1-carboxylate (300 mg, 0.585 mmol, 82.46%) as a yellow solid.

[429] **Step 9:** Benzyl 3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)pyrrolidine-1-carboxylate (306 mg, 0.597 mmol) was dissloved in hydrogen bromide (2 mL), acetic acid (1 mL) was added, and the reaction mixture was stirred at 100 °C for 1 h. TLC and ESI-MS detected the reaction was complete, and then the reaction mixture was concentrated and the residue was washed by Et_2O to give 1-((pyrrolidin-3-ylmethyl)sulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine hydrobromide (270 mg, 0.470 mmol, 78.77%) as a yellow solid.

[430] **Step 10:** 1-((pyrrolidin-3-ylmethyl)sulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine hydrobromide (92 mg, 0.200 mmol) and sodium carbonate (42.46 mg, 0.401 mmol) were dissolved in CH_3CN (3 mL), was added 2-bromoethan-1-ol (0.021 mL, 0.300 mmol), the reaction mixture was stirred at 60 °C for 4 h, filtered and concentrated, the residue was purified by Prep-TLC to give 2-(3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)pyrrolidin-1-yl)ethan-1-ol (24.3 mg, 0.052 mmol, 25.84%) as a white solid.

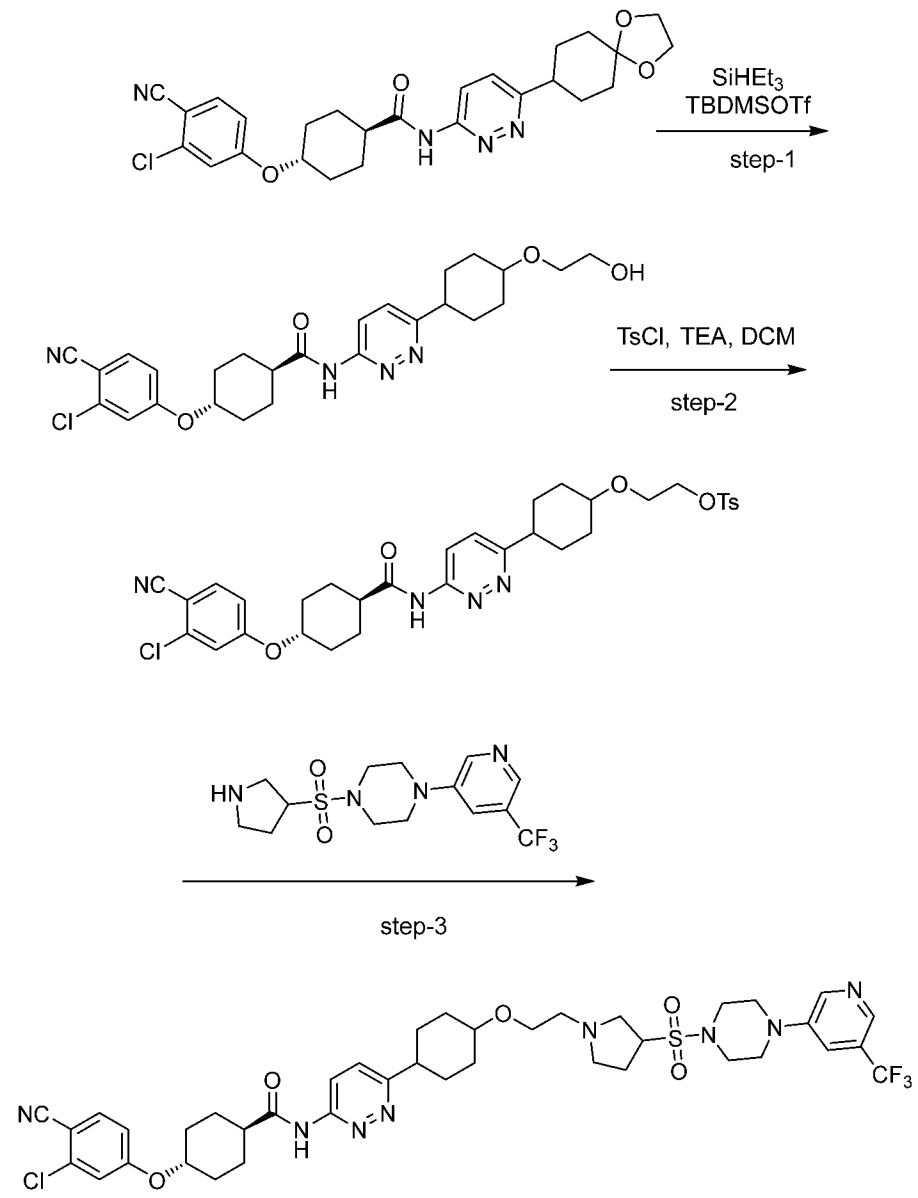
[431] **Step 11:** 2-(3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)pyrrolidin-1-yl)ethan-1-ol (23.8 mg, 0.056 mmol), triethylamine (0.023 mL, 0.168 mmol) and DMAP 4-dimethylaminopyridine (1.37 mg, 0.011 mmol) were dissolved in DCM (3 mL), 4-methylbenzenesulfonyl chloride (32.03 mg, 0.168 mmol) was added. The reaction mixture was stirred at room temperature for 3 h, filtered and concentrated, and the residue was purified by Prep-TLC to give 2-(3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)pyrrolidin-1-yl)ethyl 4-methylbenzenesulfonate (11.4 mg, 0.026 mmol, 46.17%) as a white solid.

[432] **Step 12:** 2-(3-(((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)methyl)pyrrolidin-1-yl)ethyl 4-methylbenzenesulfonate (11.4 mg, 0.026 mmol), (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-

[6-(hexahydropyridin-4-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide hydrochloride (18.58 mg, 0.039 mmol), potassium carbonate (10.78 mg, 0.078 mmol) and sodium iodide (1.17 mg, 0.008 mmol) were dissolved in CH_3CN (3 mL), and the reaction mixture was stirred at 70 °C for 3 h. ESI-MS detected the reaction was completed, and then the reaction was filtered and concentrated, and the residue was purified by Prep-TLC to give (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-{6-[1-(2-{3-[(dioxo{4-[5-(trifluoromethyl)pyridin-3-yl]piperazin-1-yl}-λ^6-sulfanyl)methyl]tetrahydro-1H-pyrrol-1-yl}ethyl)hexahydropyridin-4-yl]-1,2-diazin-3-yl}(1r,4r)-cyclohexanecarboxamide (**Compound 59**, 11.6 mg, 0.014 mmol, 53.14%) as a white solid. ESI-MS:844.3 $(M+H)^+$. ^1H NMR (400 MHz, CDCl3) δ 9.23 (s, 1H), 8.50 – 8.35 (m, 2H), 8.32 (s, 1H), 7.52 – 7.35 (m, 2H), 7.27 (s, 1H), 6.93 (d, J = 2.2 Hz, 1H), 6.78 (dd, J = 8.7, 2.3 Hz, 1H), 4.30 – 4.21 (m, 1H), 3.66 (d, J = 9.8 Hz, 1H), 3.43 (d, J = 4.3 Hz, 4H), 3.35 – 3.26 (m, 4H), 3.19 (s, 2H), 3.07 – 2.66 (m, 9H), 2.53 (s, 2H), 2.31 (dd, J = 22.5, 10.4 Hz, 4H), 2.24 – 2.07 (m, 8H), 1.70 (d, J = 13.4 Hz, 2H), 1.60 – 1.45 (m, 4H).

Example S59

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(3-(((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)sulfonyl)methyl)pyrrolidin-1-yl)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 60)



[433] **Step 1:** To a solution of (1r,4r)-N-(6-(1,4-dioxaspiro[4.5]decan-8-yl)pyridazin-3-yl)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxamide (110 mg, 1.0 eq) in DCM (3 ml) was added $SiHEt_3$ (160 mg, 6 eq), tert-butyl dimethylsilyl trifluoromethane sulfonate (60 mg, 1.0 eq) at 0 °C; the reaction was stirred at Rt overnight. The mixture was purified by pre-TLC (DCM:MeOH=20:1) to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-hydroxyethoxy)cyclohexyl)pyridazin-3-yl)cyclohexane-1-carboxamide (12 mg), ESI-MS: 499.2 $[M+H]^+$.

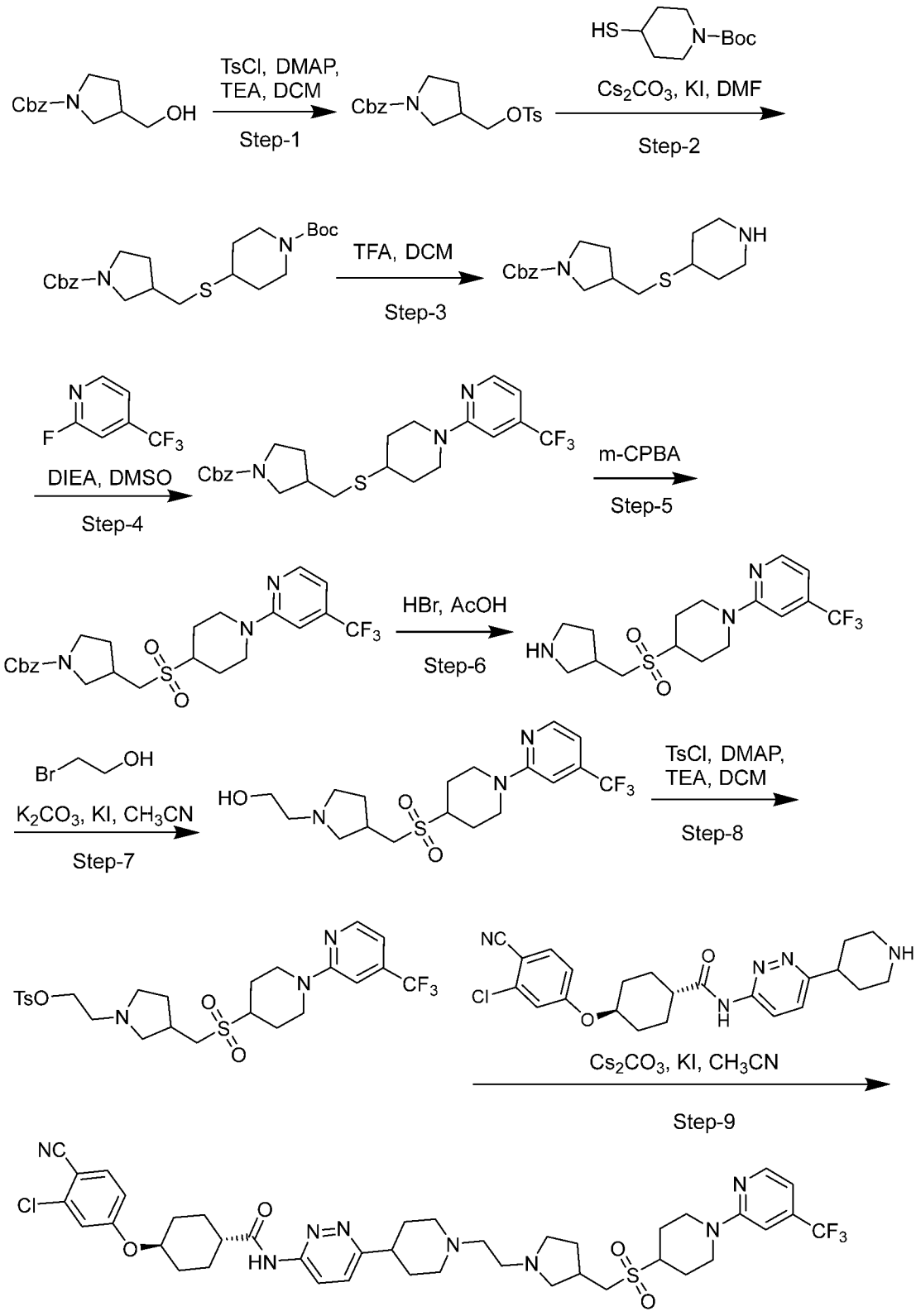
[434] **Step 2:** To a solution of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-hydroxyethoxy)cyclohexyl)pyridazin-3-yl)cyclohexane-1-carboxamide (12 mg,1.0eq) in DCM (1.5ml) was added Et_3N (7.3 mg, 3.0 eq), DMAP (0.6 mg, 0.2 eq). Then, TsCl (9.2 mg, 2 eq) was added at ice-bath. The reaction was stirred at Rt overnight. The mixture was concentrated and purified by pre-TLC (DCM:MeOH=20:1) to give 2-((4-(6-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-

carboxamido)pyridazin-3-yl)cyclohexyl)oxy)ethyl 4-methylbenzenesulfonate (11 mg) ESI-MS: 653.2 $[M+H]^+$.

[435] **Step 3:** A solution of 2-((4-(6-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxamido)pyridazin-3-yl)cyclohexyl)oxy)ethyl 4-methylbenzenesulfonate (11 mg, 1.0 eq), 1-(pyrrolidin-3-ylsulfonyl)-4-(5-(trifluoromethyl)pyridin-3-yl)piperazine (6.8 mg, 1.1 eq), K_2CO_3 (4.7 mg, 2.0 eq) and KI (1.4 mg 0.5 eq) in CH_3CN (1 ml) was stirred at 80 °C for 4 h. The solvent was removed and the mixture was purified by pre-TLC (DCM:MeOH=20:1) to afford the product (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)cyclohexyl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 60**, 5 mg) as a white solid. ESI-MS: 845.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.43 (d, J = 9.2 Hz, 1H), 8.38 (s, 1H), 7.56 (t, J = 6.2 Hz, 1H), 7.42 (d, J = 9.3 Hz, 1H), 7.32 (s, 1H), 7.00 (d, J = 2.3 Hz, 1H), 6.85 (dd, J = 8.7, 2.3 Hz, 1H), 4.41 – 4.25 (m, 1H), 3.75 (t, J = 6.4 Hz, 6H), 3.46 – 3.25 (m, 4H), 3.07 – 2.90 (m, 2H), 2.77 (s, 3H), 2.66 (t, J = 11.3 Hz, 1H), 2.34 (d, J = 11.0 Hz, 1H), 2.23 (dd, J = 16.1, 8.6 Hz, 4H), 2.12 (t, J = 14.7 Hz, 2H), 2.08 – 1.96 (m, 4H), 1.88 – 1.81 (m, 6H), 1.63 – 1.53 (m, 5H).

Example S60

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(3-(((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)sulfonyl)methyl)pyrrolidin-1-yl)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 61)



[436] **Step 1:** To a solution of benzyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (500 mg, 2.125 mmol) in DCM (20 mL) were added TEA (0.886 mL, 6.375 mmol), DMAP (259.63 mg, 2.125 mmol), and TsCl (607.70 mg, 3.188 mmol), and the reaction was stirred at room temperature for 18 hours. The reaction was complete as detected by TLC (PE:EA= 2:1). The reaction was concentrated in vacuo. The

crude product was chromatographed on silica gel (EtOAc in PE 10:100→25:100→50:100) to give benzyl 3-((tosyloxy)methyl)pyrrolidine-1-carboxylate (800 mg, 2.054 mmol, 96.66%).

[437] **Step 2:** To a solution of benzyl 3-((tosyloxy)methyl)pyrrolidine-1-carboxylate (500 mg, 1.284 mmol) in DCM (10 mL) was added Cs_2CO_3 (1254.86 mg, 3.851 mmol), potassium iodide (213.11 mg, 1.284 mmol), and 2-methylpropan-2-yl 4-sulfanylhexahydropyridine-1-carboxylate (334.81 mg, 1.541 mmol) and the reaction was stirred at 100 °C for 3 hours under nitrogen atmosphere. The reaction was complete as detected by TLC (PE: EA= 3:1). The reaction was concentrated in vacuo. The crude product was chromatographed on silica gel (PE in EtOAc 10:100→15:100→20:100) to give tert-butyl 4-(((1-((benzyloxy)carbonyl)pyrrolidin-3-yl)methyl)thio)piperidine-1-carboxylate (550 mg, 1.266 mmol, 98.58%).

[438] **Step 3:** To a solution of tert-butyl 4-(((1-((benzyloxy)carbonyl)pyrrolidin-3-yl)methyl)thio)piperidine-1-carboxylate (550 mg, 1.266 mmol) in DCM (5 mL) was added TFA (5 ml, 65.296 mmol), and the reaction was stirred at room temperature for 2 hours. The reaction was complete as detected by TLC (PE: EA= 3:1). The reaction was concentrated in vacuo to afford benzyl 3-((piperidin-4-ylthio)methyl)pyrrolidine-1-carboxylate (420 mg, 1.256 mmol, 99.22%).

[439] **Step 4:** To a solution of methyl benzyl 3-((piperidin-4-ylthio)methyl)pyrrolidine-1-carboxylate (420 mg, 1.256 mmol) in DMSO (2 mL) were added DIEA (811.48 mg, 6.278 mmol) and 2-fluoro-4-(trifluoromethyl)pyridine (228.03 mg, 1.381 mmol), and the reaction was stirred at 130 °C for 3 hours. TLC showed new spot was observed, and then the reaction mixture was poured into water (30 mL). The mixture was stirred at room temperature for 1 hour. The reaction mixture was filtered through Buchner funnel to afford benzyl 3-(((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)thio)methyl)pyrrolidine-1-carboxylate (500 mg, 1.043 mmol, 83.03%).

[440] **Step 5:** To a solution of benzyl 3-(((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)thio)methyl)pyrrolidine-1-carboxylate (480 mg, 1.001 mmol) in DCM (15 mL) were added m-CPBA (379.98 mg, 2.202 mmol), and the reaction was stirred at room temperature for 3 hours. TLC showed product was observed. The crude product was chromatographed on silica gel (methanol in DCM 0:100→2:100→4:100) to afford benzyl 3-(((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)sulfonyl)methyl)pyrrolidine-1-carboxylate (320 mg, 0.626 mmol, 62.50%).

[441] **Step 6:** To a solution of benzyl 3-(((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)sulfonyl)methyl)pyrrolidine-1-carboxylate (300 mg, 0.586 mmol) in AcOH (8 mL) were added HBr (8 mL), and the reaction was stirred at 110 °C for 6 hours. The reaction was complete as detected by TLC (DCM: MeOH= 20:1). The reaction was concentrated in vacuo to afford 2-(4-((pyrrolidin-3-ylmethyl)sulfonyl)piperidin-1-yl)-4-(trifluoromethyl)pyridine (250 mg, 0.571 mmol, 97.52%) as a pink solid.

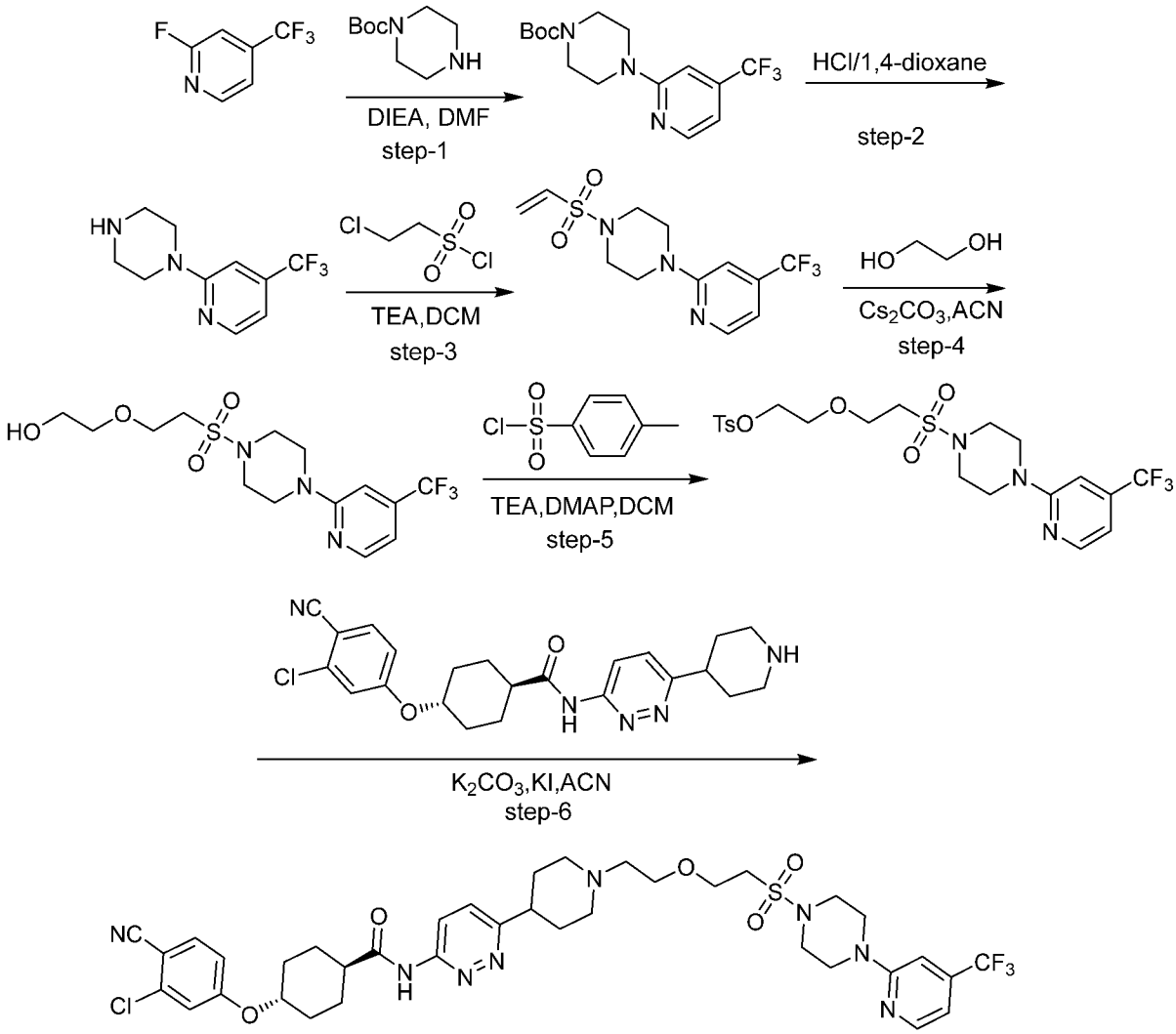
[442] **Step 7:** To a solution of 2-(4-((pyrrolidin-3-ylmethyl)sulfonyl)piperidin-1-yl)-4-(trifluoromethyl)pyridine (100 mg, 0.265 mmol) in CH3CN (2 mL) were added K_2CO_3 (109.87 mg, 0.795 mmol), KI (21.99 mg, 0.132 mmol), and 2-bromoethan-1-ol (0.038 mL, 0.530 mmol), and the reaction was stirred at 100 °C for 4 hours. The reaction was complete as detected by TLC (DCM: MeOH= 10:1). The reaction was concentrated in vacuo. The residue was purified by preparative TLC (DCM : MeOH=8:1) to afford 2-(3-(((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)sulfonyl)methyl)pyrrolidin-1-yl)ethan-1-ol (45 mg, 0.107 mmol, 40.30%) as a colorless oil.

[443] **Step 8:** To a solution of 2-(3-(((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)sulfonyl)methyl)pyrrolidin-1-yl)ethan-1-ol (40 mg, 0.095 mmol) in DCM (3 mL) were added TEA (0.040 mL, 0.285 mmol), DMAP (11.59 mg, 0.095 mmol), and TsCl (54.28 mg, 0.285 mmol), and the reaction was stirred at room temperature for 16 hours. The reaction was complete as detected by TLC (DCM: MeOH= 25:1). The reaction was concentrated in vacuo. The residue was purified by preparative TLC (DCM : MeOH=25:1) to afford 2-(3-(((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)sulfonyl)methyl)pyrrolidin-1-yl)ethyl 4-methylbenzenesulfonate (13 mg, 0.023 mmol, 23.80%).

[444] **Step 9:** To a solution of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (11.92 mg, 0.027 mmol) in CH_3CN (3 mL) were added K_2CO_3 (9.36 mg, 0.068 mmol), KI (3.75 mg, 0.023 mmol), and 2-(3-(((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)sulfonyl)methyl)pyrrolidin-1-yl)ethyl 4-methylbenzenesulfonate (13 mg, 0.023 mmol), and the reaction was stirred at 80 °C for 3 hours. The reaction was complete detected by TLC (DCM: MeOH= 10:1). The reaction was concentrated in vacuo. The residue was purified by preparative TLC (DCM : MeOH=10:1) to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(3-(((1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)sulfonyl)methyl)pyrrolidin-1-yl)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 61**, 5.3 mg, 0.006 mmol, 27.82%) as a white solid. ESI-MS: 843.2 $[M+H]^+$; **^{1}H NMR** (400 MHz, Chloroform-d) δ 9.13 (s, 1H), 8.47 (dd, J = 9.4, 4.0 Hz, 1H), 8.29 (d, J = 5.2 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.50 (d, J = 9.3 Hz, 1H), 7.00 (d, J = 2.8 Hz, 1H), 6.85 (dd, J = 8.7, 2.4 Hz, 1H), 6.82 (s, 1H), 6.79 (d, J = 5.1 Hz, 1H), 4.55 (d, J = 13.2 Hz, 2H), 4.31 (d, J = 10.1 Hz, 1H), 4.00 – 3.80 (m, 2H), 3.74 (t, J = 7.9 Hz, 1H), 3.67 – 3.47 (m, 3H), 3.19 – 2.74 (m, 10H), 2.46 (ddd, J = 35.8, 25.2, 13.5 Hz, 6H), 2.32 – 2.07 (m, 9H), 2.01 (d, J = 8.7 Hz, 2H), 1.81 – 1.70 (m, 5H).

Example S61

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 62)



[445] **Step 1:** 2-fluoro-4-(trifluoromethyl)pyridine (5 g, 30.287 mmol), tert-butyl piperazine-1-carboxylate (660 mg, 7.662 mmol) and DIEA (7.83 g, 60.573 mmol) were dissolved in DMF (15 mL), and the reaction mixture was stirred at 110 °C. After 3 hours the reaction waws completed. 20 mL of a saturated NaCl solution is then added and the product extracted with EtOAc (3×20 mL). The organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give tert-butyl 4-(4-(trifluoromethyl)pyridin-2-yl)piperazine-1-carboxylate (7.32 g, 22.092 mol, 74%) as oil.

[446] **Step 2:** tert-butyl 4-(4-(trifluoromethyl)pyridin-2-yl)piperazine-1-carboxylate (7.32 g, 22.092 mol) was dissolved in HCl/dioxane (8 mL), and the reaction mixture was stirred at RT overnight, and concentrated in vacuo to give the crude product 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (6.28g, 21.584mmol, 94%) as white solid.

[447] **Step 3:** To the mixture of 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (6.78 g, 23.302 mmol)and TEA(34.341 mL, 247.060 mmol) in DCM(50ml) was added 2-chloroethane-1-sulfonyl chloride (15 g, 92.019 mmol), the reaction mixture was stirred at RT overnight ,The residue was purified by

preparative TLC (PE: EA=3:1) to afford 1-(4-(trifluoromethyl)pyridin-2-yl)-4-(vinylsulfonyl)piperazine (4.4 g, 13.694 mmol, 58%) as white solid.

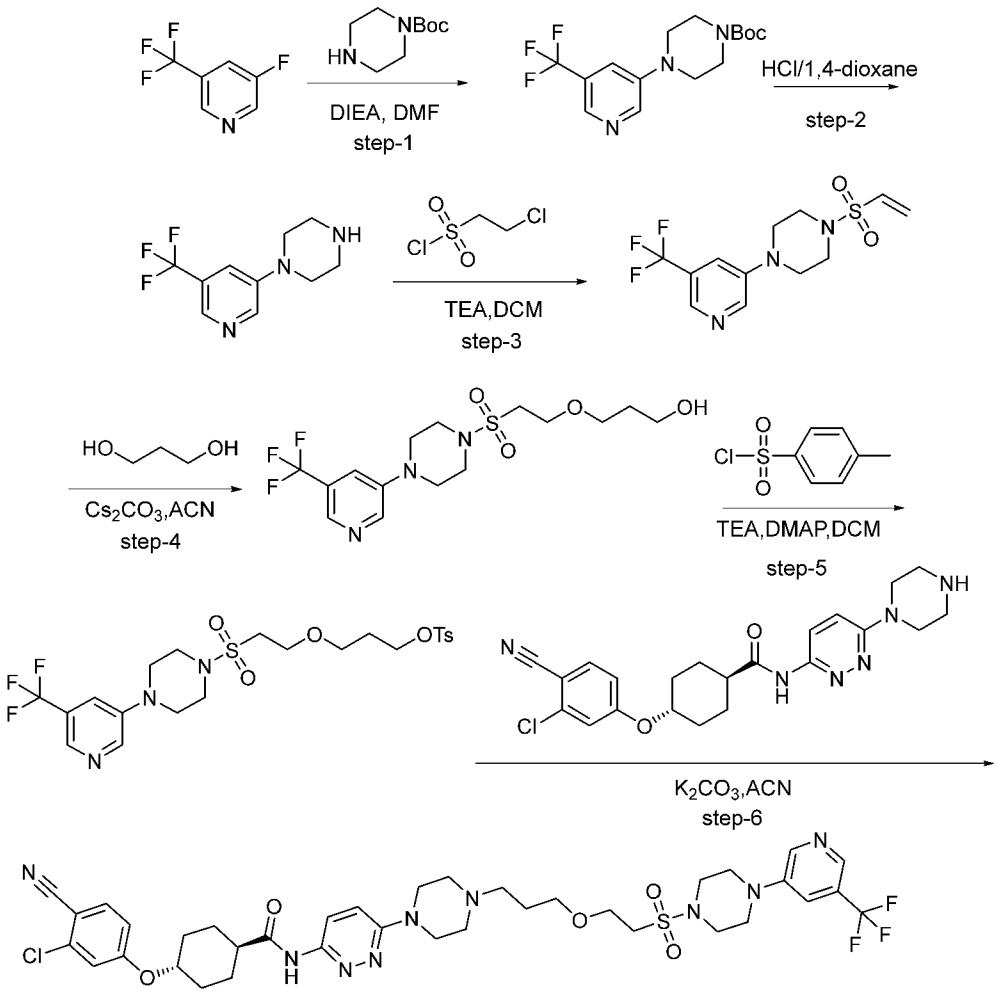
[448] **Step 4:** To the mixtured of 1-(4-(trifluoromethyl)pyridin-2-yl)-4-(vinylsulfonyl)piperazine (4.4 g, 13.694 mmol), Cs_2CO_3 (8.92 g, 27.387 mmol) in CAN (250 ml) was added ethylene glycol (1.527 mL, 27.387 mmol), the reaction mixture was stirred at 70 °C for 3 hours. The residue was purified by preparative TLC (PE: EA=3:1) to afford 2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethan-1-ol (7 g, 11.685 mmol, 64%) as white solid.

[449] **Step 5:** To the mixture of 2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethan-1-ol (7 g, 11.685 mmol), DMAP (430 mg, 3.52 mmol) and TEA (20 mL, 144.88 mmol) in DCM (200 ml) was added 4-methylbenzenesulfonyl chloride (9 g, 47.21 mmol). The reaction mixture was stirred at RT overnight. The residue was purified by preparative TLC (PE: EA=1:1) to afford 2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl 4-methylbenzenesulfonate (8.7g, 14.56 mmol, 90%) as white solid.

[450] **Step 6:** To the mixtured of 2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl 4-methylbenzenesulfonate (8.7 g, 14.56 mmol), K_2CO_3 (8.92 g, 27.387 mmol), KI (0.6 g, 3.614 mmol) in ACN (250 ml) was added (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (7.12 g, 16.184 mmol), and the reaction mixture was stirred at 85 °C overnight. The residue was purified by preparative TLC (DCM: MeOH=30:1) to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 62**, 0.8 g, 0.98 mmol, 6.08%) as white solid.

Example S62

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(3-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 64)



[451] **Step 1:** 3-fluoro-5-(trifluoromethyl)pyridine (50 mg, 0.30 mmol), tert-butyl piperazine-1-carboxylate (660 mg, 7.662 mmol) and DIEA (78.3 g, 0.60 mmol) were dissolved in DMF (5 mL). The reaction mixture was stirred at 110 °C. After 3 hours the reaction was completed. 5 mL of a saturated NaCl solution was then added and the product extracted with EtOAc (3×5mL). The organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-carboxylate (70 mg, 0.22 mol, 74%) as oil.

[452] **Step 2:** tert-butyl 4-(5-(trifluoromethyl)pyridin-3-yl)piperazine-1-carboxylate (70 mg,0.22 mol) was dissolved in HCl/dioxane (5 mL). The reaction mixture was stirred at RT overnight and concentrated in vacuo to give the crude product 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine (63 mg,0.21 mmol, 94%) as white solid.

[453] **Step 3:** To the mixture of 1-(5-(trifluoromethyl)pyridin-3-yl)piperazine (63 mg, 0.23 mmol) and TEA (0.34 mL, 2.4 mmol) in DCM (5 ml) was added 2-chloroethane-1-sulfonyl chloride (150 mg, 0.92 mmol). The reaction mixture was stirred at RT overnight. The residue was purified by preparative TLC (PE: EA=3:1) to afford 1-(5-(trifluoromethyl)pyridin-3-yl)-4-(vinylsulfonyl)piperazine (30 mg, 0.09 mmol, 50%) as white solid.

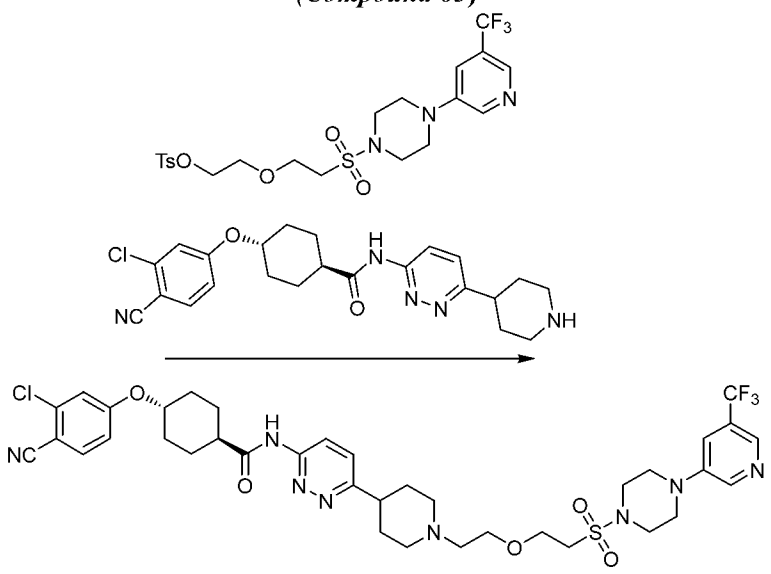
[454] **Step 4:** To the mixtured of 1-(5-(trifluoromethyl)pyridin-3-yl)-4-(vinylsulfonyl)piperazine (30 mg, 0.093 mmol), Cs_2CO_3 (60 mg, 0.184 mmol) in ACN (3 ml) was added ethylene glycol (0.007 mL, 0.093 mmol). The reaction mixture was stirred at 70 °C for 3 hours. The residue was purified by preparative TLC (PE: EA=3:1) to afford 3-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propan-1-ol (21m g, 0.054 mmol, 57%) as white solid.

[455] **Step 5:** To the mixture of 3-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propan-1-ol (21mg, 0.054 mmol), DMAP (6.46mg, 0.053mmol) and TEA (0.037 mL, 0.264 mmol) in DCM (4 ml) was added 4-methylbenzenesulfonyl chloride (15 mg, 0.079 mmol). The reaction mixture was stirred at RT overnight. The residue was purified by preparative TLC (PE: EA=1:1) to afford 3-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propyl 4-methylbenzenesulfonate (29 mg, 0.052 mmol, 98%) as white solid.

[456] **Step 6:** To the mixture of 3-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propyl 4-methylbenzenesulfonate (18 mg, 0.033 mmol) and K_2CO_3 (13.68 mg, 0.099 mmol) in ACN (250 ml) was added (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (15.75 mg, 0.033 mmol). The reaction mixture was stirred at 85 °C overnight. The residue was purified by preparative TLC (DCM: MeOH=30:1) to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(3-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)propyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 64**, 12 mg, 0.015mmol, 44%) as white solid.

Example S63

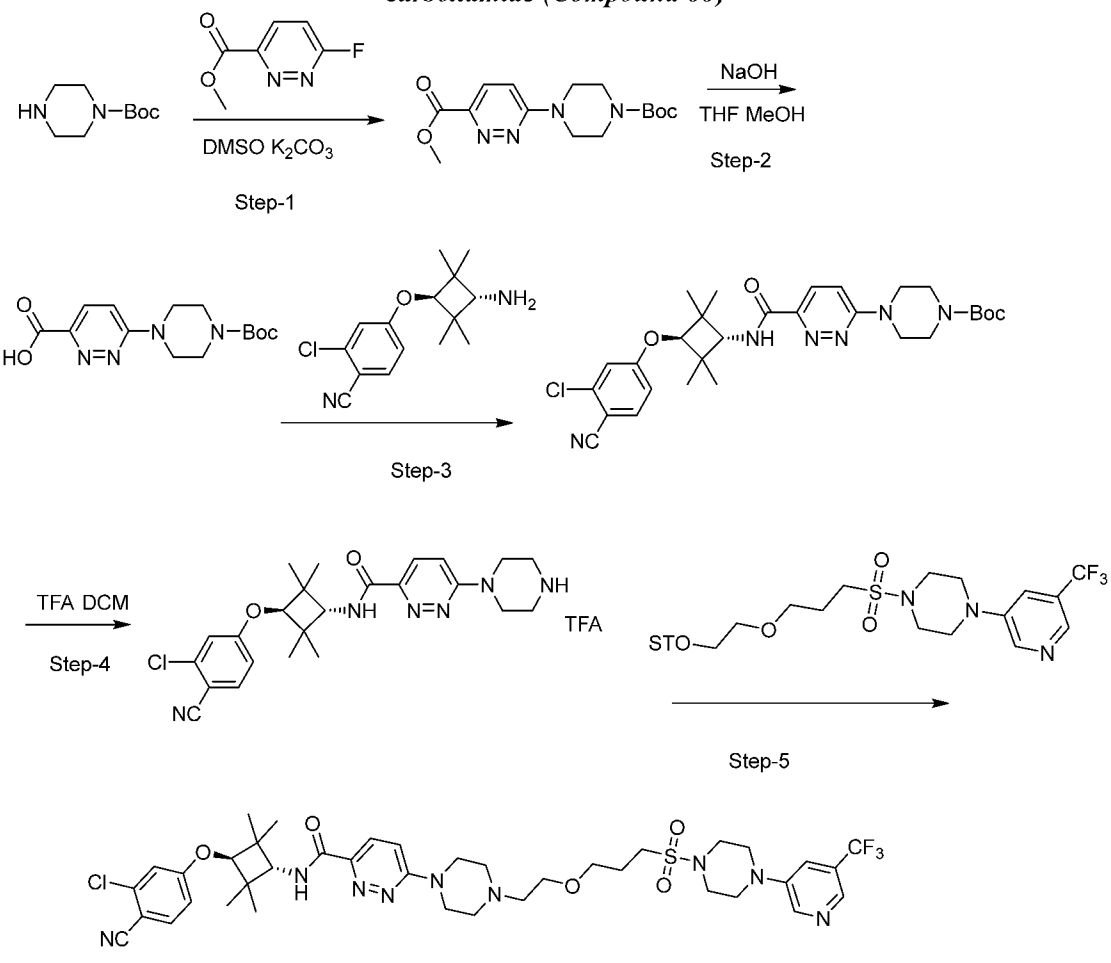
Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 65)



[457] A solution of (2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl 4-methylbenzenesulfonate (62 mg, 1.0 eq), (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (50.8 mg, 1.0 eq), K_2CO_3 (32 mg, 2.0eq) and KI (9.6 mg, 0.5eq) in CH_3CN (2ml) was stirred at 80 °C overnight. The solvent was removed and the mixture was purified by pre-TLC (DCM:MeOH=10:1) to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 65**, 15 mg) as a white solid (15 mg). ESI-MS:805.3$[M+H]^+$, ^1H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.52 (s, 1H), 8.44 (d, J = 9.2 Hz, 1H), 8.38 (s, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.41 (d, J = 9.3 Hz, 1H), 7.34 (s, 1H), 7.00 (d, J = 2.3 Hz, 1H), 6.85 (dd, J = 8.8, 2.4 Hz, 1H), 4.33 (ddd, J = 14.3, 10.3, 4.1 Hz, 1H), 3.92 (t, J = 5.8 Hz, 2H), 3.81 (s, 2H), 3.50 (dd, J = 6.2, 3.7 Hz, 4H), 3.39 (dd, J = 6.1, 3.8 Hz, 4H), 3.31 (t, J = 5.8 Hz, 3H), 2.61 (t, J = 11.3 Hz, 1H), 2.24 (s, 3H), 1.78 (d, J = 13.7 Hz, 5H), 1.61 (s, 5H), 1.35 (d, J = 15.0 Hz, 3H), 0.88 (s, 2H).

Example S64

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)pyridazine-3-carboxamide (Compound 66)



[458] **Step 1:** A mixture of methyl 6-fluoro-1,2-diazine-3-carboxylate (1000 mg, 6.405 mmol), 2-methylpropan-2-yl piperazine-1-carboxylate (885.00 mg, 4.752 mmol) and K2CO3 (1313.37 mg, 9.503 mmol) in DMSO (3 mL) was stirred at 100°C for 2 h. TLC (EA/PE=1/1, Rf=0.6) showed starting material was consumed, and the reaction had mainly a new spot. 2 ml of water was added to the reaction solution. The combined aqueous layers were extracted with EA (2 mL×3) to remove neutral impurities. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was directly purified with pre-TLC (EA/PE=1/1) to afford methyl 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridazine-3-carboxylate (300.0 mg, Yellow solid).

[459] **Step 2:** Methyl 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridazine-3-carboxylate (300 mg, 0.931 mmol) was dissolved in THF/MeOH (1 mL/1 mL). NaOH (186.12 mg, 4.653 mmol) and H_2O (0.5 mL) were added. Then the reaction was stirred at RT for 2 h, concentrated, acidified with 1M HCl aqueous to pH=3-4, concentrated, extracted with DCM/MeOH, and purified by pre-TLC eluting with DCM/MeOH=20/1 for 2 times to afford the product 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridazine-3-carboxylic acid (148 mg).

[460] **Step 3:** To a mixture of 4-[(3-amino-2,2,4,4-tetramethylcyclobutyl)oxy]-2-chlorobenzene-1-carbonitrile hydrochloride (147.22 mg, 0.467 mmol), 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridazine-3-carboxylic acid (144 mg, 0.467 mmol), and HATU (213.09 mg, 0.560 mmol) in DMF(1 mL) was added DIEA (181.09 mg, 1.401 mmol). The mixture was stirred at RT for 16 h, concentrated, and purified by pre-TLC eluting with EA/PE=1/1 to afford the product tert-butyl 4-(6-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)pyridazin-3-yl)piperazine-1-carboxylate (64 mg).

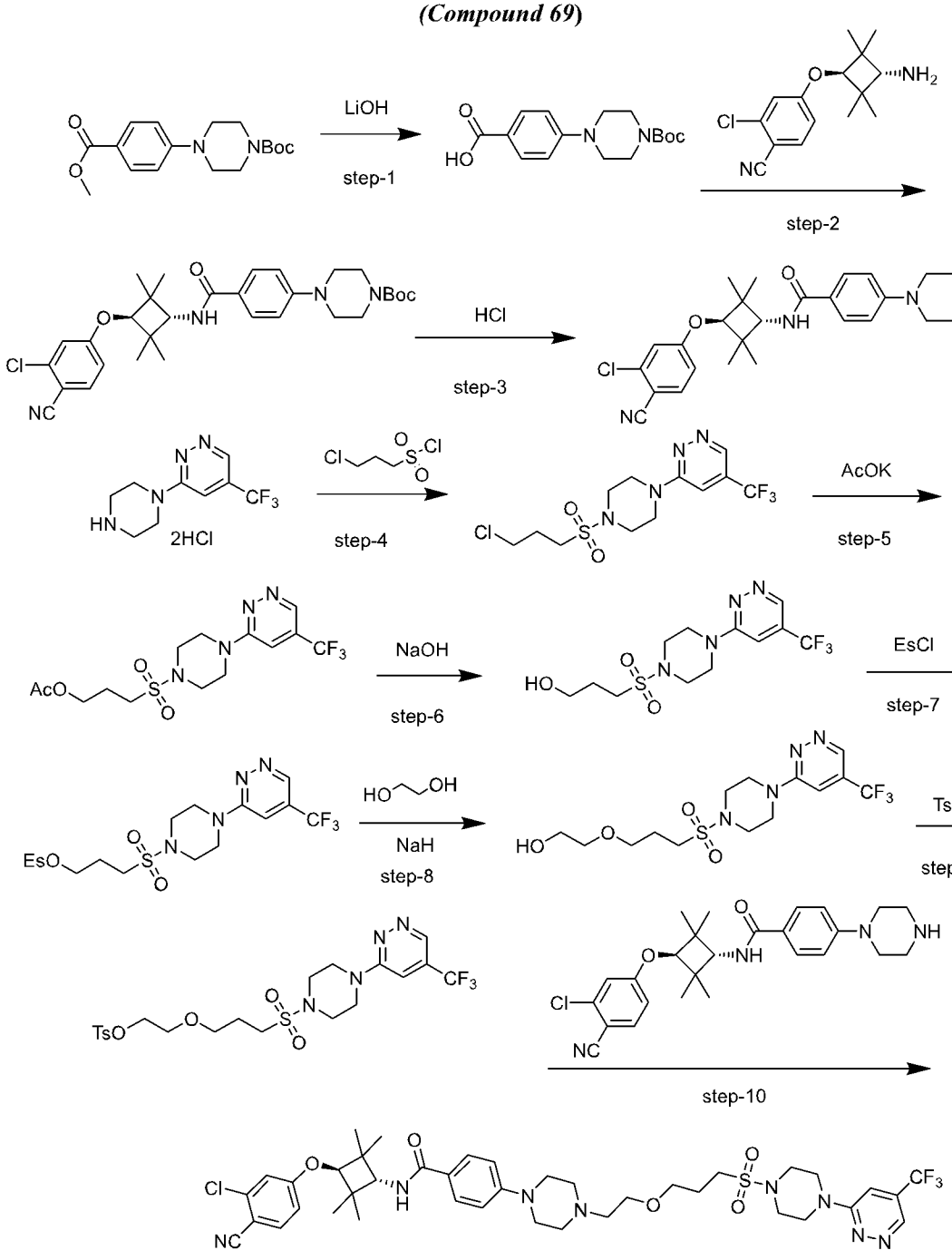
[461] **Step 4:** To a solution of tert-butyl 4-(6-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)pyridazin-3-yl)piperazine-1-carboxylate (64 mg, 0.112 mmol) in DCM (2 mL) was added TFA (2 mL, 26.118 mmol) and the reaction was stirred at room temperature for 1 hour. The reaction was complete as detected by TLC (PE: EA= 1:1). The reaction was concentrated in vacuo to afford N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(piperazin-1-yl)pyridazine-3-carboxamide TFA (52 mg).

[462] **Step 5:** To a solution of 2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl 4-methylbenzenesulfonate (100 mg, 0.181 mmol) in ACN (1.5 mL) were added N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(piperazin-1-yl)pyridazine-3-carboxamide TFA (52 mg, 0.111 mmol), K_2CO_3 (46.02 mg, 0.333 mmol), and potassium iodide (1.84 mg, 0.011 mmol), and the reaction was stirred at 80 °C for 16 h. The reaction was concentrated *in vacuo* and purified by pre-TLC to afford N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(2-(3-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)pyridazine-3-carboxamide (**Compound 66**, 31 mg). ESI-MS: 424.7, 425.6 ,848.3 $[M+H]^+$. ^1H NMR

(400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 2.4 Hz, 1H), 8.40 (s, 1H), 8.14 (d, *J* = 9.0 Hz, 1H), 8.02 (d, *J* = 9.4 Hz, 1H), 7.55 (t, *J* = 10.6 Hz, 1H), 7.32 (d, *J* = 15.1 Hz, 1H), 6.99 (dd, *J* = 12.1, 2.8 Hz, 2H), 6.81 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.19 (d, *J* = 9.0 Hz, 1H), 4.07 (s, 1H), 3.84 (s, 3H), 3.73 – 3.55 (m, 4H), 3.54 – 3.44 (m, 4H), 3.44 – 3.31 (m, 4H), 3.11 (s, 2H), 2.69 (s, 5H), 2.18 – 2.06 (m, 2H), 1.28 (s, 5H), 1.21 (s, 5H).

Example S65

Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(3-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)benzamide (Compound 69)



[463] **Step 1:** To a mixture of tert-butyl 4-(4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (1 g, 3.121 mmol) in THF (12 mL) and H_2O (3 mL) was added LiOH (0.39 g, 9.364 mmol). The reaction mixture was stirred at 40 °C for 3 hours, filtered, and concentrated in vacuo to give 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)benzoic acid (490 mg, 1.599 mmol, 51.24%) as oil.

[464] **Step 2:** 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)benzoic acid (200 mg, 0.653 mmol), 2-chloro-4-{[(1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutyl]oxy}benzene-1-carbonitrile (182.00 mg, 0.653 mmol), HATU (310.29 mg, 0.816 mmol) and DIEA (253.13 mg, 1.958 mmol) were dissolved in DMF (5 mL). The reaction mixture was stirred at rt. After 1 hour the reaction was completed. 5 mL of a saturated NaCl solution was then added and the product extracted with EtOAc (3×5mL).The organics were dried over Na_2SO_4, filtered, and the residue was purified by preparative TLC (PE: EA=1:1) to afford tert-butyl 4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazine-1-carboxylate (225 mg, 0.397 mmol, 60.77%) as solid.

[465] **Step 3:** tert-butyl 4-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperazine-1-carboxylate (225 mg, 0.397 mmol) was dissolved in HCl/dioxane (3mL). The reaction mixture was stirred at RT overnight and concentrated in vacuo to give the crude product N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benzamide(180mg, 0.85mmol, 97%) as white solid.

[466] **Step 4:** To the mixture of 3-(piperazin-1-yl)-5-(trifluoromethyl)pyridazine (500 mg, 2.153 mmol) and TEA (0.898 mL, 6.460 mmol) in DCM (10 ml) was added 3-chloropropane-1-sulfonyl chloride (762.41 mg, 4.306 mmol). The reaction mixture was stirred at RT overnight. The residue was purified by preparative TLC (PE: EA=3:1) to afford 3-(4-((3-chloropropyl)sulfonyl)piperazin-1-yl)-5-(trifluoromethyl)pyridazine (350 mg, 0.78mmol, 45%) as white solid.

[467] **Step 5:** 3-(4-((3-chloropropyl)sulfonyl)piperazin-1-yl)-5-(trifluoromethyl)pyridazine (350 mg, 0.939 mmol), KOAc (138.21 mg, 1.408 mmol) and KI (15.59 mg, 0.094 mmol) were dissolved in DMF (8 mL). The reaction mixture was stirred at 90 °C. After 1 hour the reaction was completed. 5 mL of a saturated NaCl solution was then added and the product extracted with EtOAc (3×5mL). The organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 3-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)propyl acetate (370 mg, 0.933 mmol, 99.41%) as oil.

[468] **Step 6:** To a mixture of 3-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)propyl acetate (370 mg, 0.933 mmol) in H_2O (2 mL), EtOH (4 mL) and THF (4 mL) was added NaOH (112.01 mg, 2.800 mmol). The reaction mixture was stirred at RT overnight and concentrated in vacuo to give the crude product 3-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)propan-1-ol (280 mg, 0.790 mmol, 84.65%) as white solid.

[469] **Step 7:** To a mixture of 3-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)propan-1-ol (280 mg, 0.790 mmol) and TEA (0.329 mL, 2.371 mmol) in DCM (5 mL) was added Ethanesulfonyl chloride (152.40 mg, 1.185 mmol) at 0°C. The reaction mixture was stirred at RT for 3 hours, and concentrated in vacuo to give the crude product (3-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)propoxy)einsteinium (350 mg, 0.784 mmol, 99.23%) as oil.

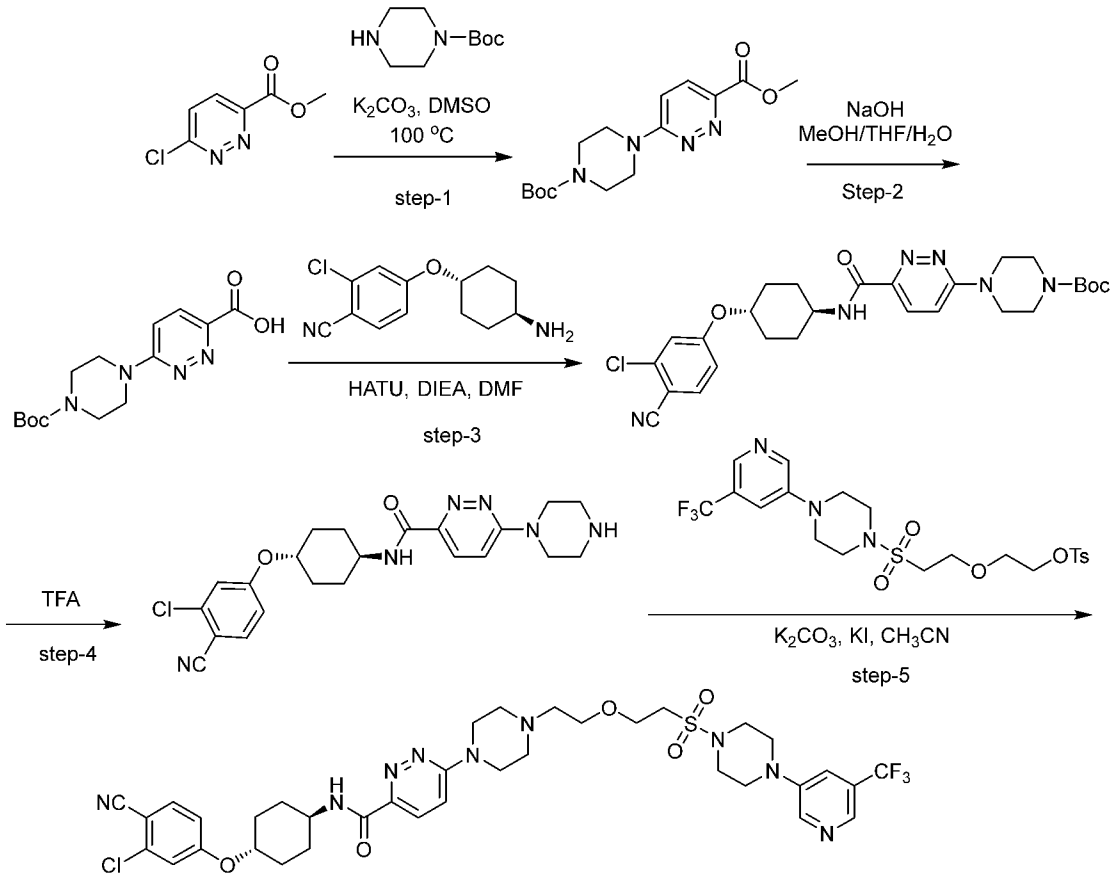
[470] **Step 8:** To ethylene glycol (10 mL, 179.314 mmol) was added NaH (75 mg, 1.875 mmol) at 0°C under N_2 with stirring for 30 minutes. (3-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)propoxy)einsteinium (350 mg, 0.784 mmol) was added dropwise, and the reaction mixture was stirred at 50°C for overnight. 5 mL of a saturated NaCl solution was then added and the product extracted with EtOAc (3×5mL). The organics were dried over Na_2SO_4, filtered, and the residue purified by preparative TLC (PE: EA=1:1) to afford 2-(3-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethan-1-ol (416 mg, 0.731 mmol, 93.24%) as white solid.

[471] **Step 9:** To a mixture of 2-(3-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethan-1-ol (416 mg, 0.731 mmol), DMAP (26.79 mg, 0.219 mmol) and TEA (0.305 mL, 2.193 mmol) in DCM (25ml) was added 4-methylbenzenesulfonyl chloride (209.04 mg, 1.097 mmol) at 0°C, and the reaction mixture was stirred at RT overnight. The residue was purified by preparative TLC (PE: EA=1:1) to afford 2-(3-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl 4-methylbenzenesulfonate (106 mg, 0.192 mmol,26%) as white solid.

[472] **Step 10:** To the mixtured of 2-(3-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl 4-methylbenzenesulfonate (50 mg, 0.090 mmol), KI (7 mg, 0.042 mmol) and K_2CO_3 (25 mg, 0.181 mmol) in ACN(5ml) was added N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(piperazin-1-yl)benzamide (42 mg, 0.090 mmol) at 80°C for overnight. The residue was purified by preparative TLC (DCM: MeOH=30:1) to afford N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(3-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)benzamide (**Compound 69** 28 mg, 0.033 mmol, 36%) as white solid.

Example S66

Synthesis of N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(2-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperazin-1-yl)pyridazine-3-carboxamide (Compound 70)



[473] **Step 1:** A solution of methyl 6-chloropyridazine-3-carboxylate (5 g, 1.0 eq), tert-butyl piperazine-1-carboxylate (5.4 g, 1.0eq), K_2CO_3 (8 g, 2.0 eq) in DMSO (30 ml) was stirred at 100 °C for 3 h. TLC showed complete reaction of starting materials. Water was added and the mixture stirred. The mixture was filtered through a Celite pad to give methyl 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridazine-3-carboxylate (7.7 g). ESI-MS:323.2$[M+H]^+$.

[474] **Step 2:** To a solution of methyl 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridazine-3-carboxylate (500 mg, 1.0 eq) in MeOH/THF/H_2O (4ml/8ml/3ml) was added NaOH (310 mg, 5.0 eq). The reaction was stirred at Rt for 3 h. The solvent was removed and 1M HCl aqueous solution added to adjust to aqueous pH=6. The mixture was extracted with EA, dried over Na_2SO_4 and concentrated to give 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridazine-3-carboxylic acid (426 mg). ESI-MS:309.2$[M+H]^+$.

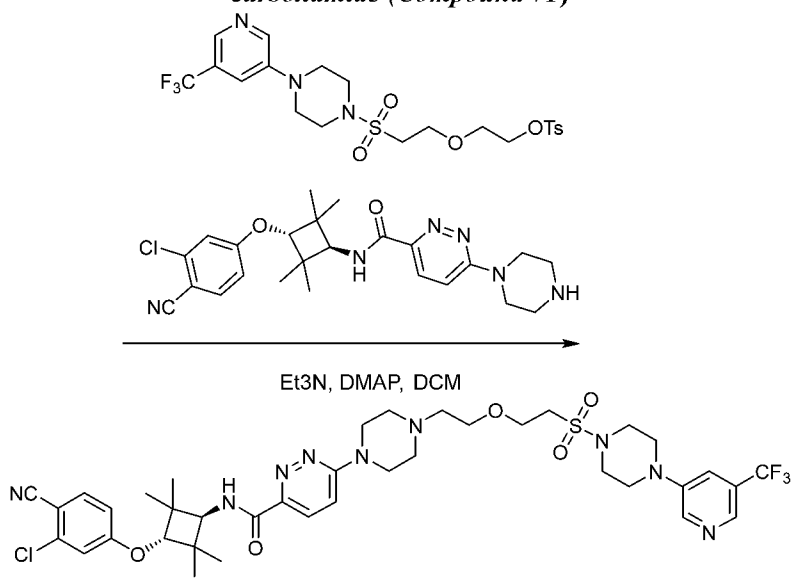
[475] **Step 3:** To a solution of 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridazine-3-carboxylic acid (210 mg, 1.0 eq) in DMF (3 ml) was added HATU (389 mg, 1.5 eq), DIEA (264 mg, 3.0 eq) and 4-(((1r,4r)-4-aminocyclohexyl)oxy)-2-chlorobenzonitrile (196 mg, 1.0 eq). The reaction was stirred at Rt for 1 h. DCM and H2O, were added, then the organic layers was washed with NaCl aqueous solution once, dried over MgSO4 and concentrated. The mixture was purified by column chromatography on silica gel eluted with PE/EA (1:1) to give tert-butyl 4-(6-(((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)carbamoyl)pyridazin-3-yl)piperazine-1-carboxylate (183 mg). ESI-MS:541.2$[M+H]^+$

[476] **Step 4:** To a solution of tert-butyl 4-(6-(((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)carbamoyl)pyridazin-3-yl)piperazine-1-carboxylate (183 mg, 1.0 eq) in DCM (8 ml) was added TFA (4 ml). The mixture was stirred at Rt for 1 h. The solvent was removed to afford N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(piperazin-1-yl)pyridazine-3-carboxamide (106 mg) ESI-MS:441.2$[M+H]^+$.

[477] **Step 5:** A solution of N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(piperazin-1-yl)pyridazine-3-carboxamide (106 mg, 1.0 eq), K_2CO_3 (67 mg, 2.0 eq), KI (20 mg, 0.5 eq) and 2-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl 4-methylbenzenesulfonate (129 mg, 1.0 eq) in CH_3CN (3 ml) was stirred at 80 °C for 4 h.The solvent was removed and DCM and H_2O were added, the organic layers were washed with NaCl aqueous solution once, dried over Na_2SO4 and concentrated. The mixture was purified by pre-TLC (DCM:MeOH=20:1) to afford the product N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(2-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperazin-1-yl)pyridazine-3-carboxamide (**Compound 70**, 25 mg). ESI-MS: 806.3$[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 2.3 Hz, 1H), 8.38 (s, 1H), 8.00 (d, J = 9.5 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.55 (t, J = 9.4 Hz, 1H), I7.33 (s, 1H), 7.00 (d, J = 2.2 Hz, 1H), 6.95 (d, J = 9.5 Hz, 1H), 6.85 (dd, J = 8.7, 2.2 Hz, 1H), 4.32 (t, J = 9.9 Hz, 1H), 4.05 (dd, J = 11.3, 7.6 Hz, 1H), 3.91 (t, J = 5.6 Hz, 2H), 3.76 (d, J = 24.0 Hz, 4H), 3.56 – 3.45 (m, 4H), 3.42 – 3.33 (m, 4H), 3.28 (t, J = 5.8 Hz, 2H), 2.68 (s, 5H), 2.20 (dt, J = 18.2, 9.4 Hz, 4H), 1.66 (dd, J = 23.6, 10.2 Hz, 5H), 1.47 (dd, J = 22.6, 10.6 Hz, 2H).

Example S67

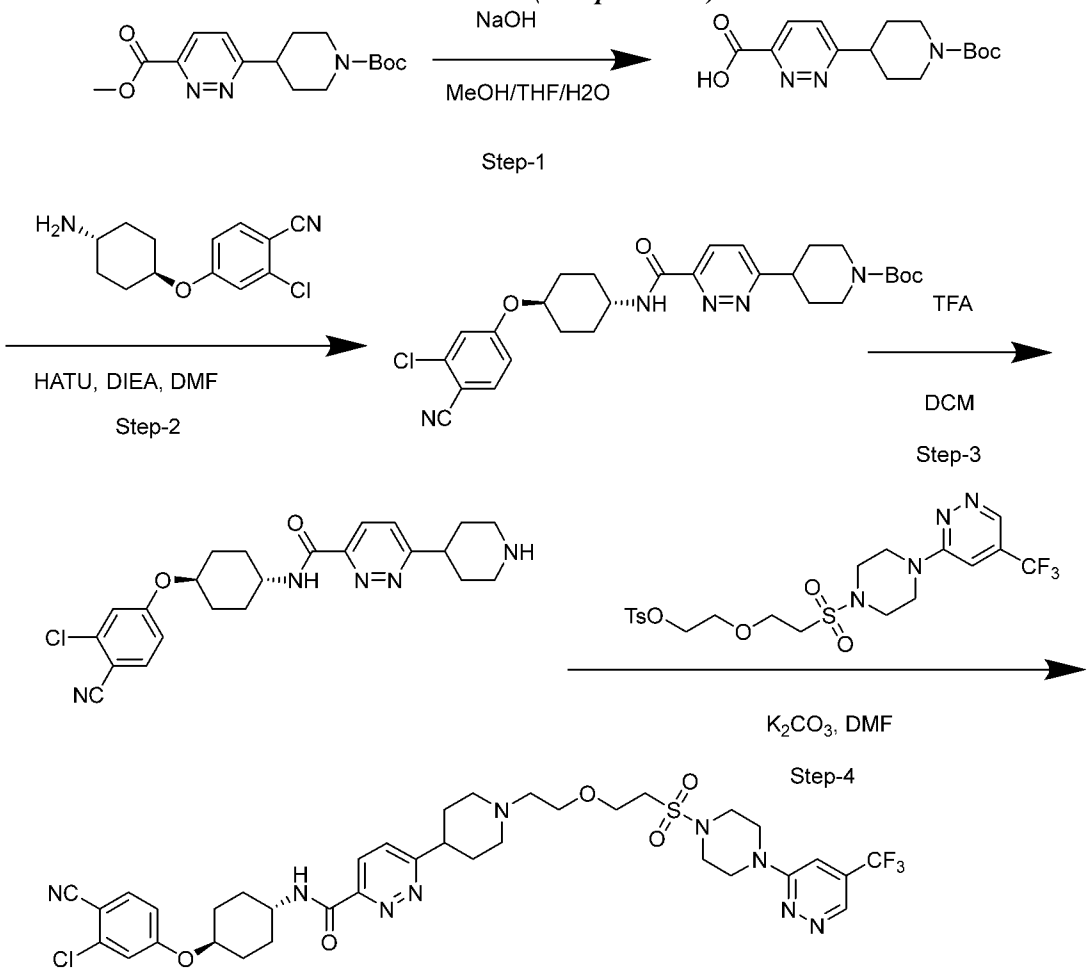
Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(2-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperazin-1-yl)pyridazine-3-carboxamide (Compound 71)



[478] A solution of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(piperazin-1-yl)pyridazine-3-carboxamide (52.4 mg, 1.0 eq), 2-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl4-methylbenzenesulfonate (60 mg, 1.0 eq), K_2CO_3 (47 mg, 3.0 eq) and KI (9.3 mg, 0.5 eq) in CH_3CN (3 ml) was stirred at 80 °C for 4 h. The mixture was filtered, and the filtrate was concentrated, then purified by pre-TLC (DCM:MeOH=20:1) to afford N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(2-(2-((4-(5-(trifluoromethyl)pyridin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperazin-1-yl)pyridazine-3-carboxamide (**Compound 71**, 18 mg), ESI-MS:834.3$[M+H]^+$, ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 2.7 Hz, 1H), 8.39 (s, 1H), 8.14 (d, J = 9.0 Hz, 1H), 8.01 (d, J = 9.4 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.33 (s, 1H), 6.98 (t, J = 5.8 Hz, 2H), 6.81 (dd, J = 8.7, 2.4 Hz, 1H), 4.19 (d, J = 9.0 Hz, 1H), 4.07 (s, 1H), 3.92 (s, 2H), 3.50 (dd, J = 6.2, 3.7 Hz, 4H), 3.38 (dd, J = 6.1, 3.8 Hz, 4H), 3.29 (t, J = 5.8 Hz, 2H), 2.69 (s, 5H), 2.25 (dd, J = 31.8, 24.2 Hz, 1H), 2.10 – 1.91 (m, 1H), 1.63 (d, J = 7.1 Hz, 5H), 1.33 – 1.22 (m, 12H).

Example S68

Synthesis of N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(1-(2-(2-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazine-3-carboxamide (Compound 72)



[479] **Step 1:** Methyl 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)pyridazine-3-carboxylate (85 mg, 0.264 mmol) was dissolved in THF/MeOH(1 mL/1 mL), and NaOH (31.74 mg, 0.793 mmol) and H_2O (0.5 mL) were added. Then the reaction was stirred at RT for 2 h. The raction was then concentrated, acidified with 1M HCl aqueous to pH=3-4, concentrated, extracted with DCM/MeOH, and purified by pre-TLC eluting with DCM/MeOH=20/1 twice to afford the product 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)pyridazine-3-carboxylic acid (80 mg).

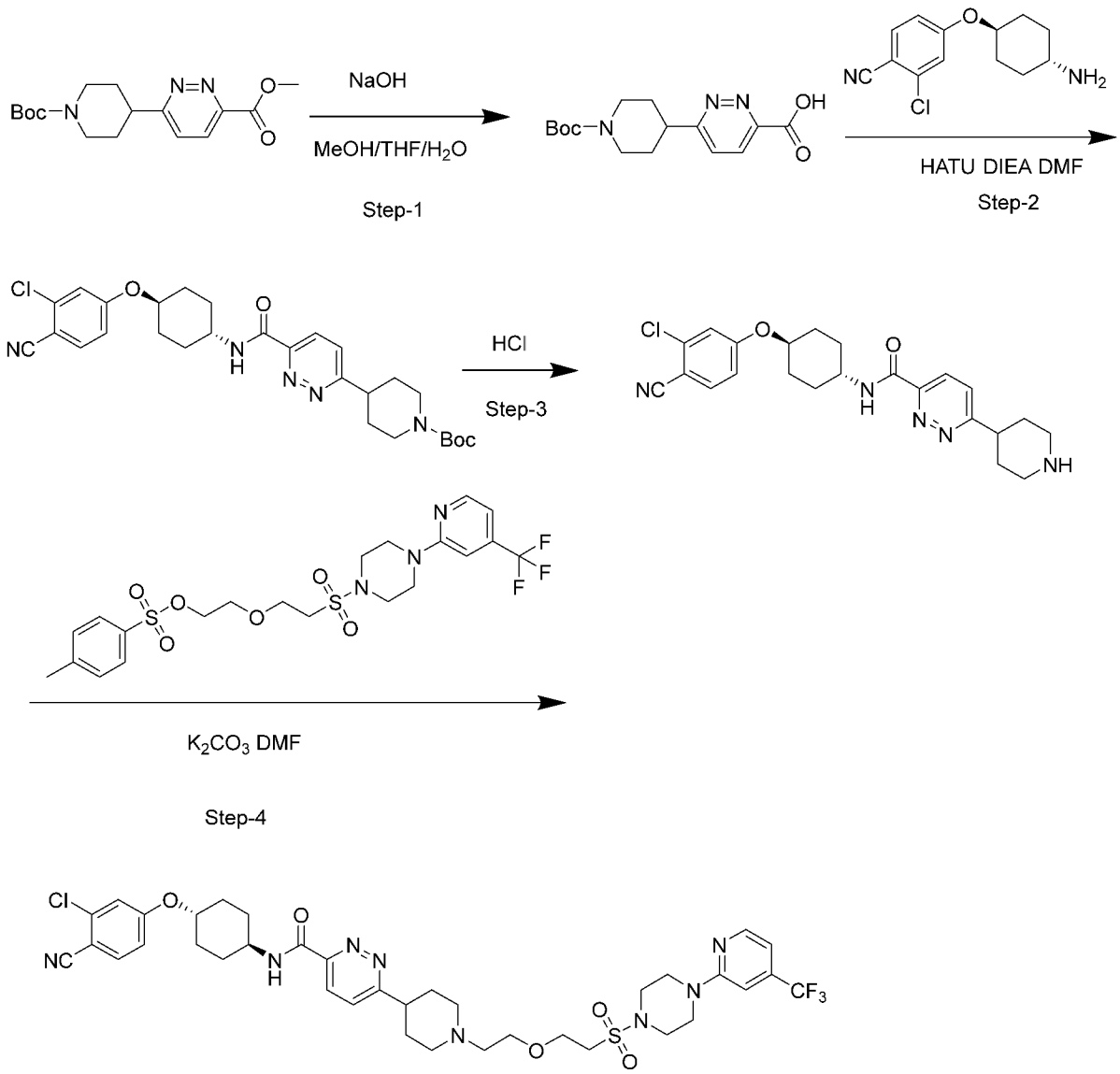
[480] **Step 2:** To a mixture of 2-chloro-4-{[(1r,4r)-4-aminocyclohexyl]oxy}benzene-1-carbonitrile (65.26 mg, 0.260 mmol), 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)pyridazine-3-carboxylic acid (80 mg, 0.260 mmol), and HATU (148.46 mg, 0.390 mmol) in DMF (1 mL) was added DIEA (100.93 mg, 0.781 mmol), and the reaction then stirred at RT for 16 h. The reaction was then concentrated and purified by pre-TLC eluting with EA/PE=1/1 to afford the product tert-butyl 4-(6-(((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)carbamoyl)pyridazin-3-yl)piperidine-1-carboxylate (75 mg).

[481] **Step 3:** To a solution of tert-butyl 4-(6-(((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)carbamoyl)pyridazin-3-yl)piperidine-1-carboxylate (75 mg, 0.139 mmol) in DCM (2 mL) was added TFA (2 mL, 26.118 mmol) and the reaction was stirred at room temperature for 1 hour. The reaction was complete as detected by TLC (PE: EA= 1:1). The reaction was concentrated in vacuo to afford the product N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(piperidin-4-yl)pyridazine-3-carboxamide (60mg).

[482] **Step 4:** To a solution 2-{[2-(dioxo{4-[5-(trifluoromethyl)-1,2-diazin-3-yl]piperazin-1-yl}-λ^6-sulfanyl)ethyl]oxy}ethyl 4-methylbenzenesulfonate (73.45 mg, 0.136 mmol) in ACN (1.5 mL) were added N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(piperidin-4-yl)pyridazine-3-carboxamide (60 mg, 0.136 mmol), K_2CO_3 (56.39 mg, 0.408 mmol), and potassium iodide (2.26 mg, 0.014 mmol), and the reaction was stirred at 80 °C for 16 h. The reaction was concentrated in vacuo and purified by pre-TLC to afford N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(1-(2-(2-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazine-3-carboxamide (**Compound 72**, 25 mg). ESI-MS: 806.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.25 (d, J = 8.7 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.55 (t, J = 10.6 Hz, 2H), 7.07 (s, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.86 (dd, J = 8.7, 2.4 Hz, 1H), 4.39 – 4.26 (m, 1H), 4.09 (dd, J = 11.3, 7.3 Hz, 1H), 3.94 – 3.86 (m, 5H), 3.72 (s, 2H), 3.58 – 3.36 (m, 4H), 3.29 (t, J = 5.7 Hz, 2H), 3.13 (d, J = 42.5 Hz, 3H), 2.69 (s, 2H), 2.20 (t, J = 12.0 Hz, 5H), 2.02 (s, 4H), 1.81 – 1.58 (m, 4H), 1.52 (dd, J = 22.7, 10.2 Hz, 2H).

Example S69

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide(Compound 73)



[483] **Step 1:** Methyl 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)pyridazine-3-carboxylate(88 mg, 0.274 mmol) was dissolved in THF/MeOH(1.5 mL/1.5 mL), and NaOH (32.86 mg, 0.821 mmol) and H_2O (1.5 mL) were added. Then the reaction was stirred at RT for 2h. The raction was then concentrated, acidified with 1M HCl aqueous to pH=3-4, concentrated, extracted with DCM/MeOH, and purified by pre-TLC eluting with DCM/MeOH=20/1 twice to afford the product 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)pyridazine-3-carboxylic acid (80 mg).

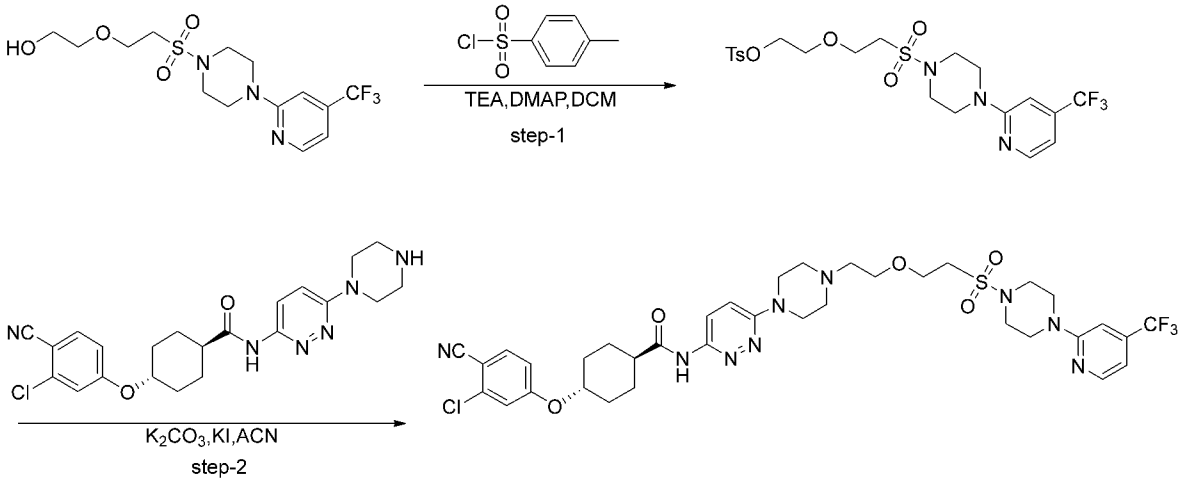
[484] **Step 2**: To a mixture of 2-chloro-4-{[(1r,4r)-4-aminocyclohexyl]oxy}benzene-1-carbonitrile (65.26 mg, 0.260 mmol), 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)pyridazine-3-carboxylic acid(80 mg, 0.260 mmol), and HATU (148.46 mg, 0.390 mmol) in DMF(1 mL) was added DIEA (100.93 mg, 0.781 mmol), and the reaction then stirred at RT for 16h. The reaction was then concentrated and purified by pre-TLC eluting with EA/PE=1/1 to afford the product tert-butyl 4-(6-(((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)carbamoyl)pyridazin-3-yl)piperidine-1-carboxylate (92 mg).

[485] **Step 3:** To a solution of tert-butyl 4-(6-(((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)carbamoyl)pyridazin-3-yl)piperidine-1-carboxylate (92 mg, 0.170 mmol) in DCM (1 mL) was added TFA (2 mL, 26.118 mmol) and the reaction was stirred at room temperature for 1 hour. The reaction was complete as detected by TLC (PE: EA= 1:1). The reaction was concentrated in vacuo to afford the product N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(piperidin-4-yl)pyridazine-3-carboxamide (71mg).

[486] **Step 4:** To a solution 2-{[2-(dioxo{4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-λ⁶-sulfanyl)ethyl]oxy}ethyl 4-methylbenzenesulfonate (90.31 mg, 0.168 mmol) in ACN (2 mL) were added 6-(hexahydropyridin-4-yl)-N-[(1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]cyclohexyl]-1,2-diazine-3-carboxamide (74 mg, 0.168 mmol), K2CO3 (69.74 mg, 0.505 mmol), and potassium iodide (2.79 mg, 0.017 mmol), and the reaction was stirred at 80℃ for 16 h. The reaction was concentrated in vacuo and purified by pre-TLC to afford N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(1-(2-(2-((4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazine-3-carboxamide (**Compound 73**, , 38 mg). ESI-MS: 806.4[M+H]+. 1H NMR (400 MHz, DMSO) δ 9.00 (d, J = 8.2 Hz, 1H), 8.33 (d, J = 5.1 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.24 – 7.07 (m, 2H), 6.90 (d, J = 5.0 Hz, 1H), 4.54 (t, J = 4.3 Hz, 1H), 3.91 (dd, J = 7.7, 3.6 Hz, 1H), 3.79 – 3.66 (m, 5H), 3.54 (s, 2H), 3.38 (t, J = 5.7 Hz, 2H), 3.31 – 3.17 (m, 5H), 2.94 (s, 3H), 2.44 (s, 2H), 2.18 – 1.96 (m, 4H), 1.91 (d, J = 10.5 Hz, 2H), 1.78 (d, J = 31.8 Hz, 3H), 1.73 – 1.60 (m, 2H), 1.54 (t, J = 11.5 Hz, 2H).

Example S70

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 74)

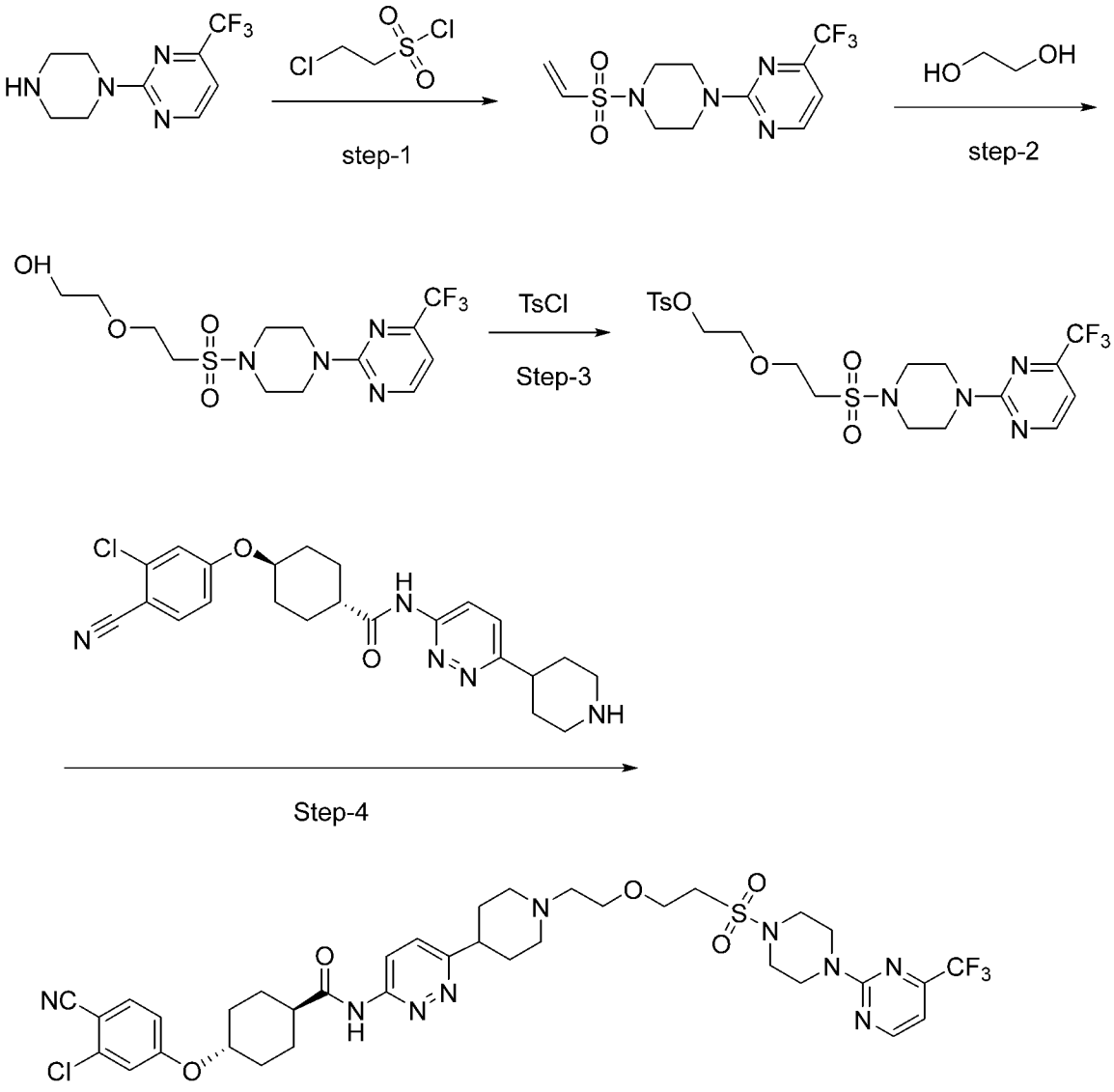


[487] **Step 1:** To a mixture of 2-{[2-(dioxo{4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-λ6-sulfanyl)ethyl]oxy}ethan-1-ol (100 mg, 0.261 mmol) and TEA (0.5 mL) in DCM (5 mL) was added 4-methylbenzenesulfonyl chloride (74.59 mg, 0.391 mmol) and DMAP (5 mg, 0.026 mmol). The reaction mixture was stirred at rt overnight, then the residue was purified by preparative TLC (PE: EA=1:1) to afford 2-{[2-(dioxo{4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-λ6-sulfanyl)ethyl]oxy}ethyl 4-methylbenzenesulfonate (50 mg, 0.093 mmol).

[488] **Step 2:** To a mixture of 2-{[2-(dioxo{4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-λ6-sulfanyl)ethyl]oxy}ethyl 4-methylbenzenesulfonate (50 mg, 0.093 mmol) and (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(piperazin-1-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide (100 mg, 0.227 mmol) in ACN (5 mL) was added K_2CO_3 (38.56 mg, 0.279 mmol) and KI (1.54 mg, 0.009 mmol). The reaction mixture was stirred at 90 °C overnight, then the residue was purified by preparative TLC (DCM: MeOH=20:1) to afford (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-{6-[4-(2-{[2-(dioxo{4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-λ6-sulfanyl)ethyl]oxy}ethyl)piperazin-1-yl]-1,2-diazin-3-yl}(1r,4r)-cyclohexanecarboxamide (**Compound 74**, 15 mg).ESI-MS: 806.4 $[M+H]^+$. ^{1}HNMR(400MHz, DMSO) δ 10.61 (s, 1H), 8.29 (d,J = 5.1Hz, 1H), 8.02 (d,J = 9.8Hz, 1H), 7.85 (d,J = 8.8Hz, 1H), 7.39 (d,J = 2.4Hz, 1H), 7.26 (d,J = 9.9Hz, 1H), 7.14 (dd,J = 7.5, 3.7 Hz, 2H), 6.87 (d,J = 5.1Hz, 1H), 4.64 – 4.51 (m, 1H), 3.76 – 3.69 (m, 5H), 3.55 (t,J = 5.6Hz, 2H), 3.39 (dd,J = 13.3, 7.6Hz, 5H), 3.31 – 3.19 (m, 5H), 2.46 (s, 5H), 2.13 (d,J = 9.7Hz, 2H), 1.92 (d,J = 11.1Hz, 2H), 1.66 (dd,J = 24.6, 11.1Hz, 2H), 1.38 (dt,J = 14.1, 6.9Hz, 2H), 1.23 (s, 3H).

Example S71

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 75)



[489] **Step 1: To a** solution of 2-(piperazin-1-yl)-4-(trifluoromethyl)pyrimidine (100 mg,0.431 mmol) and Et_3N (174 mg,1.723 mmol) in DCM (2 ml) was added dropwise 2-chloroethane-1-sulfonyl chloride (106 mg, 0.646 mmol). The mixture was stirred at rt overnight. The mixture was purified by pre-TLC eluting with EA/PE=1/2 to afford the product 4-(trifluoromethyl)-2-(4-(vinylsulfonyl)piperazin-1-yl)pyrimidine (75 mg) ESI-MS:323.1$[M+H]^+$.

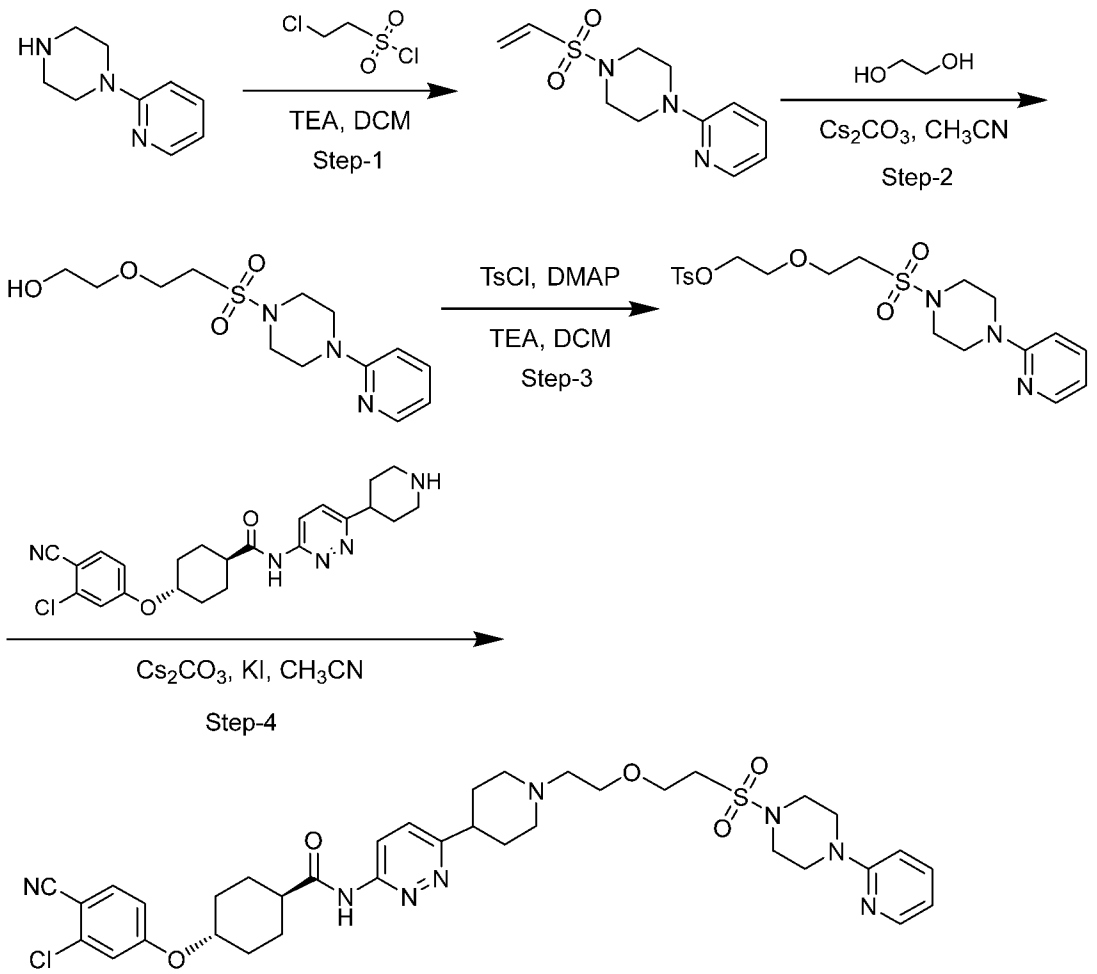
[490] **Step 2:** A solution of 4-(trifluoromethyl)-2-(4-(vinylsulfonyl)piperazin-1-yl)pyrimidine (75 mg,0.232mmol), ethane-1,2-diol (28.8 mg, 0.464 mmol) and Cs_2CO_3 (152 mg, 0.464 mmol) in CH_3CN (6 ml) was stirred at 50 °C for 3 h. The mixture was filtered and the filtrate was concentrated, then the crude was purified by pre-TLC eluting with DCM/MeOH=20/1 to afford the product 2-(2-((4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethan-1-ol(60 mg) ESI-MS:385.1$[M+H]^+$.

[491] **Step 3:** To a solution of 2-(2-((4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethan-1-ol (60 mg,0.156 mmol), Et3N (48 mg,0.469 mmol) and DMAP (4.0 mg,0.031 mmol) in DCM (2 ml) was added TsCl (75 mg,0.391 mmol) at ice-bath. The reaction was stirred at rt overnight. The mixture was concentrated and purified by pre-TLC eluting with DCM/MeOH=20/1 to afford the product 2-(2-((4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl 4-methylbenzenesulfonate (63 mg) ESI-MS:539.1$[M+H]^+$.

[492] **Step 4:** A solution of 2-(2-((4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl 4-methylbenzenesulfonate (63mg,0.117mmol), (1r,4R)-N-(6-(1-(l2-chloranyl)-1λ4-piperidin-4-yl)pyridazin-3-yl)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxamide (55.8 mg,0.117 mmol), K_2CO3 (49 mg, 0.351 mmol) and KI (9.7 mg, 0.058 mmol) in CH_3CN was stirred at 75 °C overnight. The mixture was filtered and the filtrate was concentrated, then the crude was purified by pre-TLC eluting with DCM/MeOH=10/1 to afford the product (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 75**, 18 mg). ESI-MS:806.3$[M+H]^+$, ^1H NMR (400 MHz, CDCl3) δ 9.42 (s, 1H), 8.49 (dd, J = 22.8, 7.0 Hz, 2H), 7.57 (d, J = 8.7 Hz, 1H), 7.43 (d, J = 9.2 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 6.89 – 6.77 (m, 2H), 4.41 – 4.24 (m, 1H), 4.09 – 3.94 (m, 4H), 3.90 (t, J = 5.7 Hz, 2H), 3.76 (s, 2H), 3.43 – 3.32 (m, 4H), 3.25 (t, J = 5.9 Hz, 3H), 2.67 (s, 2H), 2.30 – 2.11 (m, 5H), 2.01 (d, J = 4.9 Hz, 2H), 1.77 (dd, J = 24.4, 11.0 Hz, 3H), 1.59 (dd, J = 23.3, 9.9 Hz, 4H), 1.31 (d, J = 19.6 Hz, 3H).

Example S72

Synthesis of (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(1-{2-[(2-{dioxo[4-(pyridin-2-yl)piperazin-1-yl]-λ6-sulfanyl}ethyl)oxy]ethyl}hexahydropyridin-4-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide (Compound 76)



[493] **Step 1:** To a solution of 1-(pyridin-2-yl)piperazine (200 mg, 1.225 mmol) in DCM (10 mL) were added TEA (0.511 mL, 3.676 mmol) and 2-chloroethane-1-sulfonyl chloride (199.74 mg, 1.225 mmol), and the reaction was stirred at RT for 3 hours. The reaction was complete as detected by TLC (DCM: MeOH= 20:1). The reaction was chromatographed on silica gel (CH_3OH in DCM 0:100→1:100→2:100) to give 4-[dioxo(vinyl)-λ6-sulfanyl]-1-(pyridin-2-yl)piperazine (200 mg, 0.790 mmol, 64.45%) as a yellow solid.

[494] **Step 2:** To a solution of 4-[dioxo(vinyl)-λ6-sulfanyl]-1-(pyridin-2-yl)piperazine (180 mg, 0.711 mmol) in CH_3CN (20 mL) were added Cs_2CO_3 (463.03 mg, 1.421 mmol) and ethylene glycol (0.079 mL, 1.421 mmol), and the reaction was stirred at 50 °C for 8 hours. The reaction was complete detected by TLC (DCM: MeOH= 15:1). The reaction was concentrated in vacuo. The crude product was chromatographed on silica gel (meOH in DCM 0:100→1:100→2:100) to give 2-[(2-{dioxo[4-(pyridin-2-yl)piperazin-1-yl]-λ6-sulfanyl}ethyl)oxy]ethan-1-ol (70 mg, 0.222 mmol, 31.24%).

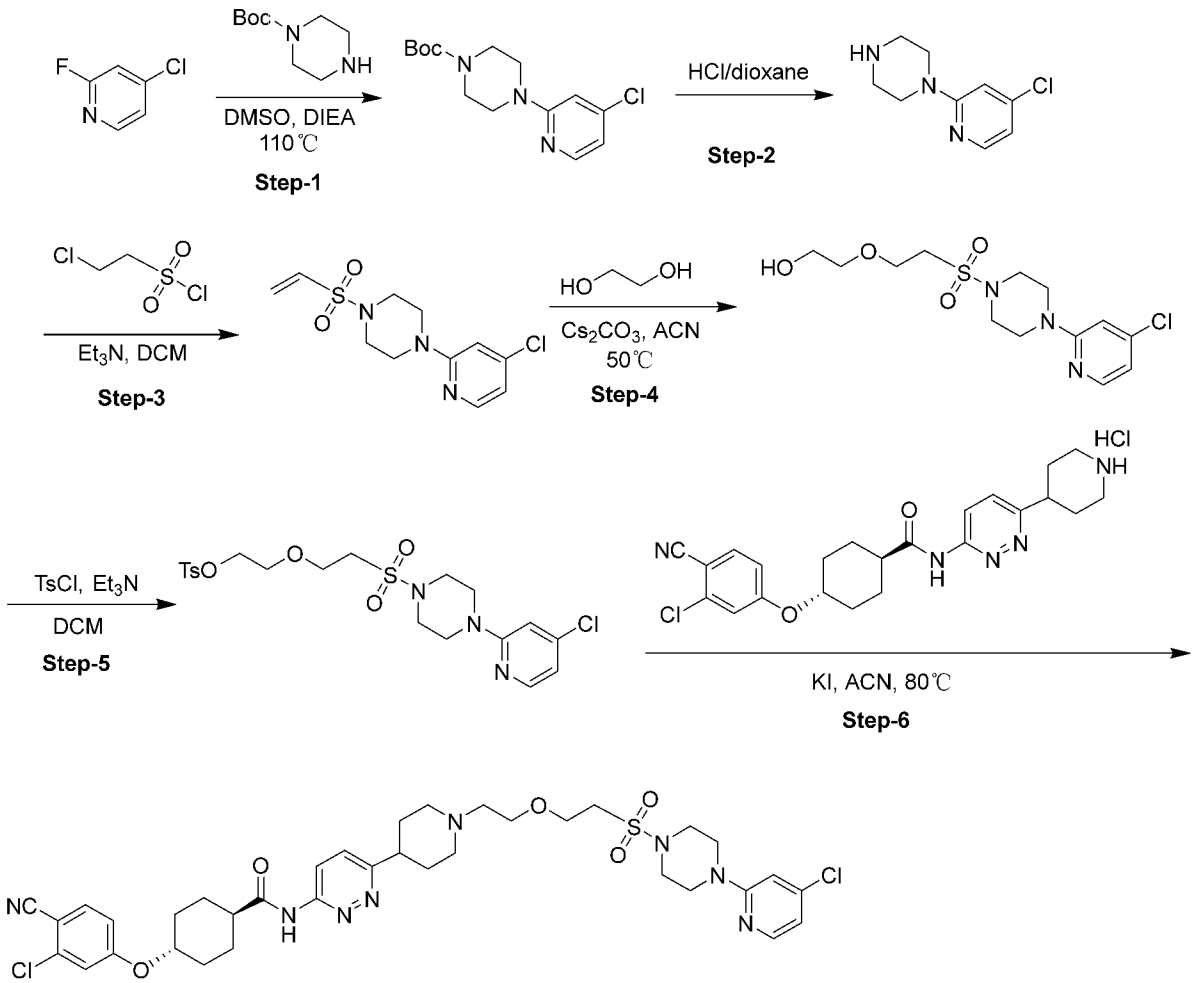
[495] **Step 3:** To a solution of 2-[(2-{dioxo[4-(pyridin-2-yl)piperazin-1-yl]-λ6-sulfanyl}ethyl)oxy]ethan-1-ol (70 mg, 0.222 mmol) in DCM (8 mL) were added TsCl (126.94 mg, 0.666

mmol), TEA (0.154 mL, 1.110 mmol), and DMAP (27.12 mg, 0.222 mmol), and the reaction was stirred at RT for 18 hours. The reaction was complete detected by TLC (DCM: MeOH= 20:1). The reaction concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=20:1) to afford 2-[(2-{dioxo[4-(pyridin-2-yl)piperazin-1-yl]-λ6-sulfanyl}ethyl)oxy]ethyl 4-methylbenzenesulfonate (65 mg, 0.138 mmol, 62.37%) as a white solid.

[496] **Step 4:** To a solution of 2-[(2-{dioxo[4-(pyridin-2-yl)piperazin-1-yl]-λ6-sulfanyl}ethyl)oxy]ethyl 4-methylbenzenesulfonate (60 mg, 0.128 mmol) in CH_3CN (8 mL) were added K_2CO_3 (52.98 mg, 0.383 mmol), potassium iodide (21.21 mg, 0.128 mmol), and (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(hexahydropyridin-4-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide hydrochloride (60.87 mg, 0.128 mmol), and the reaction was stirred at 85 °C for 4 hours. The reaction was complete detected by TLC (DCM: MeOH= 10:1). The reaction was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=10:1) to afford (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(1-{2-[(2-{dioxo[4-(pyridin-2-yl)piperazin-1-yl]-λ6-sulfanyl}ethyl)oxy]ethyl}hexahydropyridin-4-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide (***Compound 76***, 10 mg). ESI-MS: 737.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.45 (d, *J* = 9.2 Hz, 1H), 8.34 – 8.08 (m, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.42 (d, *J* = 9.3 Hz, 1H), 7.00 (d, *J* = 2.3 Hz, 1H), 6.85 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.67 (dd, *J* = 7.6, 4.9 Hz, 2H), 4.42 – 4.25 (m, 1H), 3.90 (t, *J* = 5.9 Hz, 2H), 3.77 (s, 2H), 3.66 (t, *J* = 5.1 Hz, 4H), 3.49 (s, 1H), 3.40 (t, *J* = 5.0 Hz, 4H), 3.25 (t, *J* = 5.9 Hz,3H), 3.03 (s, 1H), 2.73 (d, *J* = 49.6 Hz, 3H), 2.39 (s, 1H), 2.25 (d, *J* = 12.5 Hz, 2H), 2.15 (d, *J* = 13.2 Hz, 2H), 2.02 (s, 3H), 1.77 (q, *J* = 12.6 Hz, 3H), 1.59 (q, *J* = 12.0 Hz, 3H).

Example S73

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-chloropyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 77)



[497] **Step 1**: To a solution of 2-methylpropan-2-yl piperazine-1-carboxylate (1416.03 mg, 7.603 mmol) in DMSO (10.0 mL) were added 4-chloro-2-fluoropyridine (1000.0 mg, 7.603 mmol) and Ethyldiisopropylamine (1965.33 mg, 15.206 mmol), and the reaction was stirred at 110 °C for 5 h (PE:EA=5:1).The reaction mixture was quenched with water and solid appeared. The resulting mixture was filtered. The cake was washed with water, dried to afford 2-methylpropan-2-yl 4-[4-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxylate(1960.9 mg, 5.918 mmol, 77.84%).

[498] **Step 2**: To a flask containing 2-methylpropan-2-yl 4-(4-chloropyridin-2-yl)piperazine-1-carboxylate (1906.9 mg, 6.404 mmol) was added EA (15 mL) followed by the addition of HCl/EA (30 mL) at ice-water bath. The mixture was stirred at rt for 4h, then stirred at 40 °C for 2 h (PE:EA=2:1). The reaction was concentrated in vacuo. The residue was dissolved in EA and concentrated in vacuo, and dried to 1-(4-chloropyridin-2-yl)piperazine dihydrochloride (1729.9 mg, 6.393 mmol, 99.83%).

[499] **Step 3**: To a solution of 1-(4-chloropyridin-2-yl)piperazine dihydrochloride (865.0 mg, 3.197 mmol) in DCM (20.0 mL) was added 2-chloroethane-1-sulfonyl chloride (625.34 mg, 3.836 mmol) and Et_3N (3.110 mL, 22.378 mmol) at ice-water bath, and the reaction was stirred at room temperature for 4 hr (PE:EA=2:1). The reaction was was purified using silica gel column chromatography eluting with ethyl

acetate in petroleum ether and dried to afford 1-(4-chloropyridin-2-yl)-4-[dioxo(vinyl)-λ6-sulfanyl]piperazine (674.1 mg, 2.343 mmol, 73.28%).

[500] **Step 4**: To a solution of 1-(4-chloropyridin-2-yl)-4-[dioxo(vinyl)-λ6-sulfanyl]piperazine (674.1 mg, 2.343 mmol) in ACN (60.0 mL) were added ethylene glycol (0.261 mL, 4.685 mmol) and Cs_2CO_3 (1526.52 mg, 4.685 mmol), and the reaction was stirred at 50 °C for 5 hr (DCM:MeOH=20:1). The reaction was filtered and the filtration was concentrated. The residue was diluted with DCM and water. The organic layer was separated, washed with further saturated NaCl solution, and concentrated in vacuo. The residue was purified using silica gel column chromatography eluting with methanol in dichloroform to afford 2-[(2-{[4-(4-chloropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethan-1-ol (363.3 mg, 1.039 mmol, 44.33%). PSI-MS: 350.27, 351.31, 352.27$[M+H]^+$.

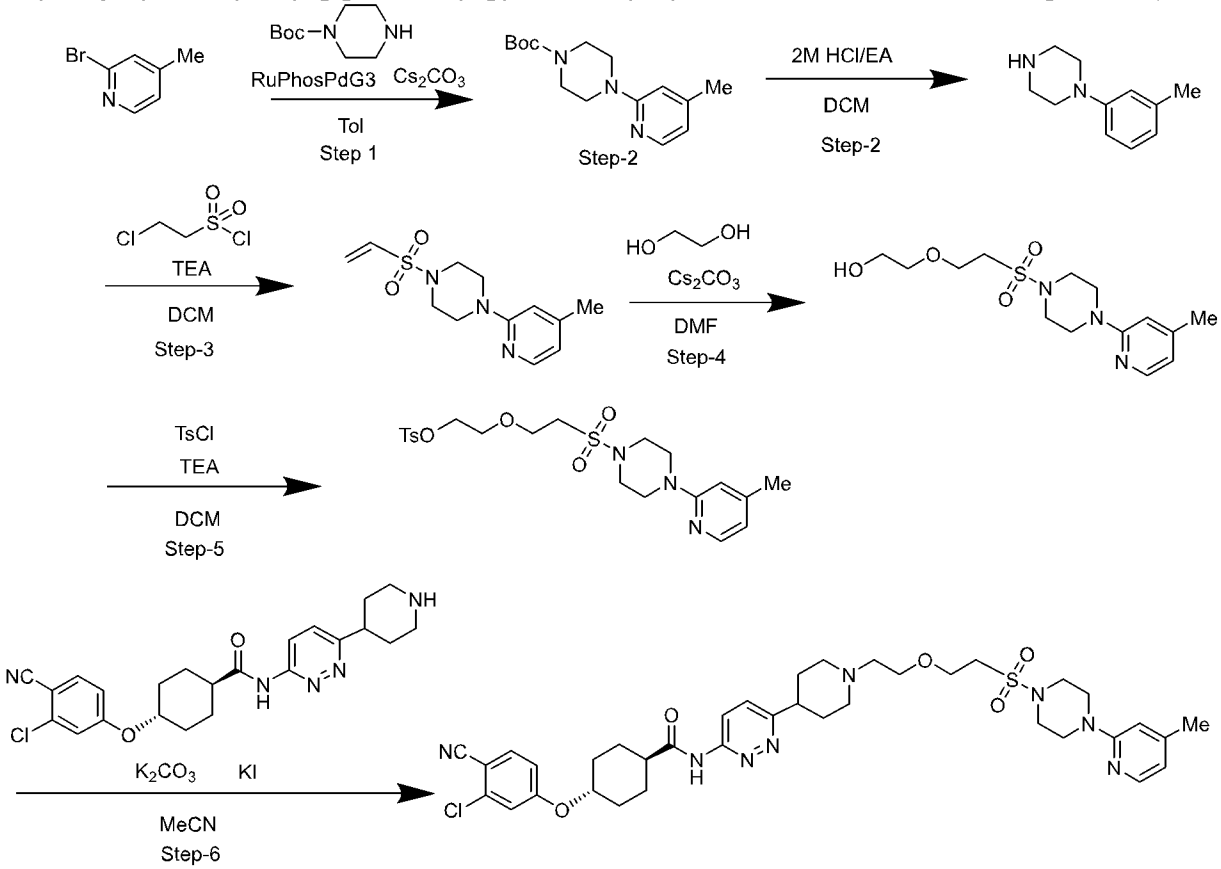
[501] **Step 5**: To a solution of 2-[(2-{[4-(4-chloropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethan-1-ol (363.3 mg, 1.039 mmol) in DCM (10.0 mL) were added TsCl (396.15 mg, 2.078 mmol), Et_3N (0.577 mL, 4.154 mmol) and DMAP (12.69 mg, 0.104 mmol), and the reaction was stirred at room temperature for overnight (DCM:MeOH=20:1). The reaction was diluted with DCM and water. The organic layer was separated, washed with further saturated NH_4Cl solution, water, saturated $NaHCO_3$ solution, water and concentrated in vacuo. The residue was purified using silica gel column chromatography eluting with methanol in dichloroform to afford 2-[(2-{[4-(4-chloropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl 4-methylbenzenesulfonate (520.3 mg, 1.032 mmol, 99.40%).

[502] **Step 6**: To a solution of (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(hexahydropyridin-4-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide hydrochloride (491.80 mg, 1.032 mmol) in ACN (15.0 mL) were added 2-[(2-{[4-(4-chloropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl 4-methylbenzenesulfonate (520.3 mg, 1.032 mmol), K_2CO_3 (356.67 mg, 2.581 mmol), and potassium iodide (85.68 mg, 0.516 mmol), and the reaction was stirred at 80 °C under N_2 overninght (DCM:MeOH=10:1). The reaction was concentrated in vacuo, the residue was diluted with DCM and water. The organic layer was separated, washed with further water, and concentrated in vacuo. 250 mg of the residue was purified by pre-TLC to afford (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(1-{2-[(2-{[4-(4-chloropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl}hexahydropyridin-4-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide (**Compound 77**, 102.8 mg, 0.133 mmol, 12.87%). PSI-MS: 771.40, 772.43,773.37$[M+H]^+$. ^{1}HNMR (400 MHz, DMSO) δ 10.98 (s, 1H), 8.24 (d,J = 9.2 Hz, 1H), 8.07 (d,J = 5.4 Hz, 1H), 7.85 (d,J = 8.8 Hz, 1H), 7.56 (d,J = 9.3 Hz, 1H), 7.40 (d,J = 2.4 Hz, 1H), 7.14 (dd,J = 8.8, 2.4 Hz, 1H), 6.97 (d,J = 1.4 Hz, 1H), 6.72 (dd,J = 5.4, 1.5 Hz, 1H), 4.59 (td,J = 10.4, 5.1 Hz, 1H), 3.74 (t,J = 5.3 Hz, 2H), 3.70 – 3.61 (m, 4H), 3.55 (s, 2H), 3.38 (t,J = 5.8 Hz, 2H), 3.32 (s, 6H), 3.28 – 3.22 (m, 4H),

2.65 – 2.55 (m, 1H), 2.14 (d,J = 9.4 Hz, 2H), 2.03 – 1.90 (m, 3H), 1.90 – 1.58 (m, 6H), 1.40 (dd,J = 22.9, 10.0 Hz, 2H).

Example S74

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-methylpyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide(Compound 78)



[503] **Step 1**: 2-bromo-4-methylpyridine (1 g, 5.813 mmol) was dissolved in Tol (20mL), and RuPhos PdG3 (0.05 g, 0.058 mmol) and Cs_2CO_3 (3.79 g, 11.626 mmol) were added. the mixture exchange N_2 for 3 times, Then the reaction was stirred at 80 °C for 16h. The reaction mixture was quenched by the addition of water (50mL), extracted with EA(3*50mL), dried over Na_2SO_4, concentrated in vacuo, The reaction was concentrated and purified by silica gel eluting with EA/PE=1/1 to afford the product 2-methylpropan-2-yl 4-(4-methylpyridin-2-yl)piperazine-1-carboxylate (334 mg).

[504] **Step 2**: To a soultion of 2-methylpropan-2-yl 4-(4-methylpyridin-2-yl)piperazine-1-carboxylate (334 mg, 1.204 mmol) in DCM (5 mL) was added 2M HCl/EA (10 mL) at 0-5 °C. Then the reaction was stirred at RT for 2 h. The reaction was concentrated in vacuo to afford the product 1-(4-methylpyridin-2-yl)piperazine hydrochloride (334 mg).

[505] **Step 3:** To a soultion of 1-(4-methylpyridin-2-yl)piperazine hydrochloride (347 mg, 1.624 mmol) in DCM (5 mL) was added 2-chloroethane-1-sulfonyl chloride (264.68 mg, 1.624 mmol) at 0-5 °C, Then the reaction was stirred at RT for 2 h.The reaction was concentrated in vacuo and purified by pre-

TLC eluting with DCM/EA=40/1 to afford the product 4-[dioxo(vinyl)-λ6-sulfanyl]-1-(4-methylpyridin-2-yl)piperazine (234 mg).

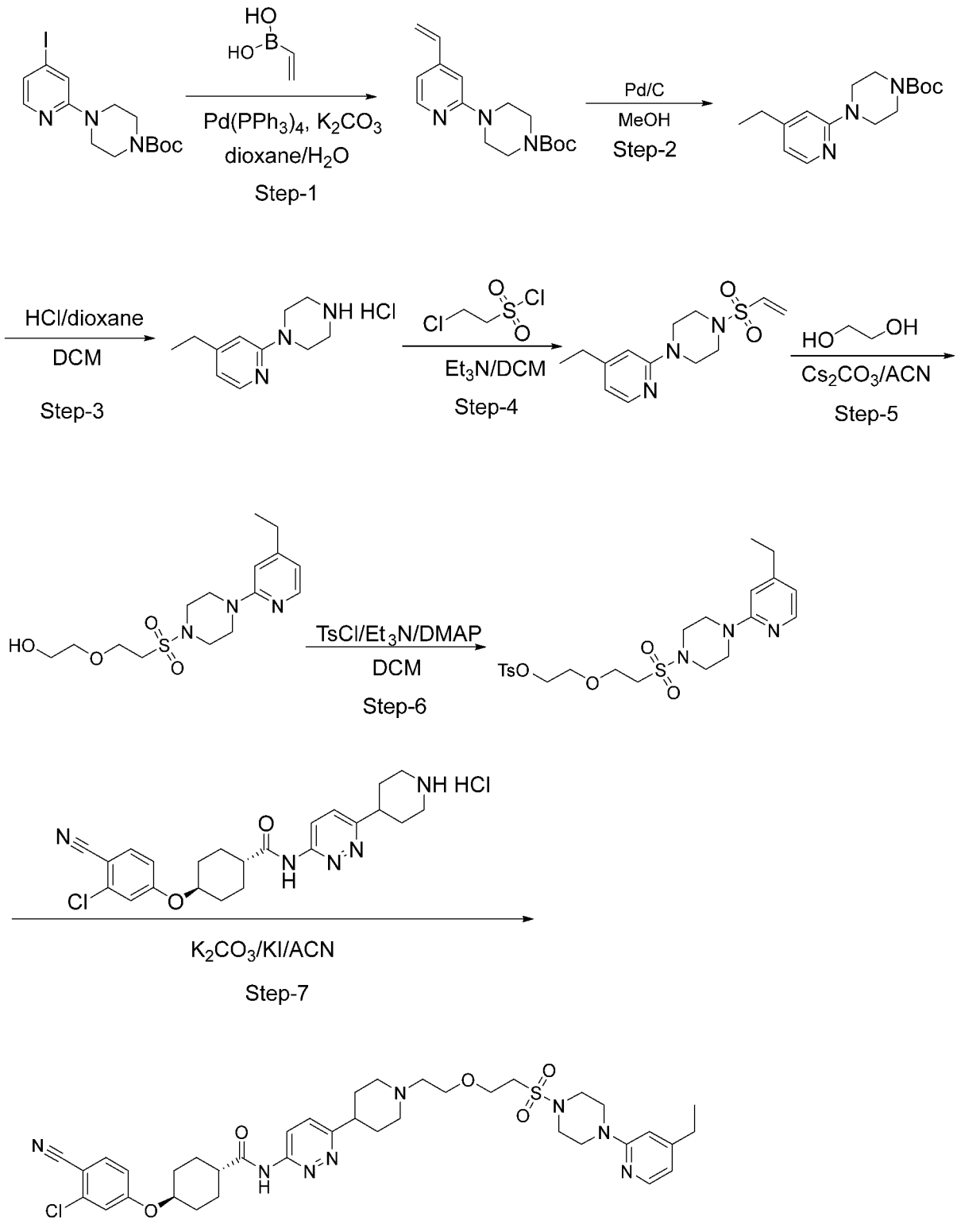
[506] **Step 4:** To a soultion of 4-[dioxo(vinyl)-λ6-sulfanyl]-1-(4-methylpyridin-2-yl)piperazine (234 mg, 0.950 mmol) in DMF (10 mL) was added ethylene glycol (0.106 mL, 1.900 mmol) and Cs_2CO_3 (926.31 mg, 2.850 mmol). Then the reaction was stirred at 80 °C for 12 h. The reaction was concentrated in vacuo and purified by pre-TLC eluting with DCM/MeOH=20/1 to afford the product 2-[(2-{[4-(4-methylpyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethan-1-ol (378 mg).

[507] **Step 5:** To a soultion of 2-[(2-{[4-(4-methylpyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethan-1-ol (378 mg, 1.147 mmol) in DCM (10 mL) was added 4-methylbenzenesulfonyl chloride (262.50 mg, 1.377 mmol), 4-methylbenzenesulfonyl chloride (262.50 mg, 1.377 mmol) and TEA (127.72 mg, 1.262 mmol) at 0-5 °C. Then the reaction was stirred at RT for 1 h. The reaction was concentrated in vacuo and purified by pre-TLC eluting with DCM/MeOH=40/1 to afford the product 2-[(2-{[4-(4-methylpyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl 4-methylbenzenesulfonate (293 mg).

[508] **Step 6:** To a soultion of 2-[(2-{[4-(4-methylpyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl 4-methylbenzenesulfonate (293 mg, 0.606 mmol)in MeCN (20 mL) was added 4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(hexahydropyridin-4-yl)-1,2-diazin-3-yl]cyclohexanecarboxamide hydrochloride (288.70 mg, 0.606 mmol), potassium carbonate (251.19 mg, 1.818 mmol) and potassium iodide (100.57 mg, 0.606 mmol). Then the reaction was stirred at 80°C for 12 h, The reaction was concentrated in vacuo and purified by pre-TLC eluting with DCM/MeOH=10/1 to afford the product 4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(1-{2-[(2-{[4-(4-methylpyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl}hexahydropyridin-4-yl)-1,2-diazin-3-yl]cyclohexanecarboxamide (56 mg). (**Compound 78**, 56 mg). ESI-MS: 751.4 [M+H]+.^{1}H NMR (400 MHz, CDCl3) δ 10.03 (s, 1H), 8.47 (d, J = 9.3 Hz, 1H), 8.05 (d, J = 5.1 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.40 (d, J = 9.3 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.85 (dd, J = 8.8, 2.4 Hz, 1H), 6.55 – 6.46 (m, 2H), 4.33 (dt, J = 10.4, 5.9 Hz, 1H), 3.88 (t, J = 6.0 Hz, 2H), 3.71 – 3.61 (m, 6H), 3.43 – 3.34 (m, 4H), 3.24 (t, J = 6.0 Hz, 2H), 3.16 (s, 1H), 2.97 (s, 1H), 2.86 – 2.78 (m, 1H), 2.68 (s, 1H), 2.31 – 2.10 (m, 9H), 1.97 (s, 4H), 1.83 – 1.54 (m, 6H).

Example S75

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-ethylpyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 79)



[509] **Step 1:** A mixture of 2-methylpropan-2-yl 4-(4-iodopyridin-2-yl)piperazine-1-carboxylate (250 mg, 0.642 mmol), vinylboranediol (69.24 mg, 0.963 mmol), K_2CO_3 (177.53 mg, 1.285 mmol) and $Pd(PPh_3)_4$ (74.22 mg, 0.064 mmol) in dioxane (10 mL) and H_2O (1 mL) was replaced with N_2 for 1 min.

Then the reaction was heated at 100 °C for 2h and purified by pre-TLC eluting with PE/EA=5/1 and got 2-methylpropan-2-yl 4-(4-vinylpyridin-2-yl)piperazine-1-carboxylate (182.1 mg).

[510] **Step 2:** 2-methylpropan-2-yl 4-(4-vinylpyridin-2-yl)piperazine-1-carboxylate (181 mg, 0.625 mmol) and Pd/C 10% (25 mg, 0.235 mmol) in MeOH (8 mL) was replaced with H_2 for 1 min. Then the reaction was stirred at RT under H_2 atmosphere for 16h. LCMS indicated no started material, filtered, concentrated and got 2-methylpropan-2-yl 4-(4-ethylpyridin-2-yl)piperazine-1-carboxylate (180.2 mg).

[511] **Step 3:** 2-methylpropan-2-yl 4-(4-ethylpyridin-2-yl)piperazine-1-carboxylate (180 mg, 0.618 mmol) in DCM (5 mL) was added HCl/dioxane (5 mL, 4mol/L) at RT. Then the reaction was stirred at RT overnight. Concentrated and got 1-(4-ethylpyridin-2-yl)piperazine hydrochloride (132.2 mg).

[512] **Step 4:** A solution of 1-(4-ethylpyridin-2-yl)piperazine hydrochloride (140 mg, 0.615 mmol) and Et_3N (0.427 mL, 3.074 mmol) in DCM (8 mL) was added 2-chloroethane-1-sulfonyl chloride (200.42 mg, 1.229 mmol). Then the reaction was stirred at RT for 16h. Purified by pre-TLC eluting with DCM/MeOH=40/1 and got 1-(4-ethylpyridin-2-yl)-4-(vinylsulfonyl)piperazine (102.2mg).

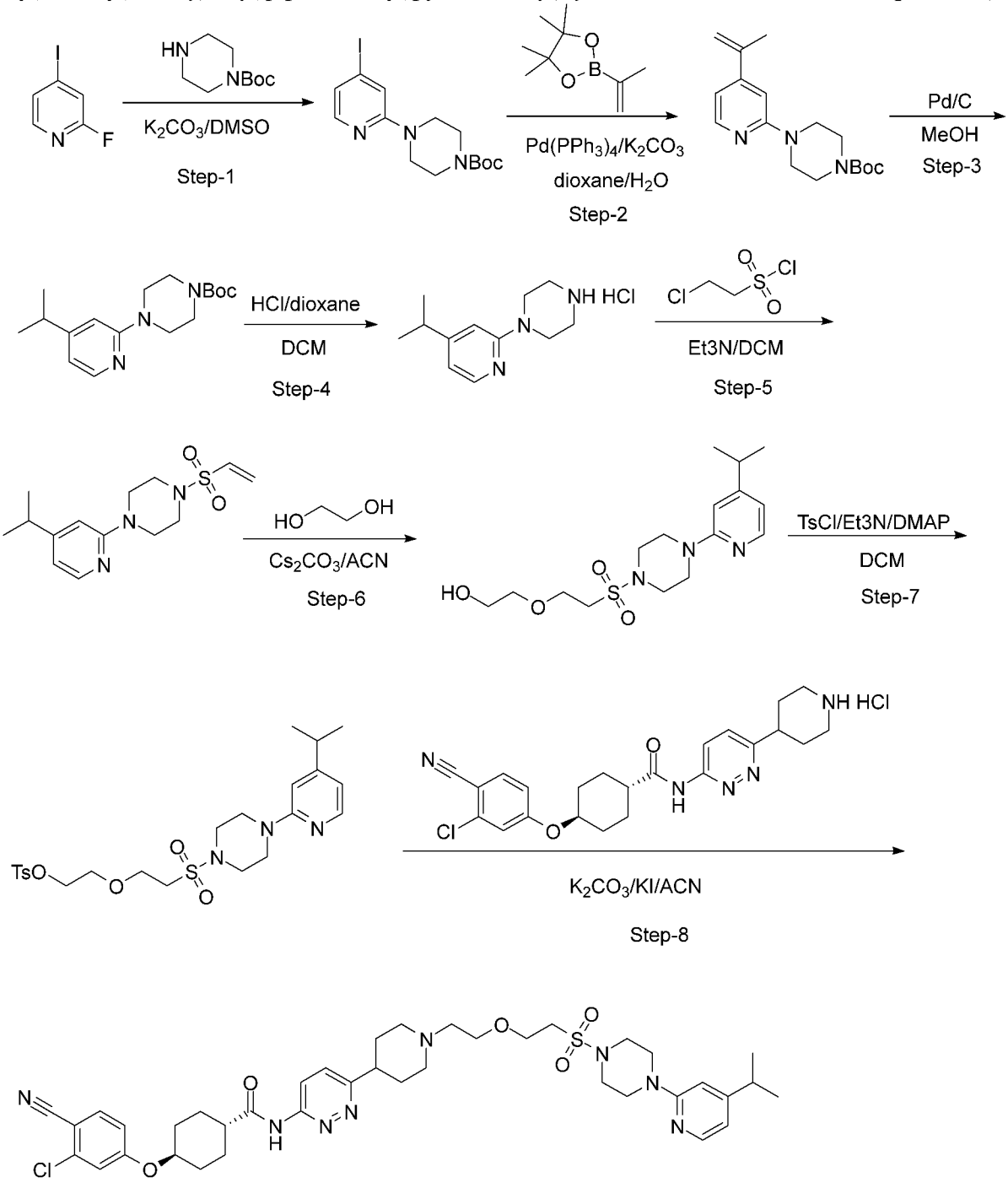
[513] **Step 5:** A solution of 1-(4-ethylpyridin-2-yl)-4-(vinylsulfonyl)piperazine (100 mg, 0.355 mmol), ethylene glycol (0.032 mL, 0.569 mmol) and Cs_2CO_3 (231.60 mg, 0.711 mmol) in ACN (4 mL) was stirred at 50 °C for 16h. Purified by pre-TLC eltuing with DCM/MeOH=20/1 and got 2-(2-((4-(4-ethylpyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethan-1-ol (49 mg).

[514] **Step 6:** A solution of 2-(2-((4-(4-ethylpyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethan-1-ol (49 mg, 0.143 mmol), DMAP (1.74mg, 0.014 mmol) and Et_3N (0.428 mL, 43.31 mmol) in DCM (3mL) was added TsCl (54.40 mg, 0.285 mmol) in portion. After addition, the reaction was stirred at RT overnight. Purified by pre-TLC eluting with PE/EA=1/1 and got 2-(2-((4-(4-ethylpyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl 4-methylbenzenesulfonate (62 mg).

[515] **Step 7:** A mixture of 2-(2-((4-(4-ethylpyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl 4-methylbenzenesulfonate (32 mg, 0.064 mmol), (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(hexahydropyridin-4-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide (28.29 mg, 0.064 mmol),KI (1.07 mg, 0.006 mmol) and K_2CO_3 (17.77 mg, 0.129 mmol)in ACN (2 mL) was heated at reflux for 3h. Purified by pre-TLC eluting with DCM/MeOH=15:1 and 10:1, got the product (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-ethylpyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 79** ,32 mg). ESI-MS: 765.5[M+H]+. ^{1}H NMR (400 MHz, DMSO) δ 11.05 (s, 1H), 10.20 (s, 1H), 8.29 (d, J = 9.2 Hz, 1H), 8.01 (d, J = 5.1 Hz, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.58 (d, J = 9.3 Hz, 1H), 7.40 (d, J = 2.1 Hz, 1H), 7.14 (dd, J = 8.7, 2.1 Hz, 1H), 6.77 (s, 1H), 6.60 (s, 1H), 4.58 (t, J = 10.4 Hz, 1H), 3.98 – 3.74 (m, 4H), 3.62 (s, 5H), 3.44 (t, J = 5.6 Hz, 2H), 3.27 (d, J = 4.1 Hz, 5H), 3.11 (s, 3H), 2.56 (s, 2H), 2.13 (d, J = 12.0 Hz, 5H), 1.94 (d, J = 11.1 Hz, 2H), 1.67 (d, J = 12.2 Hz, 2H), 1.40 (d, J = 12.3 Hz, 2H), 1.24 (s, 1H), 1.16 (t, J = 7.6 Hz, 3H).

Example S76

Synthesis of* 4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-isopropylpyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide*(Compound 80)



[516] **Step 1:** A suspension of 2-fluoro-4-iodopyridine (2 g, 8.969 mmol), 2-methylpropan-2-yl piperazine-1-carboxylate (2.51 g, 13.454 mmol) and K_2CO_3 (3.72 g, 26.907 mmol) in DMSO (10 mL) was heated at 100 °C for 24h. The mixture was concentrated, purified by column chromatography on silic

gel eluting with PE to PE/EA=10/1 and got 2-methylpropan-2-yl 4-(4-iodopyridin-2-yl)piperazine- 1-carboxylate (2.7 g, 6.937 mmol, 77.34%) as a white solid.

[517] **Step 2:** A mixture of 2-methylpropan-2-yl 4-(4-iodopyridin-2-yl)piperazine-1-carboxylate (50 mg, 0.128 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (43.02 mg, 0.256 mmol), K_2CO_3 (35.51 mg, 0.257 mmol) and $Pd(PPh_3)_4$ (14.79 mg, 0.013 mmol) in dioxane (2 mL) and H_2O (0.4 mL) was replaced with N_2 for 1 min. Then the reaction was heated at 100 °C for 2h and purified by pre-TLC eluting with PE/EA=5/1 and got 2-methylpropan-2-yl 4-[4-(prop-1-en-2-yl)pyridin-2-yl] piperazine-1-carboxylate (40 mg, 0.105 mmol, 82.11%).

[518] **Step 3:** A solution of 2-methylpropan-2-yl 4-[4-(prop-1-en-2-yl)pyridin-2-yl]piperazine-1-carboxylate (139 mg, 0.458 mmol) and Pd/C 10% (48 mg, 0.045 mmol) in MeOH (8 mL) was replaced with H_2 for 1 min. Then the reaction was stirred at RT under H_2 atmosphere for 16h. LCMS indicated no started material, filtered, concentrated and got 2-methylpropan-2-yl 4-[4-(prop-2-yl)pyridin-2-yl]piperazine-1-carboxylate (128 mg, 0.419 mmol, 91.48%).

[519] **Step 4:** A solution of 2-methylpropan-2-yl 4-[4-(prop-2-yl)pyridin-2-yl]piperazine-1-carboxylate (160 mg, 0.524 mmol) in DCM (2 mL) was added HCl/dioxane (1 mL, 4mol/L) at RT. Then the reaction was stirred at RT overnight. Concentrated and got 1-[4-(prop-2-yl)pyridin-2-yl]piperazine hydrochloride (240 mg, 0.496 mmol, 94.75%).

[520] **Step 5:** A solution of 1-[4-(prop-2-yl)pyridin-2-yl]piperazine hydrochloride (240 mg, 0.496 mmol) and Et_3N (0.345 mL, 2.482 mmol) in DCM (3 mL) was added 2-chloroethane -1-sulfonyl chloride (161.82 mg, 0.993 mmol). Then the reaction was stirred at RT for 16h. Purified by pre-TLC eluting with DCM/MeOH=40/1 and got 4-[dioxo(vinyl)-λ6- sulfanyl]-1-[4-(prop-2-yl)pyridin-2-yl]piperazine (80 mg, 0.271 mmol, 54.60%).

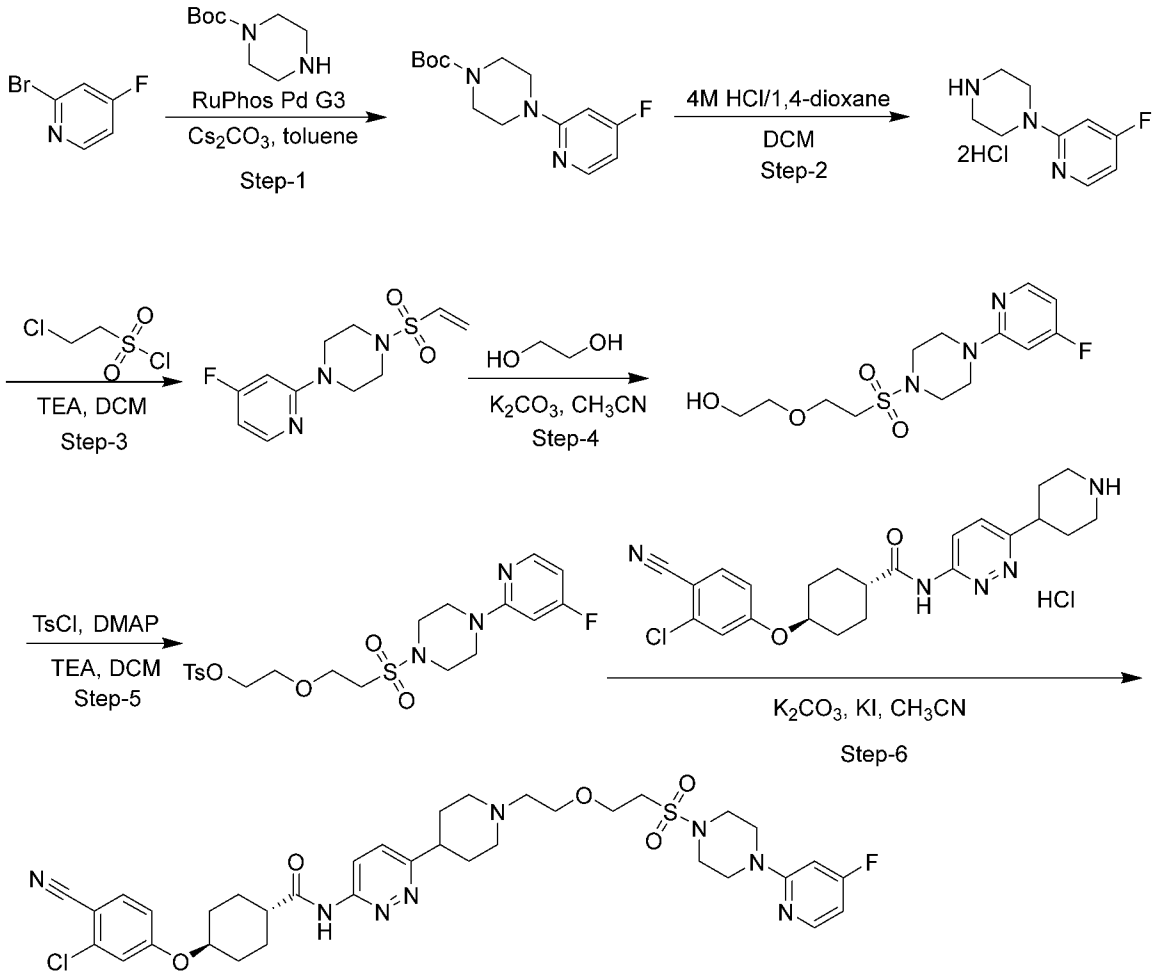
[521] **Step 6:** A solution of 4-[dioxo(vinyl)-λ6-sulfanyl]-1-[4-(prop-2-yl)pyridin-2-yl]piperazine (80 mg, 0.271 mmol), ethylene glycol (0.018 mL, 0.325 mmol) and Cs_2CO_3 (176.48 mg, 0.542 mmol) in ACN (4 mL) was stirred at 50 °C for 16h. Purified by pre-TLC eltuing with DCM/MeOH=20/1 and got 2-{[2-(dioxo{4-[4-(prop-2-yl)pyridin-2-yl]piperazin -1-yl}-λ6-sulfanyl)ethyl]oxy}ethan-1-ol (59 mg, 0.165 mmol, 60.94%).

[522] **Step 7:** To a solution of 2-{[2-(dioxo{4-[4-(prop-2-yl)pyridin-2-yl]piperazin-1-yl}-λ6-sulfanyl)ethyl]oxy}ethan-1-ol (59 mg, 0.165 mmol), DMAP (4.03 mg, 0.033 mmol) and Et_3N (0.115 mL, 0.825 mmol) in DCM (3 mL) was added TsCl (62.93 mg, 0.330 mmol) in portion. After addition, the reaction was stirred at RT overnight. Purified by pre-TLC eluting with PE/EA=1/1 and got 2-{[2-(dioxo{4-[4-(prop-2-yl)pyridin-2-yl]piperazin -1-yl}-λ6-sulfanyl)ethyl]oxy}ethyl 4-methylbenzenesulfonate (65 mg, 0.127 mmol, 76.97%).

[523] **Step 8:** A mixture of 2-{[2-(dioxo{4-[4-(prop-2-yl)pyridin-2-yl]piperazin-1-yl} -λ6-sulfanyl) ethyl]oxy}ethyl 4-methylbenzenesulfonate (32 mg, 0.063 mmol),4-[(3-chloro-4- cya nophenyl)oxy]-N-[6-(hexahydropyridin-4-yl)-1,2-diazin-3-yl]cyclohexanecarboxamide hydrochloride (29.80 mg, 0.063 mmol), KI (10.38 mg, 0.063 mmo l) and K_2CO_3 (17.26 mg, 0.125 mmol)in ACN (2 mL) was heated at reflux for 3h. Purified by pre-TLC eluting with DCM/MeOH=15:1 and 10:1, got the product 4-[(3-chloro-4-cyanophenyl)oxy]-N-{6-[1-(2-{[2-(dioxo{4-[4-(prop-2-yl)pyridin-2-yl]piperazin-1-yl}-λ6-sulfanyl)ethyl]oxy}ethyl)hexahydropyridin-4-yl]-1,2-diazin-3-yl}cyclohexanecarboxamide (**Compound 80**, 31 mg, 0.040 mmol, 63.59%).ESI-MS: 779.4 [M+H]+.1H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 8.22 (d, J = 9.2 Hz, 1H), 8.00 (d, J = 5.2 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 9.3 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.14 (dd, J = 8.8, 2.4 Hz, 1H), 6.70 (s, 1H), 6.57 (d, J = 5.2 Hz, 1H), 4.68 – 4.51 (m, 1H), 3.75 (t, J = 5.7 Hz, 2H), 3.58 (dd, J = 13.9, 8.8 Hz, 6H), 3.37 (t, J = 5.8 Hz, 2H), 3.29 – 3.22 (m, 4H), 2.96 (s, 2H), 2.75 (dt, J = 13.7, 6.8 Hz, 2H), 2.60 (t, J = 11.6 Hz, 2H), 2.43 (s, 1H), 2.14 (d, J = 9.6 Hz, 2H), 2.09 – 1.99 (m, 2H), 1.94 (d, J = 12.1 Hz, 2H), 1.86 – 1.58 (m, 6H), 1.40 (dd, J = 23.1, 10.0 Hz, 2H), 1.14 (d, J = 6.9 Hz, 6H).

Example S77

Synthesis of(1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-fluoropyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 81)



[524] **Step 1:** A solution of 2-bromo-4-fluoropyridine (1.5 g, 8.523 mmol) in toluene (15 mL) was added 2-methylpropan-2-yl piperazine-1-carboxylate (1.90 g, 10.214 mmol), Cs_2CO_3 (5.553 g, 17.023 mmol), RuPhos Pd G3 (350 mg, 0.418 mmol) at room temperature, the yellow mixture was stirred at 90 °C for overnight under N_2 atmosphere. TLC (EA/PE=1/10, Rf=0.5) showed starting material was consumed, reaction showed 3 new spots. The mixture was filtered, washed with EA (20 mL×2), concentrated in vacuo. The residue was purified with silica gel. Chromatography column eluted EA in PE 10% ~ 15% to get 2-methylpropan-2-yl 4-(4-fluoropyridin-2-yl)piperazine-1-carboxylate (300 mg, 1.111 mmol, 13.3%) colorless oil. ESI-Ms: 281.9 $[M+H]^+$.

[525] **Step2 :** To a solution of 2-methylpropan-2-yl 4-(4-fluoropyridin-2-yl)piperazine-1-carboxylate (300 mg, 1.066 mmol) in DCM (2 mL) was added 4 M HCl/1,4-dioane (3 mL) at 0 ~ 5 °C, the yellow mixture was stirred at room temperature for 3 h. TLC (EA/PE=1/10, Rf=0.0) showed starting material consumed, reaction showed mainly a new spot. The mixture was concentrated in vacuo to get 1-(4-fluoropyridin-2-yl)piperazine dihydrochloride (260 mg, crude) light yellow solid .

[526] **Step 3:** To a solution of 1-(4-fluoropyridin-2-yl)piperazine dihydrochloride (260 mg, 1.023 mmol) in DCM (3 mL) was added TEA (361.67 mg, 3.581 mmol), 2-chloroethane-1-sulfonyl chloride (216.81 mg, 1.330 mmol) at 0 ~ 5 °C, the yellow mixture was stirred at room temperature for 2 h. TLC

(MeOH/DCM=1/15, Rf=0.10) showed starting material a little remained, reaction had several new spots. The mixture was directly purified with silica gel. Chromatography column eluted MeOH in DCM 3% ~ 5% to get 4-[dioxo(vinyl)-λ6-sulfanyl]-1-(4-fluoropyridin-2-yl)piperazine (180 mg, 0.332 mmol, 32.42%, 50% purity) yellow oil. ESI-Ms: 272.19 $[M+H]^{+}$.

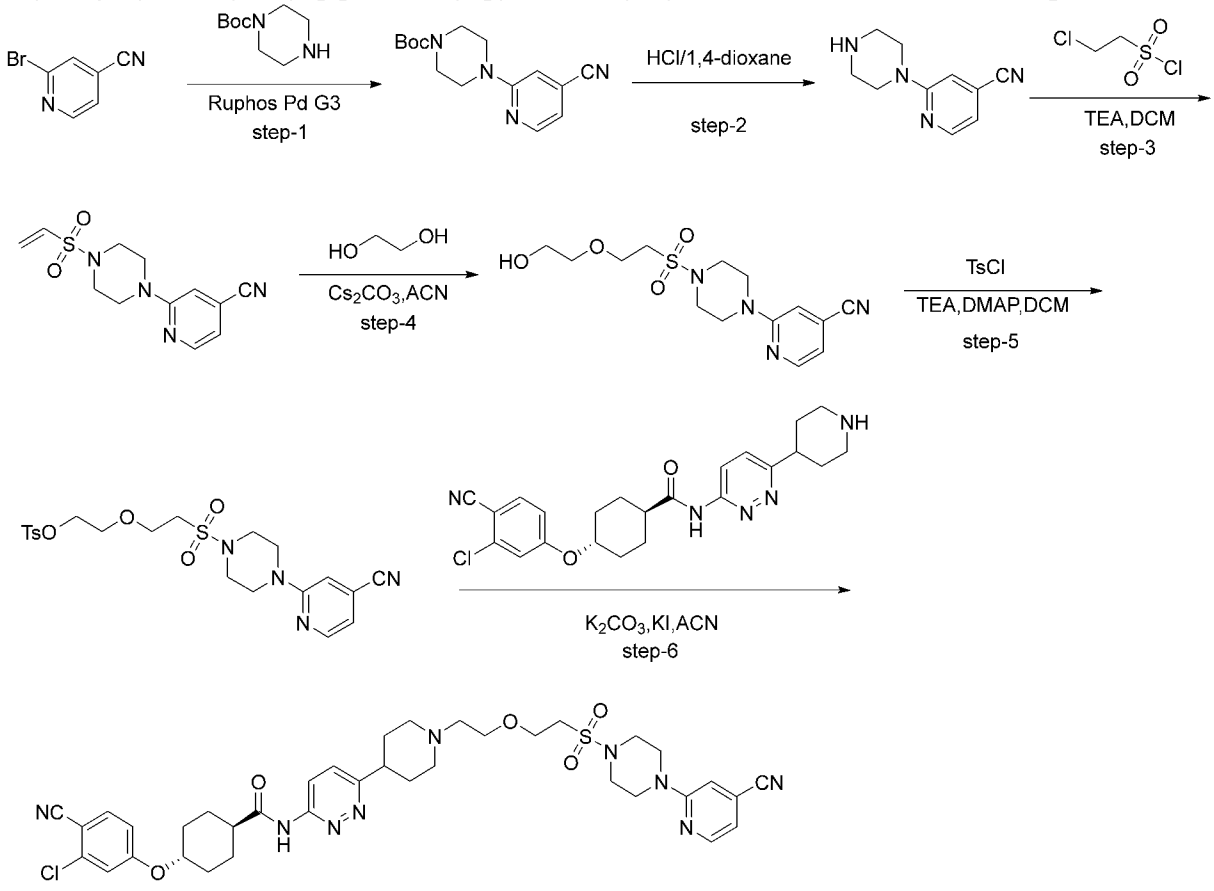
[527] **Step 4**: To a solution of 4-[dioxo(vinyl)-λ6-sulfanyl]-1-(4-fluoropyridin-2-yl)piperazine (180 mg, 0.332 mmol) in acetonitrile (5 mL) was added potassium carbonate (137.53 mg, 0.995 mmol), ethylene glycol (0.020 mL, 0.365 mmol) at room temperature, the yellow mixture was stirred at 80 °C for overnight. TLC (MeOH/DCM=1/10, Rf=0.45) showed a little starting material remained, reaction had mainly a new spot. The mixture was was filtered, washed with DCM (5 mL*2), concentrated in vacuo and the residue was directly purified with pre-TLC (MeOH/DCM=1/15) to get 2-[(2-{[4-(4-fluoropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethan-1-ol (57 mg, 0.171 mmol, 51.54%) yellow solid. ESI-Ms: 334.27 $[M+H]^{+}$.

[528] **Step 5**: To a solution of 2-[(2-{[4-(4-fluoropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethan-1-ol (57 mg, 0.171 mmol) in DCM (2 mL) was added TsCl (42.34 mg, 0.222 mmol), and TEA (51.81 mg, 0.513 mmol) at 0~5 °C, then the yellow mixture was stirred at room temperature for 1 h. TLC (MeOH/DCM=1/20, Rf=0.6) showed little starting material remained, reaction had mainly a new spot. The mixture was directly purified with silica gel. Chromatography column MeOH in DCM 3% ~ 5% to get 2-[(2-{[4-(4-fluoropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl 4-methylbenzenesulfonate (79 mg, 0.162 mmol, 94.77%) yellow semi-solid.

[529] **Step 6**: To a solution of 2-[(2-{[4-(4-fluoropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl 4-methylbenzenesulfonate (79 mg, 0.162 mmol) in acetonitrile (5 mL) was added (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(hexahydropyridin-4-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide dihydrochloride (83.10 mg, 0.162 mmol), potassium iodide (2.69 mg, 0.016 mmol), and potassium carbonate (67.18 mg, 0.486 mmol) at room temperature, then the yellow mixture was stirred at 80 °C for overnight. TLC (MeOH/DCM=1/15, Rf=0.45) showed a little starting material remained, reaction had mainly a new spot. The mixture was filtered, washed with EA (5 mL*2), concentrated in vacuo. The residue was purified with pre-TLC (MeOH/DCM=1/15) to get (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(1-{2-[(2-{[4-(4-fluoropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl}hexahydropyridin-4-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide (**Compound 81**, 12 mg, 0.016 mmol, yield:9.79%, 99.82% purity) white solid. ESI-Ms: 334.27 $[M+H]^{+}$. ^{1}H NMR (400 MHz, DMSO): δ 10.97 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 12 Hz, 1H), 6.55 (s, 1H), 4.59 (s, 1H), 3.73-3.53 (m, 6H), 3.37-3.32 (m, 6H), 3.26-3.20 (m, 4H), 2.95 (d, J = 8.0 Hz, 2H), 2.60 (s, 2H),2.51-2.43 (m, 2H), 2.13-1.93 (m, 5H), 1.77-1.66 (m, 5H), 1.35-1.24 (m, 2H).

Example S78

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-cyanopyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 82)



[530] **Step 1:** To a solution of 2-bromopyridine-4-carbonitrile (2000 mg, 10.928 mmol) in tol (20 mL) were added 2-methylpropan-2-yl piperazine-1-carboxylate (2442.49 mg, 13.114 mmol), RuPhos Pd G3 (91.40 mg, 0.109 mmol), and Cs_2CO_3 (7121.36 mg, 21.857 mmol), and the reaction was stirred at 100 degree for overnight. The reaction was filtered and loaded on a silica gel plate. The plate was developed using 5:1 PE:EA. The residue was concentrated in vacuo, and dried to afford 2-methylpropan-2-yl 4-(4-cyanopyridin-2-yl)piperazine-1-carboxylate (1500 mg, 5.202 mmol, 47.60%).

[531] **Step 2:** 2-methylpropan-2-yl 4-(4-cyanopyridin-2-yl)piperazine-1-carboxylate (1500 mg, 5.202 mmol) was dissolved in HCl/dioxane (12 mL), the reaction mixture was stirred at RT for overnight, and concentrated in vacuo to give the crude product 2-(piperazin-1-yl)pyridine-4-carbonitrile hydrochloride (1160 mg, 5.163 mmol, 99.24%) as white solid.

[532] **Step 3:** To the mixture of 2-(piperazin-1-yl)pyridine-4-carbonitrile hydrochloride (1200 mg, 5.341 mmol) and TEA (5.939 mL, 42.726 mmol) in DCM (50 mL) was added 2-chloroethane-1-sulfonyl chloride (2 mL, 19.140 mmol), then the reaction mixture was stirred at RT for overnight. The residue was

purified by preparative TLC (PE: EA=3:1) to afford 2-{4-[dioxo(vinyl)-λ6-sulfanyl]piperazin-1-yl}pyridine-4-carbonitrile (342 mg) as white solid.

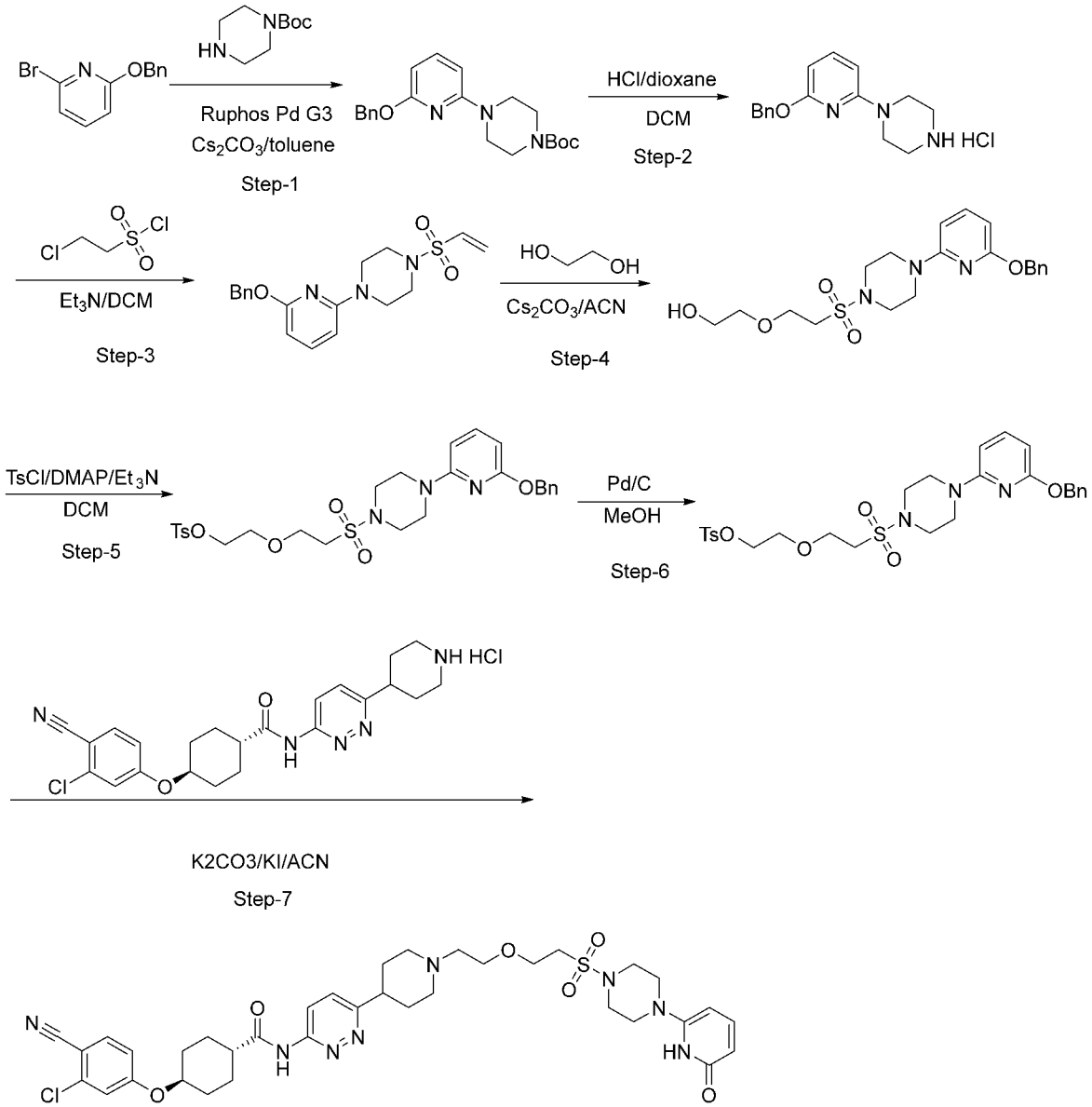
[533] **Step 4:** To the mixtured of 2-{4-[dioxo(vinyl)-λ6-sulfanyl]piperazin-1-yl}pyridine-4-carbonitrile (342 mg, 1.229 mmol), Cs_2CO_3 (800.71 mg, 2.458 mmol) in ACN (5 mL) was added ethylene glycol (0.137 mL, 2.458 mmol), then the reaction mixture was stirred at 70 °C for 3 hours, then the residue was purified by preparative TLC (PE: EA=3:1) to afford 2-[4-({2-[(2-hydroxyethyl)oxy]ethyl}dioxo-λ6-sulfanyl)piperazin-1-yl]pyridine-4-carbonitrile (176 mg, 0.517 mmol, 42.08%) as white solid.

[534] **Step 5:** To a solution of 2-[4-({2-[(2-hydroxyethyl)oxy]ethyl}dioxo-λ6-sulfanyl)piperazin-1-yl]pyridine-4-carbonitrile (176 mg, 0.517 mmol) in DCM (10 mL) were added TEA (0.5 mL, 3.597 mmol), TsCl (197.14 mg, 1.034 mmol), and DMAP (12.63 mg, 0.103 mmol), and the reaction was stirred at room temperature for overnight. The reaction was diluted with DCM and saturated NaCl solution. The organic layer was separated, and concentrated in vacuo. The residue was purified using silica gel column chromatography eluting with ethyl acetate in petroleum ether. The organic layer was collected, concentrated in vacuo, and dried to afford the 2-[(2-{[4-(4-cyanopyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl 4-methylbenzenesulfonate (197 mg, 0.398 mmol, 77.04%).

[535] **Step 6:** To a solution of 2-[(2-{[4-(4-cyanopyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl 4-methylbenzenesulfonate (98 mg, 0.198 mmol) in ACN (5 mL) were added (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(hexahydropyridin-4-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide (40 mg, 0.091 mmol), K_2CO_3 (54.73 mg, 0.396 mmol), and KI (3.29 mg, 0.020 mmol), and the reaction was stirred at 70 degree for overnight. The reaction was flited and loaded on a silica gel plate. The plate was developed using 10:1 DCM:MeOH. The residue was concentrated in vacuo, and dried to afford (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(1-{2-[(2-{[4-(4-cyanopyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl}hexahydropyridin-4-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide (**Compound 82,** 23 mg, 0.030 mmol, 15.24%). ESI-MS: 762.3 [M+H]+. 1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.29 (d, J = 5.0 Hz, 1H), 8.23 (d, J = 9.2 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 9.2 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.14 (dd, J = 8.8, 2.4 Hz, 1H), 6.98 (d, J = 5.0 Hz, 1H), 4.67 – 4.51 (m, 1H), 3.77 – 3.65 (m, 6H), 3.54 (s, 2H), 3.38 (t, J = 5.7 Hz, 2H), 3.29 – 3.24 (m, 4H), 2.95 (s, 2H), 2.78 (s, 1H), 2.59 (d, J = 11.7 Hz, 1H), 2.43 (s, 1H), 2.14 (d, J = 9.3 Hz, 2H), 2.01 – 1.89 (m, 3H), 1.85 – 1.59 (m, 6H), 1.39 (dt, J = 17.3, 8.5 Hz, 2H), 1.26 (dd, J = 14.9, 11.2 Hz, 2H).

Example S79

Synthesis of* (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(6-oxo-1,6-dihydropyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide*(Compound 83)



[536] **Step 1:** A mixture of 2-(benzyloxy)-6-bromopyridine (900 mg, 3.408 mmol), 2-methylpropan -2-yl piperazine-1-carboxylate (634.65 mg, 3.408 mmol), Cs_2CO_3 (2220.49 mg, 6.815 mmol) and RuPhos-Pd-G3 (57.00 mg, 0.068 mmol) in Toluene (8 mL) was replaced with N_2 for 1 min. Then the reaction was heated at 100 °C for 6h. Purified by pre-TLC eluting with PE/EA=8/1 and got 2-methylpropan-2-yl 4-[6-(benzyloxy)pyri- din-2-yl]piperazine-1-carboxylate (730 mg, 1.976 mmol, 57.98%).

[537] **Step 2:** To a solution of 1-[6-(benzyloxy)pyridin-2-yl]piperazine hydrochloride (80 mg, 0.262 mmol) and Et3N (0.182 mL, 1.308 mmol) in DCM (3 mL) was added 2-chloroethane -1-sulfonyl chloride (85.29 mg, 0.523 mmol) and the reaction stirred at RT for 16h. Purified by PE/EA=3/1 and got 1-[6-(benzyloxy)pyridin-2-yl] -4-[dioxo(vinyl)-λ6-sulfanyl]pip- erazine (55 mg, 0.153 mmol, 58.49%).

[538] **Step 3:** A solution of 2-methylpropan-2-yl4-[6-(benzyloxy)pyridin-2-yl]piperazine-1-carboxylate (730 mg, 1.976 mmol) in DCM (5 mL) was added HCl/dioxane (3 mL) at RT. Then the

reaction was stirred at RT for 3h. Concentrated and got 1-[6-(benzyloxy)pyridin-2-yl]piperazine hydrochloride (690 mg, 1.805 mmol, 91.35%).

[539] **Step 4:** A solution of 1-[4-(benzyloxy)pyridin-2-yl]-4-[dioxo(vinyl)-λ6-sulfanyl]piperazine (55 mg, 0.153 mmol), ethylene glycol (0.017 mL, 0.306 mmol) and Cs_2CO_3 (99.76 mg, 0.306 mmol) in ACN (3 mL) was stirred at 50 °C for 1h. Purified by pre-TLC eltuing with PE/EA=1.5/1 and got 2-{[2-({4-[4-(benzyloxy)pyridin-2-yl]piperazin-1-yl}dioxo-λ6-sulfanyl)ethyl]oxy}ethan-1-ol (30 mg, 0.071 mmol, 46.51%).

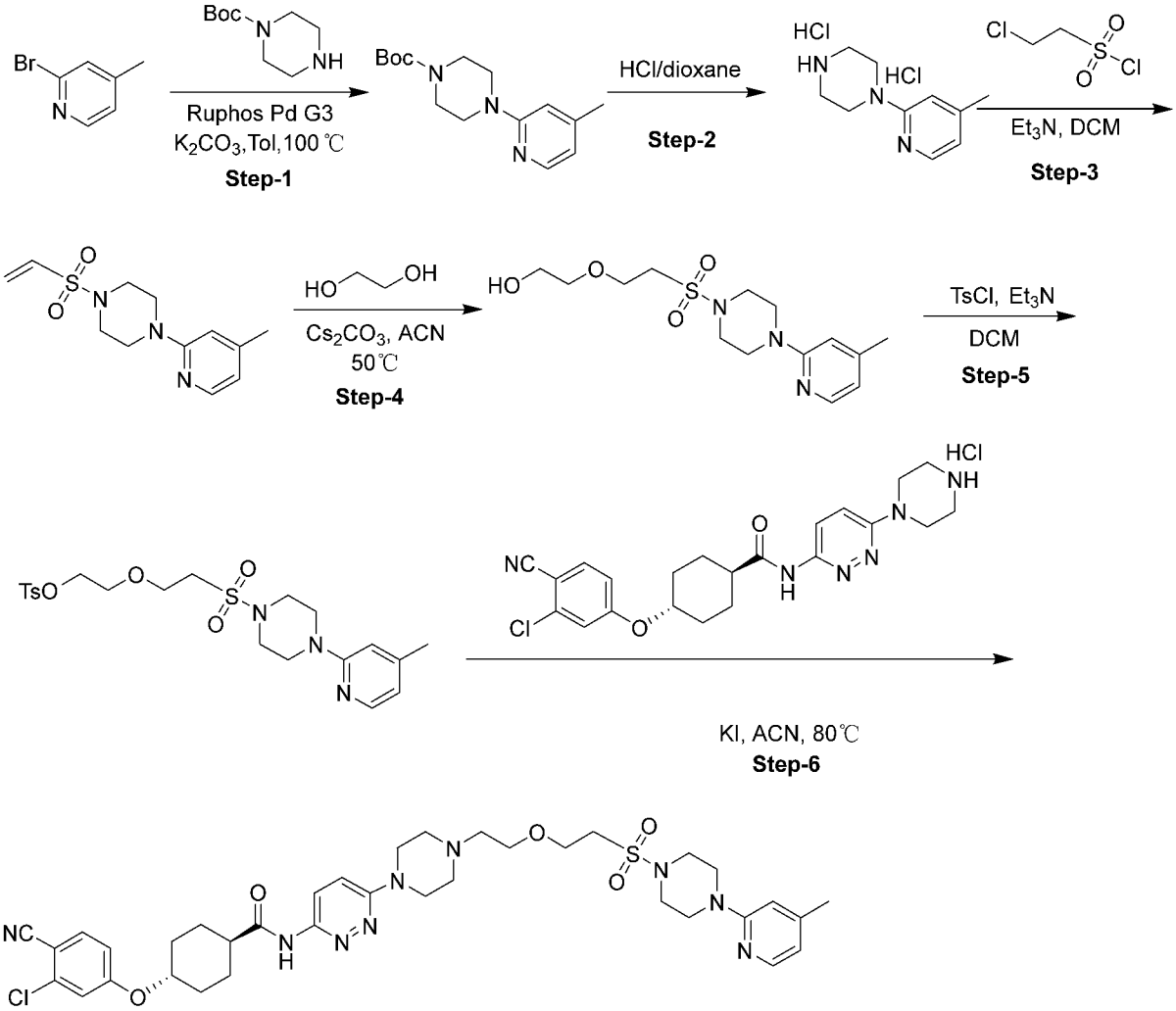
[540] **Step 5:** To a solution of 2-{[2-({4-[4-(benzyloxy)pyridin-2-yl]piperazin-1-yl}dioxo-λ6-sulfany- l)ethyl]oxy}ethan-1-ol (30 mg, 0.071 mmol), DMAP (1.74 mg, 0.014 mmo l) and Et3N (0.049 mL, 0.356 mmol) in DCM (2 mL) was added TsCl (27.14 mg, 0.142 mmol) in portion. After addition, the reaction was stirred at RT overnight. Purified by pre-TLC eluting with PE/EA=1/1 and got 2-{[2-({4-[4-(benzyloxy)pyridin-2-yl]piperazin-1-yl}dioxo-λ6-sulfanyl)ethyl]oxy}ethyl4-methylbenzenesulfonate (30 mg, 0.052 mmol, 73.22%).

[541] **Step 6**: A solution of 2-{[2-({4-[6-(benzyloxy)pyridin-2-yl]piperazin-1-yl}dioxo-λ6-sulfany-l)ethyl]oxy}ethyl 4-methylbenzenesulfonate (30 mg, 0.052 mmol) and Pd/C 10% (15 mg, 0.141 mmol) in MeOH (3 mL) and DCM (1 mL) was replaced with H_2 for 3 times. Then the reaction was stirred at RT under H_2 for 1h. TLC indicated no starting material. Filtered, concentrated and got 2-[(2-{[4-(6-hydroxypyridin-2-yl)piperazin- 1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl4-methylbenzenesulfonate (22 mg, 0.045 mmol, 86.96%).

[542] **Step 7**: A mixture of 2-[(2-{[4-(6-hydroxypyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl 4-methylbenzenesulfonate (22 mg, 0.045 mmol), (1r,4r)-4-[(3-chloro-4 -cyanopheny- l)oxy]-N-[6-(hexahydropyridin -4-yl)-1,2-diazin-3-yl](1r,4r)-cyclo- hexanecarboxamide hydrochloride (21.58 mg, 0.045 mmol), potassium iodide (7.52 mg, 0.045 mmol) and K_2CO_3 (12.52 mg, 0.091 mmol) in ACN (2 mL) was heated at 80 °C for 16h. Purified by pre-TLC eluting with DCM/MeOH=7/1 and got (1r,4r)-4-[(3-chloro- 4-cyanophenyl)oxy]-N-[6-(1-{2-[(2-{[4-(6-hydroxypyridin- 2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl}hexahydropyridin-4-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide (**Compound 83**,12 mg, 0.016 mmol, 35.16%). ESI-MS: 753.4[M+H]+.1H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 10.20 (s, 1H), 8.23 (d, J = 9.2 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 9.3 Hz, 1H), 7.43 – 7.31 (m, 2H), 7.14 (dd, J = 8.8, 2.4 Hz, 1H), 6.16 (s, 1H), 5.89 (d, J = 7.9 Hz, 1H), 4.66 – 4.51 (m, 1H), 3.75 (t, J = 5.8 Hz, 2H), 3.56 (s, 2H), 3.51 (s, 3H), 3.37 (t, J = 5.8 Hz, 2H), 3.28 – 3.21 (m, 4H), 2.99 (s, 2H), 2.80 (s, 1H), 2.59 (dd, J = 23.6, 11.8 Hz, 2H), 2.19 – 1.99 (m, 4H), 1.94 (d, J = 12.2 Hz, 2H), 1.87 – 1.59 (m, 6H), 1.51 – 1.26 (m, 4H).

Example S80

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(2-((4-(4-methylpyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 84)



[543] **Step 1:** To a solution of 2-methylpropan-2-yl piperazine-1-carboxylate (1299.19 mg, 6.976 mmol) in toluene (12.0 mL) were added 2-bromo-4-methylpyridine (1000.0 mg, 5.813 mmol), RuPhos Pd G3 (243.09 mg, 0.291 mmol), and Cs_2CO_3 (3787.94 mg, 11.626 mmol), and the reaction was stirred at 100 °C for 8 h (PE:EA=5:1). The reaction mixture was concentrated in vacuo, The residure was diluted with DCM and water. The organic layer was separated, washed with further water, and concentrated in vacuo. The residue was purified using silica gel column chromatography eluting with ethyl acetate in petroleum ether to afford 2-methylpropan-2-yl 4-(4-methylpyridin-2-yl)piperazine-1-carboxylate (432.1 mg, 1.558 mmol, 26.80%).

[544] **Step 2:** To a flask containing 2-methylpropan-2-yl 4-(4-methylpyridin-2-yl)piperazine-1-carboxylate (432.1 mg, 1.558 mmol) was added 1,4-dioxne (5.0 mL) followed by the addition of HCl/1,4-dioxane (15.0 mL). The mixture was stirred at rt for 4 h (PE:EA=5:1). The reaction was concentrated in

vacuo. The residue was dissolved in EA, concentrated in vacuo and dried to afford 1-(4-methylpyridin-2-yl)piperazine dihydrochloride (392.9 mg, 1.571 mmol, 100.80%).

[545] **Step 3:** To a solution of 1-(4-methylpyridin-2-yl)piperazine dihydrochloride (392.9 mg, 1.571 mmol) in DCM (5.0 mL) were added 2-chloroethane-1-sulfonyl chloride (307.21 mg, 1.885 mmol) and Et_3N (1.528 mL, 10.994 mmol), and the reaction was stirred at room temperature for 4 hr (PE:EA=2:1). The reaction was was purified using silica gel column chromatography eluting with ethyl acetate in petroleum ether and dried to afford 1-(4-chloropyridin-2-yl)-4-[dioxo(vinyl)-λ6-sulfanyl]piperazine (246.2 mg, 0.856 mmol, 58.92%).

[546] **Step 4:** To a solution of 4-[dioxo(vinyl)-λ6-sulfanyl]-1-(4-methylpyridin-2-yl)piperazine (246.2 mg, 0.921 mmol) in ACN (250.0 mL) were added Cs_2CO_3 (600.09 mg, 1.842 mmol) and ethylene glycol (0.103 mL, 1.842 mmol), and the reaction was stirred at 50 °C for overnight (DCM:MeOH=20:1). The reaction was filtered and the filtration was concentrated. The residue was diluted with DCM and water. The organic layer was separated, washed with further water, saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo to afford crude 2-[(2-{[4-(4-chloropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethan-1-ol (363.3 mg, 1.039 mmol, 44.33%).ESI-MS: 330.2[M+H]+.

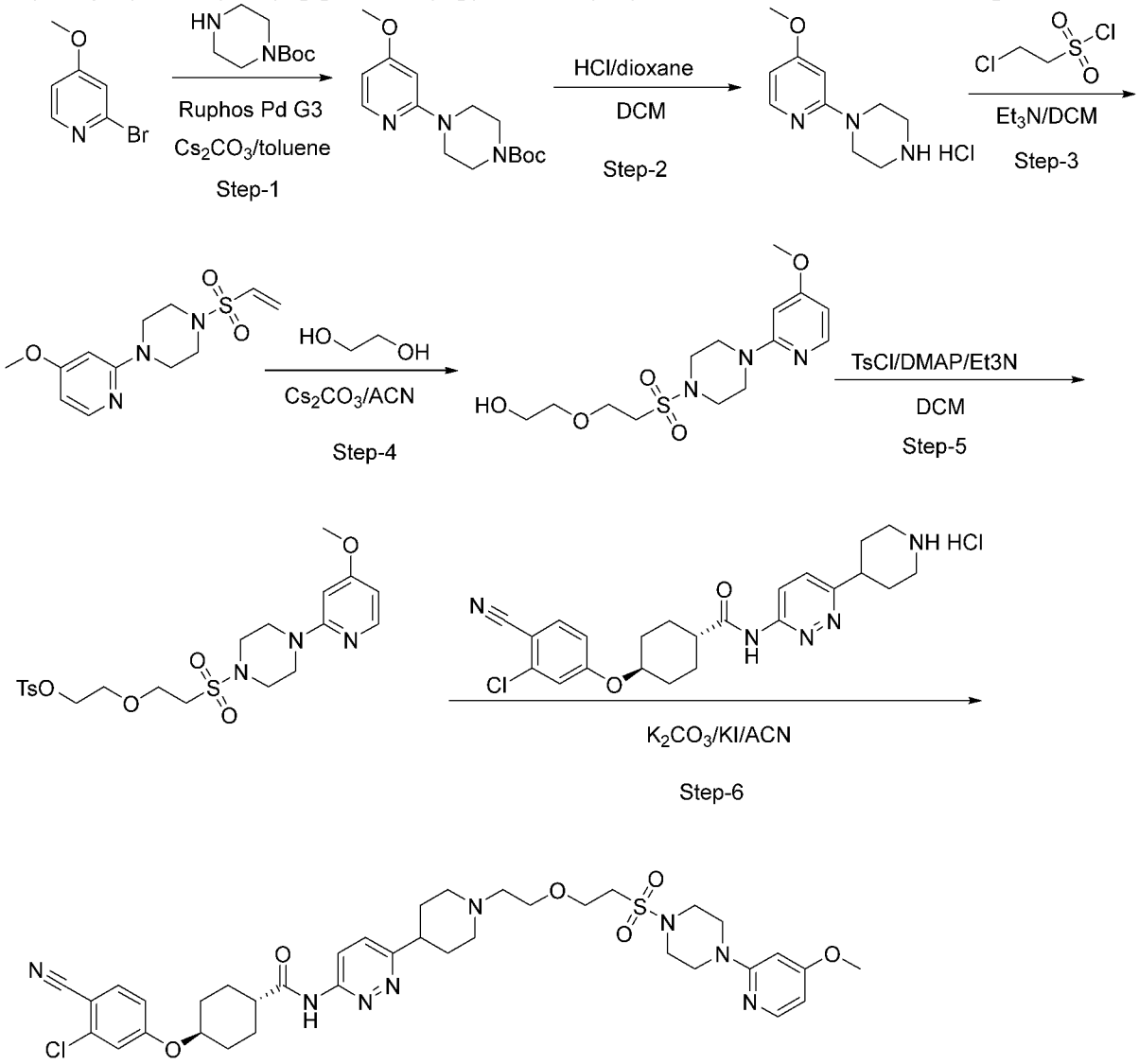
[547] **Step 5**: To a solution of 4-[dioxo(vinyl)-λ6-sulfanyl]-1-(4-methylpyridin-2-yl)piperazine (246.2 mg, 0.921 mmol) in ACN (250.0 mL) were added Cs_2CO_3 (600.09 mg, 1.842 mmol) and ethylene glycol (0.103 mL, 1.842 mmol), and the reaction was stirred at 50 °C for overnight (DCM:MeOH=20:1). The reaction was filtered and the filtration was concentrated. The residue was diluted with DCM and water. The organic layer was separated, washed with further water, saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo to afford crude 2-[(2-{[4-(4-chloropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethan-1-ol (363.3 mg, 1.039 mmol, 44.33%).

[548] **Step 6:** To a solution of (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(piperazin-1-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide hydrochloride (221.5 mg, 0.464 mmol) in ACN (7.0 mL) were added 2-[(2-{[4-(4-methylpyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl 4-methylbenzenesulfonate (224.38 mg, 0.464 mmol), K_2CO_3 (160.31 mg, 1.160 mmol) and potassium iodide (38.51 mg, 0.232 mmol), and the reaction was stirred at 80 °C under N_2 for overninght (DCM:MeOH=10:1). The reaction was concentrated in vacuo, the residue was diluted with DCM and water. The organic layer was separated, washed with further water, and concentrated in vacuo. The residue was purified by pre-TLC and lyophilized to afford (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(4-{2-[(2-{[4-(4-methylpyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl}piperazin-1-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide (**Compound 84,** 82.0 mg, 0.108 mmol, 23.22%). ESI-MS: 753.2[M+H]+, 751.3[M-H]-. 1HNMR (400 MHz, CDCl3) δ 9.34 (s, 1H), 8.27 (d,J = 9.8 Hz, 1H), 8.03 (d,J = 5.1 Hz, 1H), 7.56 (d,J = 8.7 Hz, 1H), 6.98 (dd,J = 10.4, 6.1 Hz, 2H), 6.84 (dd,J = 8.7, 2.4 Hz, 1H), 6.51

(d, J = 5.1 Hz, 1H), 6.47 (s, 1H), 3.88 (t,J = 6.0 Hz, 2H), 3.65 (dd,J = 16.8, 12.1 Hz, 10H), 3.44 – 3.35 (m, 4H), 3.24 (t,J = 6.0 Hz, 2H), 2.69 (s, 5H), 2.22 (s, 1H), 2.12 (d,J = 11.6 Hz, 2H), 1.83 – 1.69 (m, 4H), 1.55 (dt,J = 23.3, 6.6 Hz, 3H), 1.26 (s, 4H), 0.87 (dd,J = 16.6, 10.1 Hz, 1H).

Example S81

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-methoxypyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 85)



[549] **Step 1**: A mixture of 2-bromo-4-methoxypyridine (100 mg, 0.532 mmol), 2-methylpropan-2-yl piperazine-1-carboxylate (99.06 mg, 0.532 mmol), Cs_2CO_3 (346.58 mg, 1.064 mmol) and RuPhos-Pd-G3 (8.90 mg, 0.011 mmol) in Toluene (2 mL) was replaced with N_2 for 1 min. Then the reaction was heated at 100 °C for 6h. Purified by pre-TLC eluting with PE/EA=4/1 and got 2-methylpropan-2-yl 4-(4-methoxypyridin- 2-yl)piperazine-1-carboxylate (28 mg, 0.095 mmol, 17.95%).

[550] **Step 2:** A solution of 2-methylpropan-2-yl4-(4-methoxypyridin-2-yl)piperazine-1-carboxylate (28 mg, 0.095 mmol) in DCM (1 mL) was added HCl/dioxane (1 mL) at RT. Then the reaction was stirred at RT for 2h. TLC indicated no starting material remained. Concentrated and got the crude product 1-(4-methoxypyridin-2-yl)piperazine hydrochloride (26 mg, 0.091 mmol, 95.31%).

[551] **Step 3:** A solution of 1-(4-methoxypyridin-2-yl)piperazine hydrochloride (26 mg, 0.091 mm ol) and Et_3N (0.063 mL, 0.453 mmol) in DCM (2 mL) was added 2-chloroethane-1 -sulfonyl chloride (29.52 mg, 0.181 mmol). Then the reaction was stirred at RT for 16h. Purified by pre-TLC eluting with DCM/MeOH=40/1 and got 4-[dioxo(vinyl) -λ6-sulfanyl]-1-(4-methoxypyridin-2-yl)piperazine (14 mg, 0.049 mmol, 54.56%).

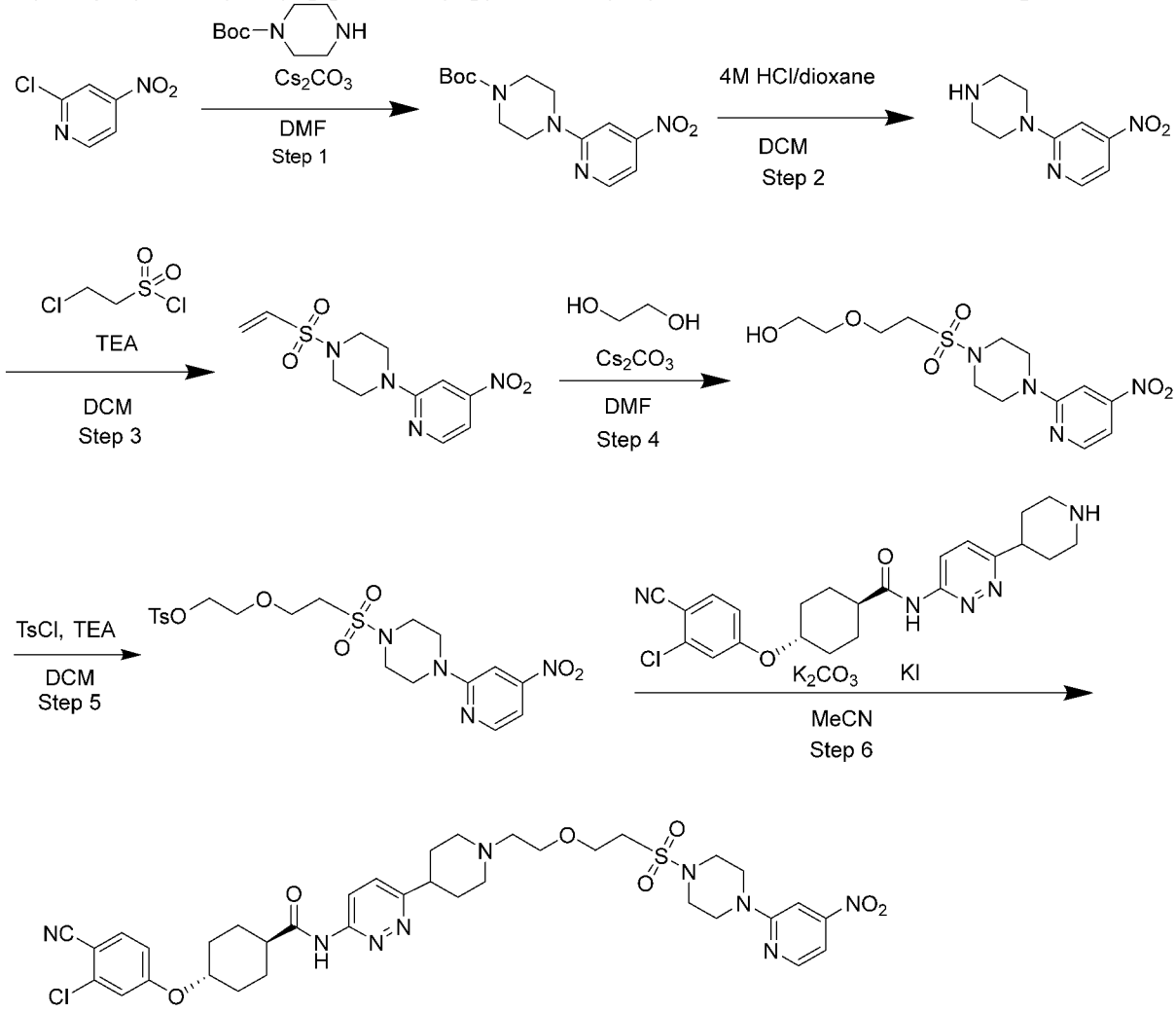
[552] **Step 4:** A solution of 4-[dioxo(vinyl)-λ6-sulfanyl]-1-(4-methoxypyridin-2-yl)piperazine (14 mg, 0.049 mmol), ethylene glycol (0.006 mL, 0.099 mmol) and Cs_2CO_3 (32.20 mg, 0.099 mmol) in ACN (1 mL) was stirred at 50 °C for 16h. Purified by pre-TLC eltuing with DCM/MeOH=20/1 and got 2-[(2-{[4-(4-methoxypyridin-2-yl)piperazin-1-yl]dio- xo-λ6-sulfanyl}ethyl)oxy]ethan-1-ol (9 mg, 0.026 mmol, 52.72%).

[553] **Step 5:** A solution of 2-[(2-{[4-(4-methoxypyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}eth-yl)oxy]ethan-1-ol (44 mg, 0.127 mmol), DMAP (3.11 mg, 0.025 mmol) and Et_3N (0.089 mL, 0.637 mmol) in DCM (3 mL) was added TsCl (48.57 mg, 0.255 mmol) in portion. After addition, the reaction was stirred at RT overnight. Purified by pre-TLC eluting with PE/EA=1/1 and got 2-[(2-{[4-(4-methoxypyridin-2-yl)piperazin-1-y l]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl4-methylbenzenesulfonate (60 mg, 0.120 mmol, 94.28%).

[554] **Step 6**: A mixture of 2-{[2-(dioxo{4-[5-(trifluoromethyl)pyridin-3-yl]piperazin-1-yl}-λ6-sulfanyl)ethyl]oxy}ethyl 4-methylbenzenesulfonate (141 mg, 0.262 mmol), 4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(piperazin-1-yl)-1,2-diazin-3-yl]cyclohexanecarboxamide hydrochloride (125.22 mg, 0.262 mmol), KI (9.97 mg, 0.060 mmol) and K_2CO_3 (16.57 mg, 0.120 mmol) in MeCN was heated at reflux for 3h. Purified by pre-TLC eluting with DCM/MeOH=15:1 and 10:1, got the product 4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(1-{2-[(2-{[4-(4-methoxypyri- din-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl}hexahydropyridin-4-yl)-1,2-diazin-3-yl]cyclohexanecarboxamide (**Compound 85**, 26 mg, 0.034 mmol, 56.42%).ESI-MS: 767.3 [M+H]+. ^{1}H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 8.23 (d, J = 9.2 Hz, 1H), 7.93 (d, J = 5.7 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.14 (dd, J = 8.8, 2.4 Hz, 1H), 6.41 – 6.24 (m, 2H), 4.67 – 4.51 (m, 1H), 3.80 – 3.71 (m, 5H), 3.59 (dd, J = 13.5, 8.4 Hz, 5H), 3.37 (t, J = 5.8 Hz, 2H), 3.28 – 3.22 (m, 4H), 2.97 (s, 2H), 2.79 (s, 1H), 2.60 (t, J = 11.8 Hz, 2H), 2.20 – 1.98 (m, 4H), 1.94 (d, J = 11.8 Hz, 2H), 1.87 – 1.59 (m, 6H), 1.40 (dd, J = 23.0, 10.0 Hz, 4H).

Example S82

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-nitropyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 86)



[555] **Step 1**: To a soultion of 2-chloro-4-nitropyridine (2 g, 12.615 mmol) in N,N-dimethylmethanamide (10 mL) was added Cs_2CO_3 (6.17 g, 18.923 mmol) and 2-methylpropan-2-yl piperazine-1-carboxylate (2.35 g, 12.615 mmol), Then the reaction was stirred at 90 °C for 3 h. The reaction was concentrated and purified by silica gel eluting with EA/PE=2/1 to afford the product 2-methylpropan-2-yl 4-(4-nitropyridin-2-yl)piperazine-1-carboxylate (1.55 g).

[556] **Step 2**: To a soultion of 2-methylpropan-2-yl 4-(4-nitropyridin-2-yl)piperazine-1-carboxylate (1.51 g, 4.897 mmol) in DCM (10 mL) was added 6M HCl/dioxane (10 mL) at 0-5 °C, Then the reaction was stirred at RT for 2 h. The reaction was concentrated in vacuo to afford the product 1-(4-nitropyridin-2-yl)piperazine hydrochloride (1.488 g).

[557] **Step 3:** To a soultion of 1-(4-nitropyridin-2-yl)piperazine hydrochloride (1 g, 4.087 mmol) in DCM (10 mL)was added triethylamine (2.840 mL, 20.435 mmol) and 2-chloroethane-1-sulfonyl chloride

(0.73 g, 4.496 mmol) at 0-5 °C, Then the reaction was stirred at RT for 2 h.The reaction was concentrated in vacuo and purified by pre-TLC eluting with DCM/EA=30/1 to afford the product 4-[dioxo(vinyl)-λ6-sulfanyl]-1-(4-nitropyridin-2-yl)piperazine (512 mg).

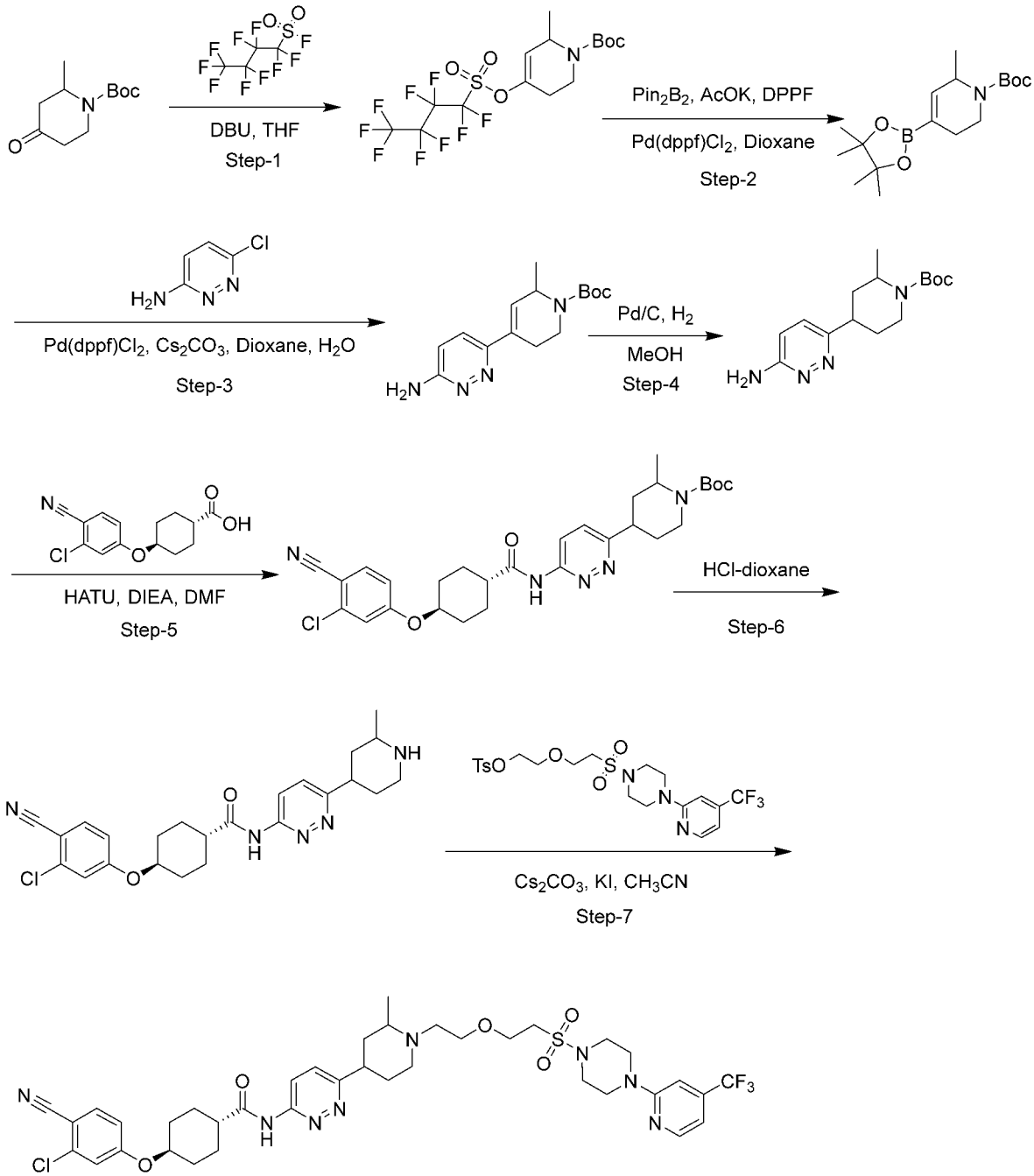
[558] **Step 4**: To a soultion of 4-[dioxo(vinyl)-λ6-sulfanyl]-1-(4-nitropyridin-2-yl)piperazine (512 mg, 0.980 mmol) in DMF (10 mL) was added ethylene glycol (0.074 mL, 1.321 mmol) and Cs_2CO_3 (645.48 mg, 1.981 mmol), Then the reaction was stirred at 80 °C for 12 h. The reaction was concentrated in vacuo and purified by pre-TLC eluting with DCM/MeOH=15/1 to afford the product 2-[(2-{[4-(4-nitropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethan-1-ol (200 mg).

[559] **Step 5**: To a soultion of 2-[(2-{[4-(4-nitropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethan-1-ol (200 mg, 0.555 mmol) in DCM (10 mL) was added 4-methylbenzenesulfonyl chloride (126.96 mg, 0.666 mmol), 4-methylbenzenesulfonyl chloride (126.96 mg, 0.666 mmol) and TEA (112.31 mg, 1.110 mmol) at 0-5 °C, Then the reaction was stirred at RT for 1 h, The reaction was concentrated in vacuo and purified by pre-TLC eluting with DCM/MeOH=40/1 to afford the product 2-[(2-{[4-(4-nitropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl 4-methylbenzenesulfonate (260 mg).

[560] **Step 6:** To a soultion of 2-[(2-{[4-(4-nitropyridin-2-yl)piperazin-1-yl]dioxo-λ6-sulfanyl}ethyl)oxy]ethyl 4-methylbenzenesulfonate (177 mg, 0.344 mmol)in MeCN (20 mL) was added 4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(hexahydropyridin-4-yl)-1,2-diazin-3-yl]cyclohexanecarboxamide hydrochloride (288.70 mg, 0.606 mmol), potassium carbonate (142.61 mg, 1.032 mmol) and potassium iodide (57.10 mg, 0.344 mmol). Then the reaction was stirred at 80 °C for 6 h. The reaction was then concentrated in vacuo and purified by pre-TLC eluting with DCM/MeOH=15/1 to afford the product (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-nitropyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-4-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (20 mg). (**Compound 86**, 20 mg). ESI-MS: 782.43 [M+H]+.1H NMR (400 MHz, CDCl3) δ 9.33 (s, 1H), 8.44 (d, J = 9.2 Hz, 1H), 8.38 (d, J = 5.4 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.41 (d, J = 9.3 Hz, 1H), 7.36 (d, J = 1.8 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 6.85 (dd, J = 8.8, 2.4 Hz, 1H), 4.33 (dt, J = 10.5, 5.9 Hz, 1H), 3.90 (t, J = 5.8 Hz, 2H), 3.82 – 3.75 (m, 6H), 3.44 (t, J = 5.1 Hz, 4H), 3.29 (t, J = 5.8 Hz, 3H), 2.99 (s, 1H), 2.78 (s, 1H), 2.69 – 2.59 (m, 1H), 2.26 (d, J = 12.6 Hz, 3H), 2.16 (d, J = 13.4 Hz, 3H), 2.02 (s, 3H), 1.84 – 1.64 (m, 9H), 1.48 (p, J = 7.3 Hz, 2H).

Example S83

Synthesis of (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-{6-[1-(2-{[2-(dioxo{4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-λ6-sulfanyl)ethyl]oxy}ethyl)-2-methylhexahydropyridin-4-yl]-1,2-diazin-3-yl}(1r,4r)-cyclohexanecarboxamide (Compound 87)



[561] **Step 1:** To a solution of 2-methylpropan-2-yl 2-methyl-4-oxohexahydropyridine-1-carboxylate (2000 mg, 9.377 mmol) in THF (10 mL) were added DBU (4282.82 mg, 28.132 mmol) and 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (5.053 mL, 28.132 mmol) at 0 °C, and the reaction was stirred at RT for 3 hours. The reaction was complete as detected by TLC (PE:EA= 5:1). The reaction was diluted with water and extracted with ethyl acetate (50 mL × 4). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed on silica gel (EA in PE 0:100→1:100) to give 6-methyl-1-{[(2-methylprop-2-yl)oxy]carbonyl}-1,2,3,6-tetrahydropyridine-4-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (4600 mg, 9.286 mmol, 99.03%).

[562] **Step 2:** To a solution of 6-methyl-1-{[(2-methylprop-2-yl)oxy]carbonyl}-1,2,3,6-tetrahydropyridine-4-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (1500 mg, 3.028 mmol) in dioxane (10 mL) were added potassium acetate (1040.12 mg, 10.598 mmol), bis(cyclopentyldiphenylphosphane) iron(0) (85.46 mg, 0.151 mmol), and bis[5-(diphenylphosphanyl)cyclopenta-1,3-dienyl]-λ2-iron(II) palladium chloride (110.78 mg, 0.151 mmol), and the reaction was stirred at 85 °C for 3 hours under N_2 atmosphere. TLC showed no starting material remained. The reaction was concentrated in vacuo. The crude product was chromatographed on silica gel (CH3OH in CH_2Cl_2 0:100→1:100→5:100) to give 2-methylpropan-2-yl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate (680 mg, 2.104 mmol, 77.86%) as a colorless oil.

[563] **Step 3:** To a solution of 2-methylpropan-2-yl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate (680 mg, 2.104 mmol) in dioxane (5 mL), H_2O (0.5 mL) were added Cs_2CO_3 (2056.28 mg, 6.311 mmol), 6-chloro-1,2-diazin-3-amine (272.53 mg, 2.104 mmol), and Pd(dppf)Cl_2 (76.96 mg, 0.105 mmol), and the reaction was stirred at 100 °C for 3 hours under N_2 atmosphere. TLC showed new spot was observed, and LCMS showed product was observed. The crude product was chromatographed on silica gel (CH_3OH in CH_2Cl_2 0:100→2:100→3:100) to give 2-methylpropan-2-yl 4-(6-amino-1,2-diazin-3-yl)-6-methyl-1,2,3,6-tetrahydropyridine-1-carboxylate (400 mg, 1.378 mmol, 65.48%) as a white solid.

[564] **Step 4:** To a solution of 2-methylpropan-2-yl 4-(6-amino-1,2-diazin-3-yl)-6-methyl-1,2,3,6-tetrahydropyridine-1-carboxylate (400 mg, 1.378 mmol) in MeOH (10 mL) were added Pd/C 10% (146.60 mg, 1.378 mmol), and the reaction was stirred at RT for 16 hours under H_2 atmosphere. TLC showed new spot was observed. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated to give 2-methylpropan-2-yl 4-(6-amino-1,2-diazin-3-yl)-2-methylhexahydropyridine-1-carboxylate (200 mg, 0.684 mmol, 49.66%) as a yellow solid.

[565] **Step 5:** To a solution of 2-methylpropan-2-yl 4-(6-amino-1,2-diazin-3-yl)-2-methylhexahydropyridine-1-carboxylate (190 mg, 0.650 mmol) in DMF (5 mL) were added (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]cyclohexane-1-carboxylic acid (181.77 mg, 0.650 mmol), DIEA (251.98 mg, 1.950 mmol), and HATU (617.74 mg, 1.625 mmol), and the reaction was stirred at RT for 3 hours. The reaction was complete as detected by TLC. The reaction was concentrated in vacuo. The crude product was chromatographed on silica gel (CH_3OH in CH_2Cl_2 0:100→1:100→2:100) to give 2-methylpropan-2-yl 4-[6-({[(1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]cyclohexyl]carbonyl}amino)-1,2-diazin-3-yl]-2-methylhexahydropyridine-1-carboxylate (360 mg, 0.650 mmol, 99.98%) as a yellow solid.

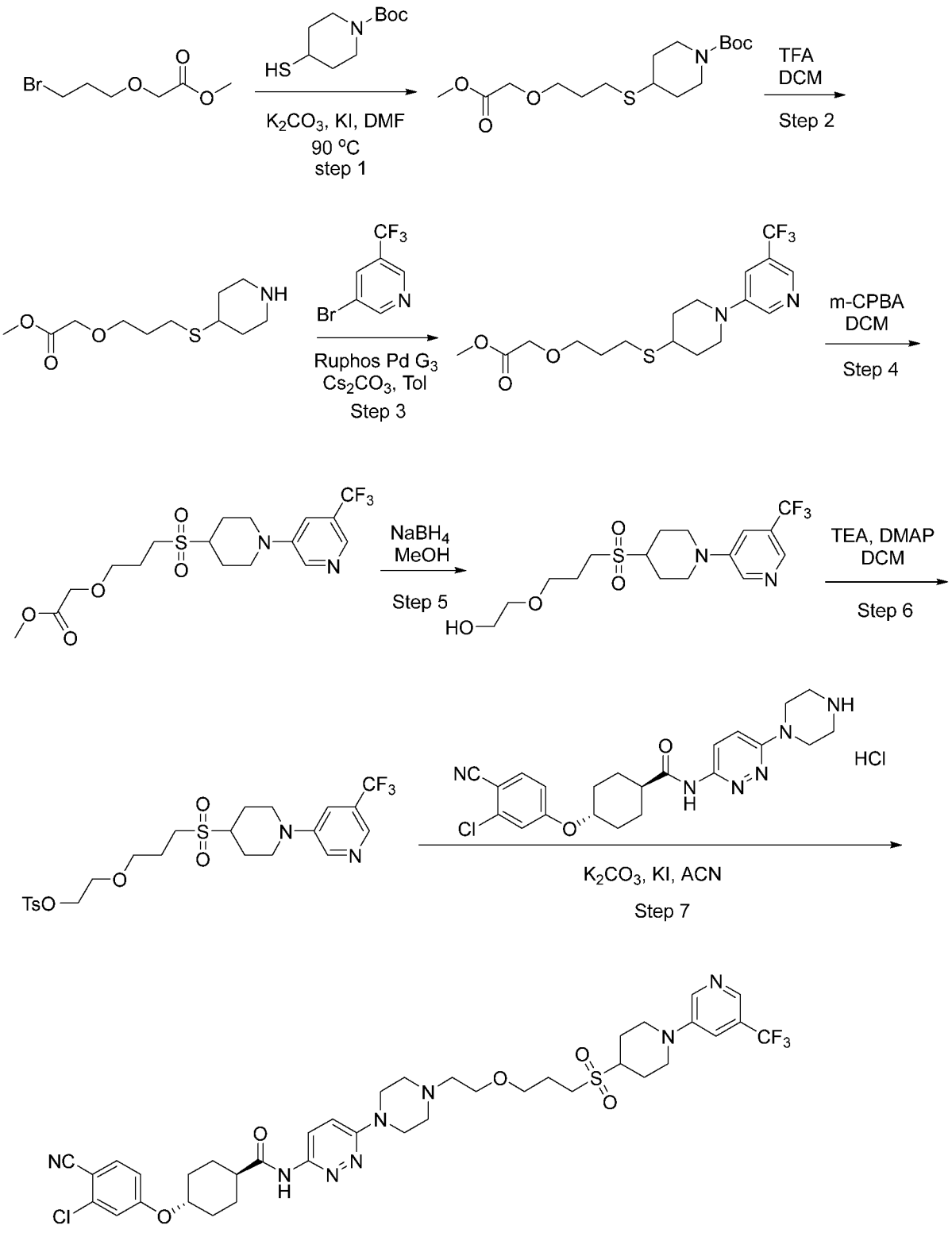
[566] **Step 6:** A solution of 2-methylpropan-2-yl 4-[6-({[(1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]cyclohexyl]carbonyl}amino)-1,2-diazin-3-yl]-2-methylhexahydropyridine-1-carboxylate (60 mg, 0.108 mmol) in HCl-dioxane (2 mL) was stirred at RT for 16 hours. The reaction was complete as

detected by TLC (DCM: MeOH= 10:1). The reaction was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=10:1) to afford (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(2-methylhexahydropyridin-4-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide (50 mg, 0.102 mmol, 94.39%) as a white solid.

[567] **Step 7:** To a solution of (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(2-methylhexahydropyridin-4-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide (41.97 mg, 0.086 mmol) in CH_3CN (2 mL) were added 2-{[2-(dioxo{4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-λ6-sulfanyl)ethyl]oxy}ethyl 4-methylbenzenesulfonate (46 mg, 0.086 mmol), K_2CO_3 (35.48 mg, 0.257 mmol), and potassium iodide (14.20 mg, 0.086 mmol), and the reaction was stirred at 100 °C for 8 hours. The reaction was complete as detected by TLC (DCM: MeOH= 10:1). The reaction was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=13:1) to afford (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-{6-[1-(2-{[2-(dioxo{4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-λ6-sulfanyl)ethyl]oxy}ethyl)-2-methylhexahydropyridin-4-yl]-1,2-diazin-3-yl}(1r,4r)-cyclohexanecarboxamide (8.6 mg, 0.010 mmol, 12.27%) as a white solid. (**Compound 87**, 10 mg). ESI-MS: 819.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 8.34 (d, J = 5.2 Hz, 1H), 8.25 (d, J = 9.4 Hz, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 9.5 Hz, 1H), 7.40 (d, J = 2.5 Hz, 1H), 7.22 – 7.08 (m, 2H), 6.92 (d, J = 5.2 Hz, 1H), 4.57 (d, J = 11.7 Hz, 1H), 4.06 – 3.59 (m, 8H), 3.33 (s, 3H), 3.27 (s, 8H), 2.59 (d, J = 11.5 Hz, 2H), 2.19 – 2.10 (m, 2H), 1.98 (td, J = 15.8, 5.6 Hz, 4H), 1.67 (q, J = 12.6 Hz, 3H), 1.40 (q, J = 11.8 Hz, 3H), 1.24 (s, 3H).

Example S84

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(3-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 88)



[568] **Step 1:** A solution of methyl 2-(3-bromopropoxy)acetate (300 mg,1.41 mmol), tert-butyl 4-mercaptopiperidine-1-carboxylate (306 mg, 1.41 mmol), K_2CO_3 (388 mg, 2.82 mmol) and KI (23.4 mg,

0.141 mmol) in DMF was stirred at 90°C for 2h. Added EA and H_2O, the organic layers were washed with NaCl aqueous solution three times, dried over Na_2SO_4 and concentrated to give the curde product tert-butyl 4-((3-(2-methoxy-2-oxoethoxy)propyl)thio)piperidine-1-carboxylate (475 mg). ESI-MS:348.2[M+H]+.

[569] **Step 2:** To a solution of tert-butyl 4-((3-(2-methoxy-2-oxoethoxy)propyl)thio)piperidine-1-carboxylate (470 mg) in DCM (2 ml) was added TFA (1.5 ml). The mixture was stirred at rt for 40 min. The solvent was removed to afford the product methyl 2-(3-(piperidin-4-ylthio)propoxy)acetate (330 mg). ESI-MS:248.1[M+H]+.

[570] **Step 3:** A solution of methyl 2-(3-(piperidin-4-ylthio)propoxy)acetate (330 mg, 1.336 mmol), 3-bromo-5-(trifluoromethyl)pyridine (300 mg, 1.336 mmol), Ruphos Pd G3(55 mg, 0.067 mmol) and Cs_2CO_3 (870 mg, 2.672 mmol) in toluene (4 ml) was stirred at 95 °C under N_2 overnight. DCM was added and the mixture was filtered and the filtrate was concentrated, then the crude was purified by column chromatography on silica gel eluted with PE/EA =5/1-3/1 to give the product methyl 2-(3-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)thio)propoxy)acetate(76 mg). ESI-MS:393.1[M+H]+.

[571] **Step 4:** To a solution of methyl 2-(3-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)thio)propoxy)acetate (75 mg, 0.191 mmol) in DCM (2 ml) was added m-CPBA(75%) (88 mg, 0.383 mmol). The reaction was stirred at rt for 3h. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$. The organic layers were washed by $Na_2S_2O_4$ aqueous solution, dried over Na_2SO_4 and concentrated. The mixture was purified by pre-TLC eluting with EA to afford the product methyl 2-(3-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)propoxy)acetate (31 mg), ESI-MS:425.1[M+H]+.

[572] **Step 5:** To a solution of methyl 2-(3-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)propoxy)acetate (30 mg,0.071 mmol) in MeOH(1.5 ml) was added $NaBH_4$ (8 mg,0.213 mmol) at ice-bath.The mixture was stirred at rt for 3h. The mixture was purified by pre-TLC eluting with DCM/MeOH=20/1 to afford the product 2-(3-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)propoxy)ethan-1-ol (12 mg) ESI-MS:397.1[M+H]+.

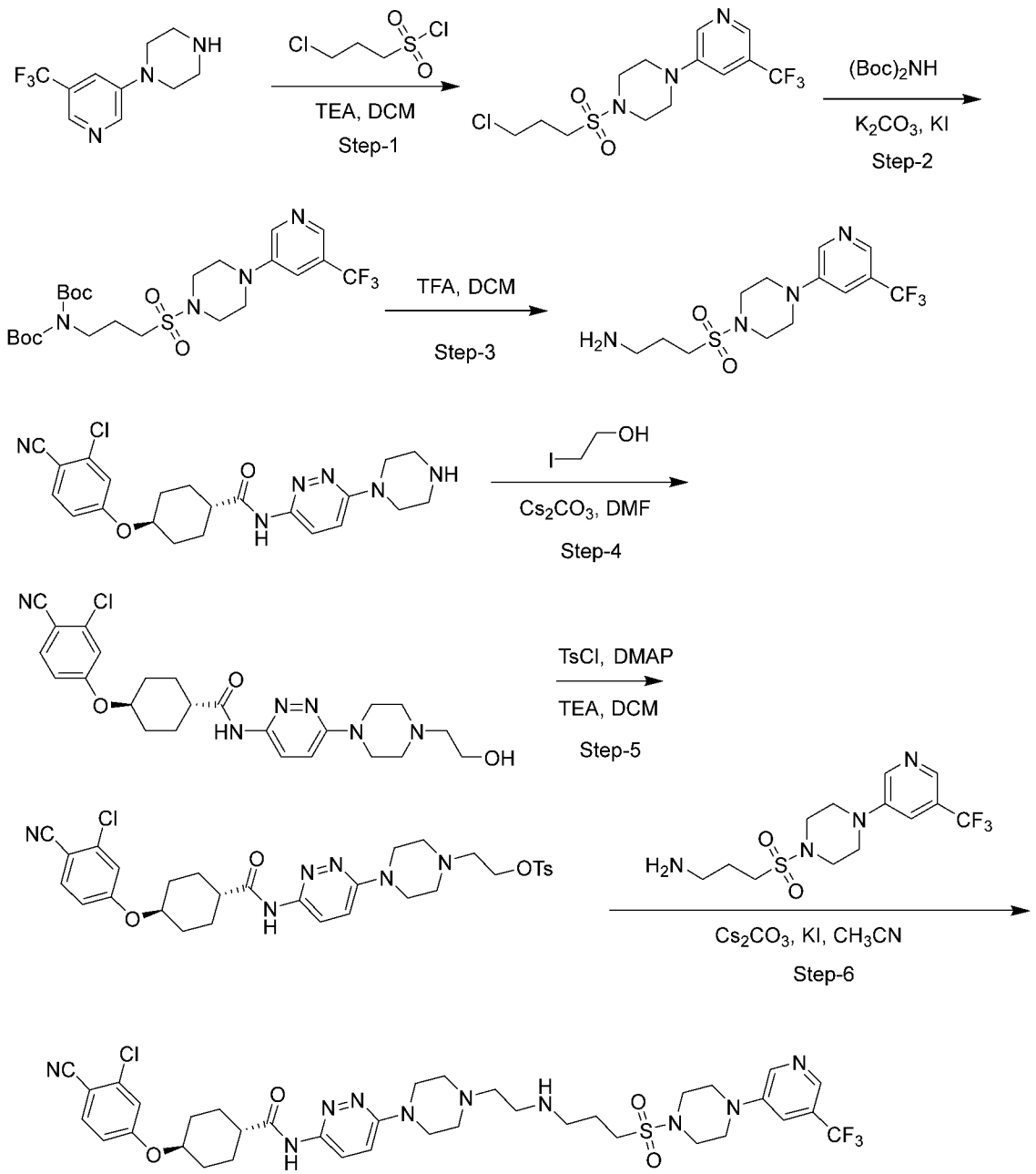
[573] **Step 6:** To a solution of 2-(3-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)propoxy)ethan-1-ol (12 mg,0.03 mmol), Et_3N (9.2 mg, 0.091 mmol) and DMAP (0.74 mg, 0.006 mmol) in DCM (1.5 ml) was added TsCl (12 mg, 0.06 mmol) at ice-bath. The reaction was stirred at rt overnight.The mixture was concentrated and purified by pre-TLC eluting with DCM/MeOH=20/1 to afford the product 2-(3-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)propoxy)ethyl 4-methylbenzenesulfonate(13 mg) ESI-MS:551.1[M+H]+.

[574] **Step 7:** A solution of 2-(3-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)propoxy)ethyl 4-methylbenzenesulfonate (13mg, 0.024 mmol), (1r,4R)-N-(6-(4-(l2-chloranyl)-

4l4-piperazin-1-yl)pyridazin-3-yl)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxamide (12.4 mg, 0.026 mmol), K_2CO_3 (8.2 mg, 0.06 mmol) and KI (2 mg, 0.012 mmol) in CH3CN was stirred at 80 °C for 6h. The mixture was filtered and the filtrate was concentrated,then the crude was purified by pre-TLC eluting with DCM/MeOH=10/1 to afford the product (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(4-(2-(3-((1-(5-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)sulfonyl)propoxy)ethyl)piperazin-1-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 88**, 7 mg) ESI-MS:819.3[M+H]+ 1H NMR (500 MHz, Chloroform) δ 8.64 (d, J = 1.3 Hz, 1H), 8.41 (d, J = 1.3 Hz, 1H), 8.00 (d, J = 7.5 Hz, 1H), 7.82 (t, J = 1.4 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.16 (d, J = 1.4 Hz, 1H), 7.09 – 6.96 (m, 2H), 6.03 (s, 1H), 4.62 – 4.54 (m, 1H), 3.65 – 3.57 (m, 4H), 3.56 – 3.39 (m, 8H), 3.21 (dt, J = 12.5, 6.4 Hz, 2H), 3.05 – 2.95 (m, 1H), 2.88 (dd, J = 6.6, 3.4 Hz, 3H), 2.67 (dt, J = 10.1, 6.1 Hz, 4H), 2.58 – 2.44 (m, 4H), 2.21 (td, J = 6.1, 3.6 Hz, 2H), 2.18 – 2.08 (m, 4H), 2.05 (td, J = 6.0, 2.7 Hz, 2H), 1.98 (td, J = 6.1, 3.6 Hz, 2H).

Example S85

Synthesis of (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-{6-[4-(2-{[3-(dioxo{4-[5-(trifluoromethyl)pyridin-3-yl]piperazin-1-yl}-λ6-sulfanyl)propyl]amino}ethyl)piperazin-1-yl]-1,2-diazin-3-yl}(1r,4r)-cyclohexanecarboxamide (Compound 89)



[575] **Step 1:** To a solution of 1-[5-(trifluoromethyl)pyridin-3-yl]piperazine (100 mg, 0.432 mmol) in DCM (3 mL) were added TEA (0.240 mL, 1.730 mmol)and 3-chloropropane-1-sulfonyl chloride (114.72 mg, 0.648 mmol), and the reaction was stirred at RT for 16 hours. The reaction was complete as detected by TLC (DCM: MeOH= 20:1). The reaction was diluted with water and extracted with ethyl acetate (10 mL × 4). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=30:1) to afford 4-[(3-chloropropyl)dioxo-λ6-sulfanyl]-1-[5-(trifluoromethyl)pyridin-3-yl]piperazine (87 mg, 0.234 mmol, 54.17%).

[576] **Step 2:** To a solution of 4-[(3-chloropropyl)dioxo-λ6-sulfanyl]-1-[5-(trifluoromethyl)pyridin-3-yl]piperazine (47 mg, 0.126 mmol) in DMF (2 mL) were added K_2CO_3 (52.41 mg, 0.379 mmol),

potassium iodide (20.98 mg, 0.126 mmol), and 2-methylpropan-2-yl ({[(2-methylprop-2-yl)oxy]carbonyl}amino)methanoate (41.20 mg, 0.190 mmol), and the reaction was stirred at 80 °C for 6 hours. TLC showed new spot was observed, and trace starting material remained. The reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (PE:EA=3:2) to afford 2-methylpropan-2-yl [8-(dioxo{4-[5-(trifluoromethyl)pyridin-3-yl]piperazin-1-yl}-λ6-sulfanyl)-2,2-dimethyl-4-oxo-5-aza-3-oxaoct-5-yl]methanoate (42 mg, 0.076 mmol, 60.12%).

[577] **Step 3:** To a solution of 2-methylpropan-2-yl [8-(dioxo{4-[5-(trifluoromethyl)pyridin-3-yl]piperazin-1-yl}-λ6-sulfanyl)-2,2-dimethyl-4-oxo-5-aza-3-oxaoct-5-yl]methanoate (42 mg, 0.076 mmol) in DCM (1.5 mL) were added TFA (1.5 mL, 19.589 mmol), and the reaction was stirred at RT for 2 hours. The reaction was complete as detected by TLC (DCM: MeOH= 20:1). The reaction was concentrated in vacuo to afford 3-(dioxo{4-[5-(trifluoromethyl)pyridin-3-yl]piperazin-1-yl}-λ6-sulfanyl)propan-1-amine (44 mg, 0.076 mmol, 99.75%).

[578] **Step 4:** To a solution of (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-[6-(piperazin-1-yl)-1,2-diazin-3-yl](1r,4r)-cyclohexanecarboxamide (100 mg, 0.227 mmol) in DMF (10 mL) were added Cs_2CO_3 (221.68 mg, 0.680 mmol), and 2-iodoethan-1-ol (117.00 mg, 0.680 mmol), and the reaction was stirred at 100 °C for 8 hours. TLC (DCM: MeOH= 10:1) showed new product was observed. The reaction was concentrated in vacuo. The crude product was chromatographed on silica gel (CH_3OH in CH_2Cl_2 0:100→1:100→5:100) to give (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-1,2-diazin-3-yl}(1r,4r)-cyclohexanecarboxamide (50 mg, 0.103 mmol, 45.46%).

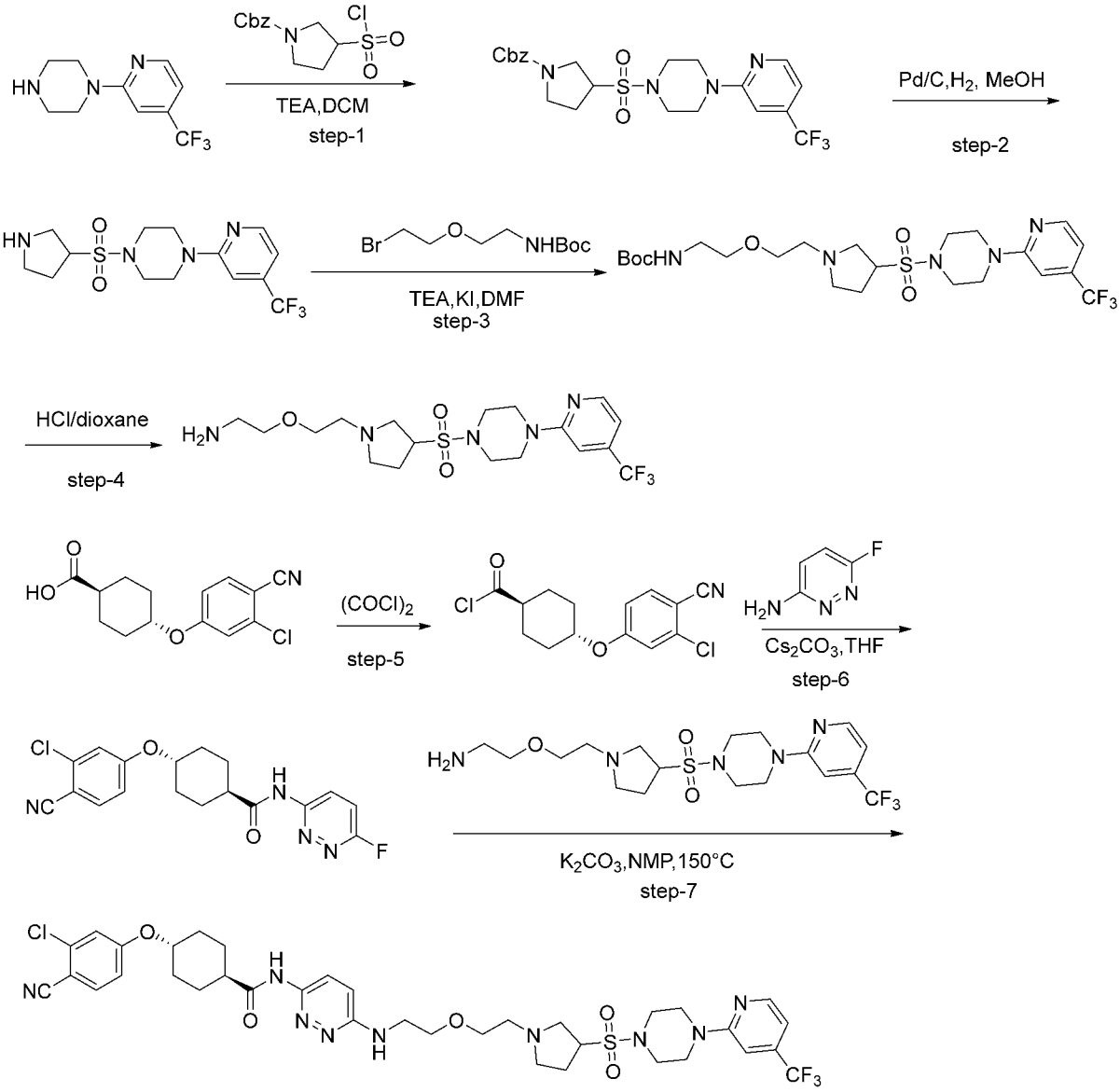
[579] **Step 5:** To a solution of (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]-N-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-1,2-diazin-3-yl}(1r,4r)-cyclohexanecarboxamide (50 mg, 0.103 mmol) in DCM (3 mL) were added DMAP (12.60 mg, 0.103 mmol), TEA (0.043 mL, 0.309 mmol), and TsCl (58.96 mg, 0.309 mmol), and the reaction was stirred at RT for 16 hours. TLC showed new spot was observed, The reaction was concentrated in vacuo. The residue was purified by preparative TLC (DCM: MeOH=25:1) to afford 2-{4-[6-({[(1r,4r)-4-[(3-chloro-4 cyanophenyl)oxy]cyclohexyl]carbonyl}amino)-1,2-diazin-3-yl]piperazin-1-yl}ethyl 4-methylbenzenesulfonate (30 mg, 0.047 mmol, 45.57%).

[580] **Step 6:** To a solution of 2-{4-[6-({[(1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]cyclohexyl]carbonyl}amino)-1,2-diazin-3-yl]piperazin-1-yl}ethyl 4-methylbenzenesulfonate (30 mg, 0.047 mmol) in CH_3CN (3 mL) were added Cs_2CO_3 (45.88 mg, 0.141 mmol), potassium iodide (7.79 mg, 0.047 mmol), and 3-(dioxo{4-[5-(trifluoromethyl)pyridin-3-yl]piperazin-1-yl}-λ6-sulfanyl)propan-1-amine (16.54 mg, 0.047 mmol), and the reaction was stirred at 80 °C for 3 hours. LCMS showed product was observed, the reaction was concentrated in vacuo to afford crude product, the crude product was purified by preparative TLC (DCM: MeOH=10:1) to afford (1r,4r)-4-

[(3-chloro-4-cyanophenyl)oxy]-N-{6-[4-(2-{[3-(dioxo{4-[5-(trifluoromethyl)pyridin-3-yl]piperazin-1-yl}-λ6-sulfanyl)propyl]amino}ethyl)piperazin-1-yl]-1,2-diazin-3-yl}(1r,4r)-cyclohexanecarboxamide (**Compound 89**, 6.2 mg). ESI-MS: 819.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 8.93 (s, 1H), 8.48 (d, J = 2.8 Hz, 1H), 8.38 (s, 1H), 8.31 (s, 1H), 7.58 – 7.51 (m, 1H), 7.34 (s, 1H), 7.05 – 6.95 (m, 2H), 6.84 (dd, J = 8.8, 2.4 Hz, 1H), 4.31 (s, 1H), 3.74 (s, 1H), 3.68 – 3.59 (m, 1H), 3.49 (s, 5H), 3.36 (s, 5H), 3.14 (s, 3H), 2.85 (s, 2H), 2.66 (s, 3H), 2.47 (s, 2H), 2.33 (s, 1H), 2.22 (t, J = 7.6 Hz, 4H), 1.75 (d, J = 12.7 Hz, 3H), 1.67 – 1.50 (m, 5H).

Example S86

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-((2-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)ethyl)amino)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 90)



[581] **Step 1:** To the mixture of 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine (1200 mg, 5.341 mmol) and TEA (2.224 mL, 15.999 mmol) in DCM (20 mL) was added benzyl 3-(chlorodioxo-λ6-sulfanyl)tetrahydropyrrole-1-carboxylate (1.62 g, 5.333 mmol), then the reaction mixture was stirred at RT for overnight. The residue was purified by preparative TLC (PE: EA=2:1) to afford benzyl 3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidine-1-carboxylate(1g, 2.006mmol) as white solid.

[582] **Step 2:** To the mixture of benzyl 3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidine-1-carboxylate(1g, 2.006mmol) in MeOH(20 mL) was added Pd/C (100mg). The reaction mixture was stirred at RT for overnight under H_2 atmosphere, filtered and concentrated in vacuo to give the crude product 1-(pyrrolidin-3-ylsulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazinehydrochloride (850 mg) as white solid.

[583] **Step 3:** To a solution of 1-(pyrrolidin-3-ylsulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazine (50 mg, 0.137 mmol) in DMF (5 mL) were added tert-butyl (2-(2-bromoethoxy)ethyl)carbamate (36.79 mg, 0.137 mmol), TEA (0.057 mL, 0.412 mmol), and KI (22.78 mg, 0.137 mmol), and the reaction was stirred at 80 °C overnight. The reaction was filtered and loaded on a silica gel plate. The plate was developed using 20:1 DCM:MeOH. The residue was concentrated in vacuo, and dried to afford tert-butyl (2-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)ethyl)carbamate (72 mg, 0.131 mmol, 95%).

[584] **Step 4:** tert-butyl (2-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)ethyl)carbamate (72 mg, 0.131 mmol) was dissolved in HCl/dioxane (5 mL), the reaction mixture was stirred at RT overnight, and concentrated in vacuo to give the crude product 2-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)ethan-1-amine (55 mg, 0.122 mmol, 92.99%) as white solid.

[585] **Step 5:** To a solution of 4-[(3-chloro-4-cyanophenyl)oxy]cyclohexane-1-carboxylic acid (200 mg, 0.715 mmol) in DCM (6 mL) were added Oxalyl chloride (0.3 mL, 3.517 mmol), and the reaction was stirred at room temperature for overnight, and then concentrated in vacuo to give the (1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carbonyl chloride (200 mg, 0.671 mmol, 93.82%).

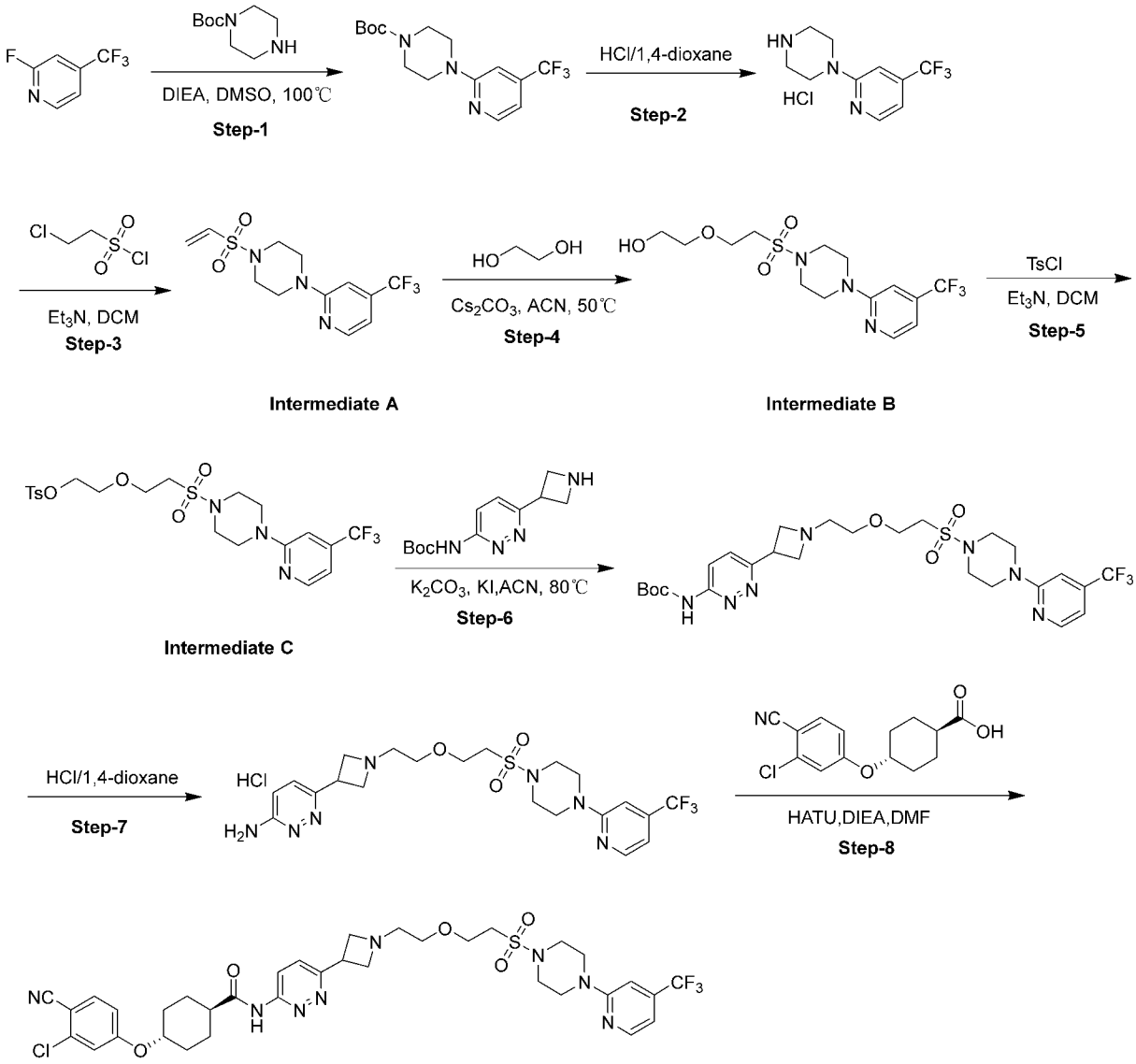
[586] **Step 6:** To a mixture of 6-fluoro-1,2-diazin-3-amine (120 mg, 1.061 mmol) and Cs_2CO_3 (440 mg, 1.350 mmol) in THF (6 mL) was added 4-[(3-chloro-4-cyanophenyl)oxy]cyclohexane-1-carbonyl chloride (200 mg, 0.671 mmol), and the reaction mixture was stirred at RT for overnight. The residue was purified by preparative TLC (DCM: MeOH=20:1) to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-fluoropyridazin-3-yl)cyclohexane-1-carboxamide (43 mg, 0.115 mmol) as white solid.

[587] **Step 7:** To a solution of 4-[(3-chloro-4-cyanophenyl)oxy]-N-(6-fluoro-1,2-diazin-3-yl)cyclohexanecarboxamide (43.17 mg, 0.115 mmol) in NMP (1 mL) were added 2-(2-(3-((4-(4-

(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)ethan-1-amine (52 mg, 0.115 mmol) and K_2CO_3 (47.75 mg, 0.346 mmol), and the reaction was stirred at 150 °C overnight. The reaction was filtered and loaded on a silica gel plate. The plate was developed using 10:1 DCM:MeOH. The residue was concentrated in vacuo, and dried to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-((2-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethoxy)ethyl)amino)pyridazin-3-yl)cyclohexane-1-carboxamide (**Compound 90**, 7 mg, 0.009 mmol). ESI-MS: 806.2 [M+H]+. 1H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.32 (s, 1H), 8.16 (d, J = 9.6 Hz, 1H), 7.60 – 7.53 (m, 1H), 7.00 (s, 2H), 6.84 (d, J = 12.9 Hz, 3H), 5.97 (s, 1H), 5.35 (s, 1H), 4.30 (s, 1H), 3.91 (s, 1H), 3.69 (d, J = 16.8 Hz, 10H), 3.45 (s, 4H), 3.24 (s, 1H), 2.98 (d, J = 33.0 Hz, 4H), 2.42 (d, J = 49.4 Hz, 4H), 2.22 (s, 4H), 1.63 – 1.47 (m, 3H).

Example S87

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)azetidin-3-yl)pyridazin-3-yl)cyclohexane-1-carboxamide(Compound 96)



[588] **Step-1**: DIEA (19.77g, 153.25 mmol) was added to a solution of 2-fluoro-4-(trifluoromethyl)pyridine (5060 mg, 30.650 mmol) and 2-methylpropan-2-yl piperazine-1-carboxylate (7300 mg, 39.195 mmol) in DMSO (20 ml). After stirred 3 h at 100 °C, the mixture was concentrated and the residue was recrystallized by 30ml ethanol and 100 ml H_2O to get 2-methylpropan-2-yl-4-[4-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxylate (3100 mg, 30.53%).

[589] **Step-2**: HCl (5 ml, 4 mol/L in dioxane) was added to a solution of 4-[4-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxylate (3100 mg, 9.356 mmol) in dioxane (10 ml). After stirred 12 h at rt, the reaction solution was concentrated to afford the 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine hydrochloride (2.45 g, 98%).

[590] **Step-3**: Et_3N (1.85g, 18.31 mmol) and 2-chloroethane-1-sulfonyl chloride (1.78g, 18.34mmol) was slowly added to a solution of 1-(4-(trifluoromethyl)pyridin-2-yl)piperazine hydrochlorid (2.45 g, 9.17 mmol) in DCM(15 ml) at 0°C respectively. Then the reaction was stirred at rt for 2h. The

reaction mixture was concentrated and the residue was purified by silica gel chromatography eluted with DCM to give 1-(4-(trifluoromethyl)pyridin-2-yl)-4-(vinylsulfonyl)piperazine (2.51 g, 85%), which was labelled as Intermediate A.

[591] **Step-4**: ethane-1,2-diol (1.94 g, 31.28 mmol) was added to a solution of 1-(4-(trifluoromethyl)pyridin-2-yl)-4-(vinylsulfonyl)piperazine (2.51 g, 7.82 mmol) and Cs_2CO_3 (5.1 g, 15.65 mmol) in ACN (10 ml). After stirred 5 h at 90°C, the suspension was filtered and the filtrate was concentrated and the residue was then recrystallized by ethyl acetate (20 ml) to generate 2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethan-1-ol (2.47g, 82.5%), which was labelled as Intermediate B.

[592] **Step-5**: 4-methylbenzenesulfonyl chloride (1.59 g, 8.38 mmol) was added to a solution of 2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethan-1-ol (2.47 g, 6.45 mmol) and Et_3N (1.96 g, 19.35 mmol) in DCM (15 ml) at 0°C. Then the solution was stirred at rt overnight. H_2O (10 ml) and DCM (15 ml) was added to the reaction. The mixture was separated and the organic layer was concentrated and purified by silica gel chromatography to get 2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl 4-methylbenzenesulfonate (3.15 g, 91%), which was labelled as Intermediate C.

[593] **Step-6**: K_2CO_3 (2.43 g, 17.6 mmol), KI (9.73 g, 5.86 mmol) was added to a solution of 2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl 4-methyl- -benzenesulfonate (3.15 g, 5.86 mmol) and tert-butyl (6-(azetidin-3-yl)pyridazin-3-yl)carbamate (1.47 g, 5.88 mmol) in ACN (20 ml). After stirred 8 h at 80°C, H_2O (20 ml) was added to the reaction and extracted with ethyl acetate (20 ml×3), the organic layer was washed by saturated saline water (10 ml), dried by Na_2SO_4 , concentrated and purified by silica gel chromatography to give tert-butyl (6-(1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)azetidin-3-yl)pyridazin-3-yl)carbamate (2.3 g, 64%).

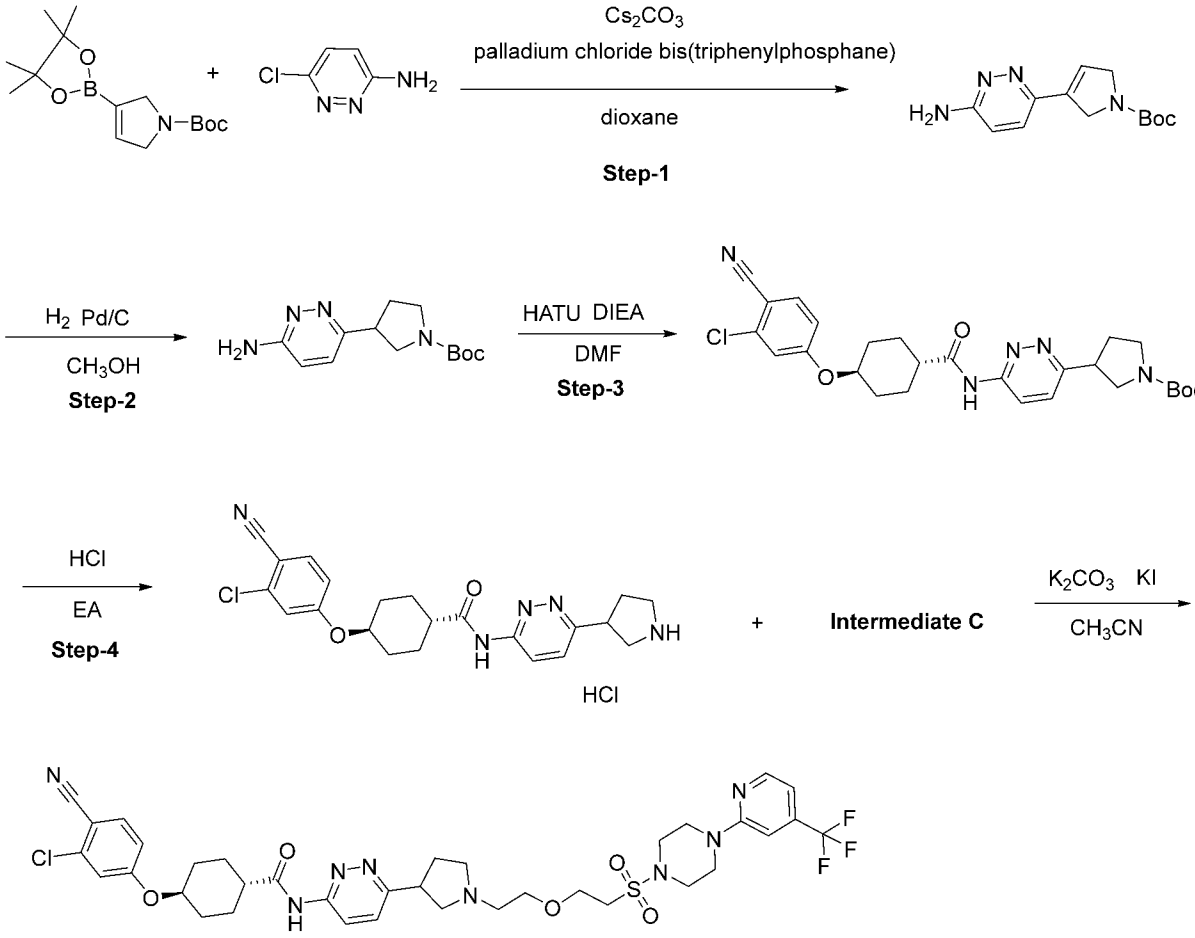
[594] **Step-7**: HCl (4 ml, 4 mol/L in dioxane) was added to a solution of ert-butyl (6-(1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)azetidin-3-yl)pyridazin-3-yl)carbamate (2.3 g, 3.74 mmol) in dioxane (10 ml). After stirred 12 h at rt, the reaction solution was concentrated to afford 6-(1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl) piperazin-1-yl)sulfonyl)ethoxy)ethyl)azetidin-3-yl)pyridazin-3-amine hydrochloride (1.89 g, 91.7%).

[595] **Step-8**: DIEA(1.77 g, 13.72 mmol) and HATU (1.95 g, 5.13 mmol)was added to a solution of 6-(1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl) ethoxy)ethyl) azetidin-3-yl)pyridazin-3-amine hydrochloride (1.89 g, 3.43 mmol) and (1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxylic acid (1.15 g, 4.12 mmol) in DMF (8 ml) and the reaction was stirred at rt overnight. The mixture was diluted with water (30 ml) and filtered. The filter cake was dried and purified by recrystallization from ethyl acetate to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-

(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)azetidin-3-yl)pyridazin-3-yl)cyclohexane-1-carboxamide(**Compound 96**, 1.86 g, 70%). ESI-MS = 777.3, [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.32 (dd, J = 19.7, 7.2 Hz, 2H), 7.86 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.22-7.09 (m, 2H), 6.92 (d, J = 5.0 Hz, 1H), 4.66-4.53 (m, 1H), 4.04 (s, 4H), 3.83-3.64 (m, 6H), 3.54 (s, 2H), 3.37 (t, J = 5.9 Hz, 2H), 3.30-3.21 (m, 4H), 2.99 (s, 2H), 2.62 (t, J = 11.6 Hz, 2H), 2.14 (d, J = 9.5 Hz, 2H), 1.95 (d, J = 11.1 Hz, 2H), 1.66 (dd, J = 25.0, 10.4 Hz, 2H), 1.40 (dd, J = 23.1, 10.0 Hz, 2H).

Example S88

Synthesis of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)pyrrolidin-3-yl)pyridazin-3-yl)cyclohexane-1-carboxamide (Compound 97)



[596] **Step-1**: 6-chloro-1,2-diazin-3-amine (500 mg, 3.860 mmol) was dissolved in dioxane (10 mL) , and then 2-methylpropan-2-yl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1- carboxylate (1253.22 mg, 4.245 mmol), palladium chloride bis(triphenylphosphane) (135.45 mg, 0.193 mmol) and Cs_2CO_3 (2515.01 mg, 7.719 mmol) were added, the reaction mixture was stirred at 100°C for 6 h under N_2 atomsphere. The reaction solution was concentrated and the residue was purified

by silica gel chromatography to give 2-methylpropan-2-yl 3-(6-amino-1,2-diazin-3-yl)-2,5-dihydro-1H-pyrrole-1- carboxylate (800 mg, 79.02%) .

[597] **Step-2**: 10% Pd/C (818 mg) was added to a solution of 2-methylpropan-2-yl 3-(6-amino-1,2-diazin-3-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (800 mg, 3.05 mmol) in methanol (5 ml). The suspension was degassed under vacuum and purged with H_2 for four times and stirred at rt overnight. The reaction was filtered and filtrate was concentrated to get tert-butyl 3-(6-aminopyridazin-3-yl)pyrrolidine-1-carboxylate (800 mg, 100%).

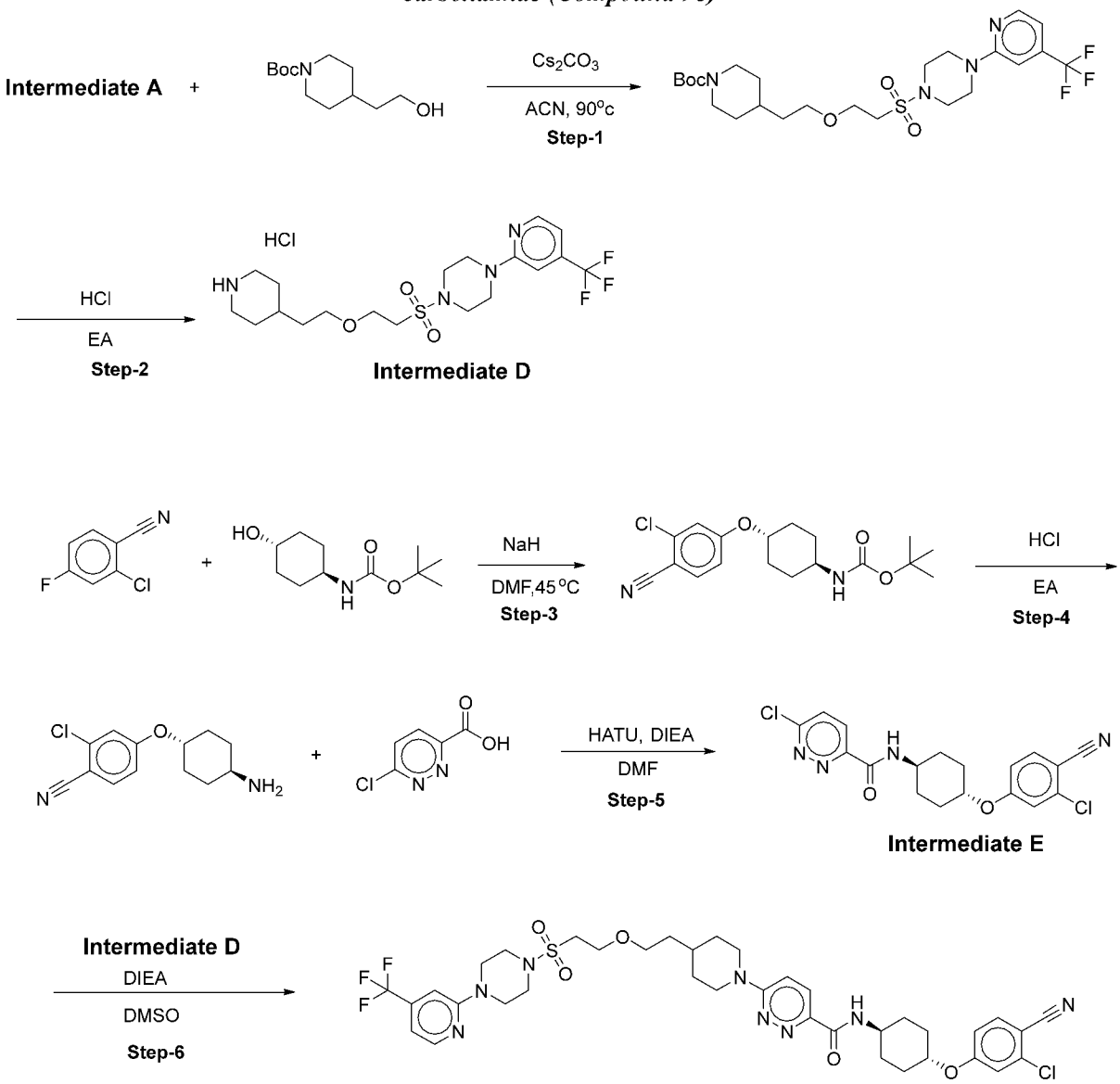
[598] **Step-3**: DIEA (1.16 g, 9 mmol) and HATU (1.71 g, 4.5 mmol) was added to a solution of (1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]cyclohexane-1-carboxylic acid (837 mg, 3 mmol) and tert-butyl 3-(6-aminopyridazin-3-yl)pyrrolidine-1-carboxylate (800 mg, 3 mmol) in DMF (5 mL). After stirred at rt for 12 h, the water was added and the reaction mixture was extracted with EtOAc (15 ml×3). The organic layer was then washed with water (15 ml), and dried over Na_2SO_4. The crude product was obtained by removing solvent under vacuum and purified by flash column chromatography to give tert-butyl-3-(6-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexane-1-carboxamido)pyridazin-3-yl)pyrrolidine-1-carboxylate (787 mg, 50%).

[599] **Step-4**: HCl (1 ml, 4 mol/L in ethyl acetate) was added to a solution of tert-butyl 3-(6-((1r,4r)-4- (3-chloro-4-cyanophenoxy)cyclohexane-1-carboxamido)pyridazin-3-yl)pyrrolidine-1-carboxylate (787 mg, 1.5mmol) in ethyl acetate (4 ml). After stirred 12 h at rt, the reaction solution was concentrated to afford (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(pyrrolidin-3-yl)pyridazin-3-yl)c yclohexane-1-carboxamide hydrochloride(680 mg, 98.4%).

[600] **Step-5**: K_2CO_3 (609 mg, 4.42 mmol), KI (24.4 mg, 0.147 mmol) was added to a solution of (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(pyrrolidin-3-yl)pyridazin-3-yl)cyclohexane-1-carboxamide hydrochloride (680 mg, 1.47 mmol) and Intermediate C (789 mg, 1.47 mmol) in ACN (10 ml). After stirred 5 h at 80°C, water was added (30 ml) and stirred for additional 10 min. The mixture was filtered and the filter cake was dried and recrystallized by ethyl acetate to give (1r,4r)-4-(3-chloro-4-cyanophenoxy)-N-(6-(1-(2-(2- ((4-(4-(trifluoromethyl)pyridin -2-yl)piperazin-1-yl)sulfonyl)ethoxy) ethyl)pyrrolidin-3-yl)pyridazin-3-yl) cyclohexane-1-carboxamide (**Compound 97**, 836 mg, 72%). ESI-MS = 791.3, [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 8.33 (d, J = 5.1 Hz, 1H), 8.25 (d, J = 9.2 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 9.3 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.21-7.10 (m, 2H), 6.91 (dd, J = 5.2, 1.3 Hz, 1H), 4.59-4.45 (m, 1H), 3.73 (dt, J = 10.4, 5.4 Hz, 6H), 3.56 (s, 4H), 3.38 (t, J = 5.8 Hz, 2H), 3.27 (t, J = 5.1 Hz, 4H), 2.97 (s, 2H), 2.61-2.45 (m, 1H), 2.22 (s, 1H), 2.18-2.10 (m, 2H), 2.05-1.90 (m, 3H), 1.73-1.59 (m, 2H), 1.47-1.31 (m, 2H), 1.23 (s, 2H).

Example S89

Synthesis of N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-1-yl)pyridazine-3-carboxamide (Compound 98)



[601] **Step-1**: Tert-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (357 mg, 1.56 mmol) was added to a solution of 1-(4-(trifluoromethyl)pyridin-2-yl)-4-(vinylsulfonyl)piperazine (500 mg, 1.56 mmol) and Cs_2CO_3 (1.13 mg,3.46 mmol) in ACN (10 ml). After stirred 5 h at 90°C, water (20 ml) was added to the mixture and filtered. The filter cake was washed with 10 ml of H2O, dried in vacuum and recrystallized with ethyl acetate to afford tert-butyl 4-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl) piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidine-1-carboxylate (628 mg, 73%).

[602] **Step-2**: HCl (1 ml, 4 mol/L in ethyl acetate) was added to a solution of tert-butyl 4-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidine-1-carboxylate(628 mg,1.14mmol) in ethyl acetate (4 ml). After stirred 12 h at rt, the reaction solution was concentrated to

afford 1-((2-(2-(piperidin-4-yl)ethoxy)ethyl)sulfonyl)-4-(4-(trifluoromethyl) pyridin-2-yl)piperazine hydrochloride(550 mg, 99.27%), which was labelled as Intermediate D.

[603] **Step-3**: Sodium hydride (278.69 mg, 6.967 mmol) was added to a solution of 2-methylpropan-2-yl {[(1r,4r)-4-hydroxycyclohexyl]amino}methanoate (1000 mg, 4.645 mmol) in N,N-dimethylmethanamide (10 mL) at 0°C and stirred for 0.5h. Then 2-chloro-4-fluorobenzene-1-carbonitrile (648 mg, 4.166 mmol) in DMF(5ml), was added to the reaction mixture and stirred at rt overnight. Saturated ammonium chloride (30mL) was added to the reaction at 0°C and then extracted with EA (30 ml×3). The organic layer was washed by washed with water, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography to give 1.2-methylpropan-2-yl {[(1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]cyclohexyl] amino} methanoate (1470 mg, 90.21%).

[604] **Step-4**: HCl (10 ml, 4 mol/L in ethyl acetate) was added to a solution of 2-methylpropan-2-yl {[(1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]cyclohexyl]amino}methanoate (1600 mg, 4.560 mmol) in ethyl acetate (10 ml). After stirred 12 h at rt, the reaction solution was concentrated to afford 2-chloro-4-{[(1r,4r)-4-aminocyclohexyl]oxy}benzene-1-carbonitrile (1100 mg, 96.20%).

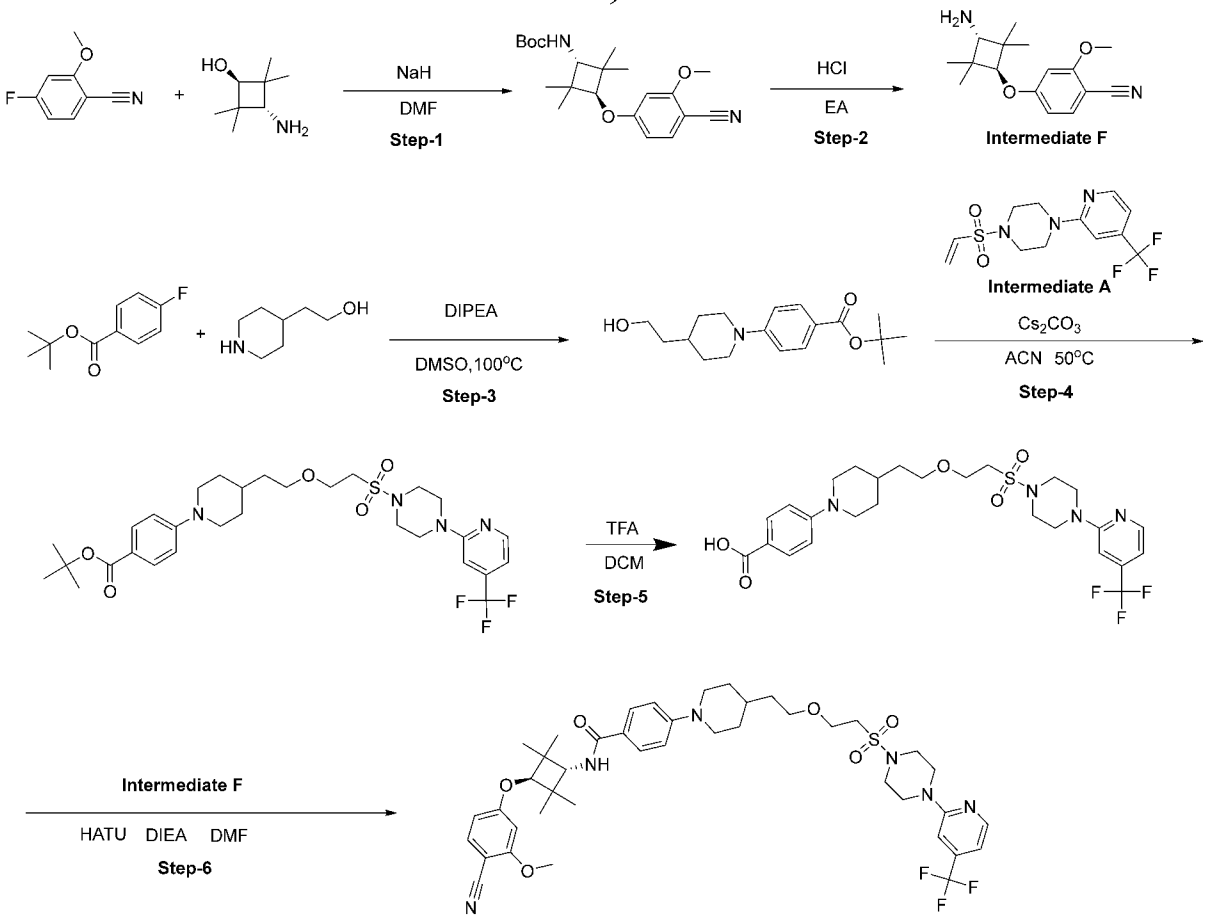
[605] **Step-5**: DIEA (308.83 mg, 2.394 mmol) and HATU (303.24 mg, 0.798 mmol) was added to a solution of 2-chloro-4-{[(1r,4r)-4-aminocyclohexyl]oxy} benzene-1- carbonitrile (200 mg, 0.798 mmol) and 6-chloro-1,2-diazine-3-carboxylic acid (139.11 mg, 0.877 mmol) in DMF (5 mL). The reaction mixture was stirred at rt overnight, quenched with H_2O (10 ml) and extracted with EA (20 ml×3). The organic layers were separated, washed with brine (10 ml), dried, and concentrated. The crude product was purified by flash column chromatography to give 6-chloro-N-[(1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy] cyclohexyl]-1,2- diazine-3-carboxamide (170 mg, 54.4%), which was labelled as Intermediate E.

[606] **Step-6**: DIEA (281 mg, 2.18mmol) was added to a solution of 4-[(2-{[2-(hexahy dropyridin-4-yl)ethyl]oxy}ethyl)dioxo-λ6-sulfanyl]-1-[4-(trifluoromethyl)pyridin-2-yl]piperazine hydrochloride (Intermediate D, 212 mg, 0.436 mmol) and 6-chloro-N- [(1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]cyclohexyl]-1,2-diazine-3-carboxamide (170 mg, 0.436 mmol) in DMSO (3 ml). After stirred 5h at 80°C, water (10 ml) was added and extracted with (10 ml×3), the organic layers were separated, washed with brine, dried, and concentrated. The residue was purified by flash column chromatography to give 6-[4-(2-{[2-(dioxo{4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}- λ6-sulfanyl)ethyl]oxy}ethyl)-hexahydropyridin-1-yl]-N-[(1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]cyclohexyl]-1,2-diazine-3-carboxamide (**Compound 98**, 207 mg, 59%). ESI-MS = 805.3, [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.58 (d, J = 8.2 Hz, 1H), 8.31 (d, J = 5.1 Hz, 1H), 7.86-7.77 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 9.7 Hz, 1H), 7.18-7.10 (m, 2H), 6.88 (dd, J = 5.2, 1.3 Hz, 1H), 4.56-4.51 (m, 1H), 4.41 (d, J = 13.1 Hz, 2H), 3.90-3.82 (m, 1H), 3.71-3.64 (m, 6H), 3.45 (t, J = 6.5 Hz, 2H), 3.37 (t, J = 5.7

Hz, 2H), 3.26 (t, J = 5.1 Hz,4H), 2.88 (t, J = 12.0 Hz, 2H), 2.12-2.09 (m, 2H), 1.91-1.897 (m, 2H), 1.69 - 1.59 (m, 5H), 1.55-1.46 (m, 2H), 1.39-1.34 (m, 2H), 1.10-1.01 (m, 2H).

Example S90

Synthesis of N-((1r,3r)-3-(4-cyano-3-methoxyphenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)ethoxy)ethyl)piperidin-1-yl)benzamide (Compound 99)



[607] **Step-1**: A suspension of NaH (317.58 mg, 7.9 mmol) in DMF (4 mL) was added in to a solution of 2-methylpropan-2-yl {[(1r,3r)-3-hydroxy-2,2,4,4-tetramethylcyclobutyl]amino}methanoate (966 mg, 3.97 mmol) in DMF (5 ml) dropwise in an ice bath. Then the reaction was stirred at rt for 30 min. 4-chloro-2-methoxybenzene- 1-carbonitrile (1.2, 7.16 mmol) in DMF (4 ml) was added to the mixture in an ice bath. The reaction was stirred at rt for 3h. And the mixture was poured into H_2O (10 ml) and extracted with EA (10 ml×3). The organic layers were washed with H_2O, concentrated and purified by flash column chromatography to give 2-methylpropan-2-yl {[(1r,3r)-3-[(4-cyano-3-methoxyphenyl)oxy]-2,2,4,4-tetramethylcyclobutyl] amino}methanoate (930 mg, 62.56%).

[608] **Step-2**: To a solution of 2-methylpropan-2-yl {[(1r,3r)-3-[(4-cyano-3-methoxyphenyl)oxy] -2,2,4,4-tetramethyl cyclobutyl]amino}methanoate (930 mg, 2.48 mmol) in EA (5 mL), 4M HCl in EA (2

mL, 8 mmol) was added and stirred at rt for overnight. The reaction mixture was concentrated to give 4-{[(1r,3r)-3-amino- 2,2,4,4-tetram ethylcyclobutyl]oxy}- 2-methoxybenz ene-1-carbonitrile hydrochloride (768 mg, 99.49%), which is labelled as intermediate F.

[609] **Step-3**: DIPEA (2.022 mL, 11.610 mmol) was added to a solution of 2-methylpropan-2-yl 4-fluorobenzoate (0.76 g, 3.870 mmol) and 2-(hexahydropyridin-4-yl)ethan-1-ol (1 g, 7.740 mmol) in DMSO (5 ml). After stirred 12h at 110°C, water (20 ml) was added and the mixture was extracted with EA (10 ml×3). The organic layers were washed with H_2O, concentrated and purified by flash column chromatography to get tert-butyl 4-(4-(2-hydroxyethyl)piperidin-1-yl)benzoate (1000 mg, 84.60%).

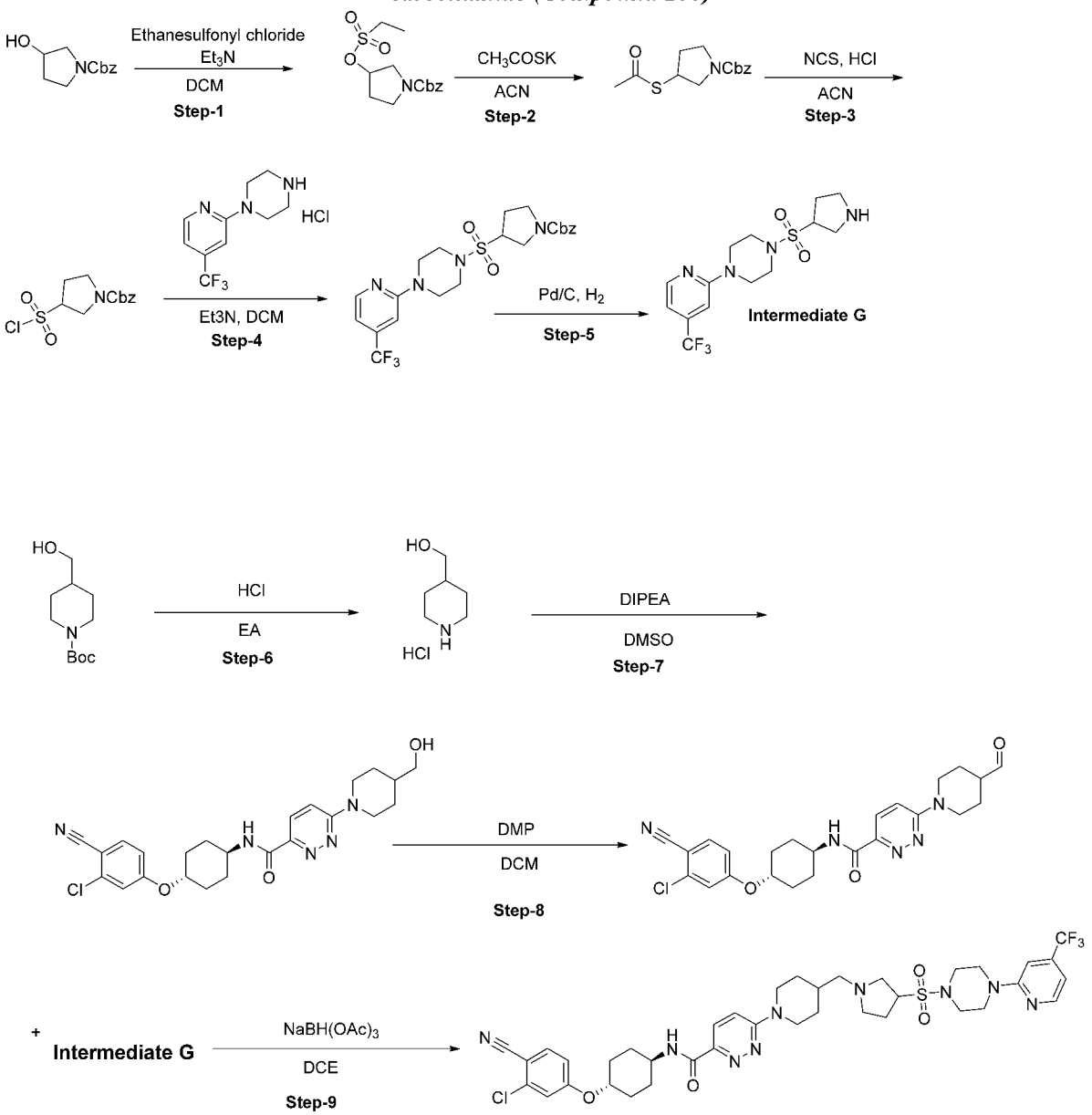
[610] **Step-4**: Cs_2CO_3 (969.81 mg, 2.977 mmol) was added to a solution of 2-methylpropan-2-yl 4-[4-(2-hydroxyethyl)hexahydropyridin-1-yl]benzoate (500 mg, 1.637 mmol) and 1-[dioxo(vinyl)-λ6-sulfanyl]-4-[4-(trifluoromethyl) pyridin-2-yl]piperazine (intermediate A, 478.21 mg, 1.488 mmol) in ACN (15 ml). After stirred 12 h at 50°C, water (20 ml) was added and the mixture was extracted with EA (10ml×3). The organic layers were washed with H_2O (10 ml), concentrated and purified by flash column chromatography to get tert-butyl 4-(4-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl) sulfonyl)ethoxy)ethyl)piperidin-1-yl)benzoate (835 mg, 89.52%).

[611] **Step-5**: TFA (0.489 mL, 6.382 mmol) was added to a solution of 2-methylpropan-2-yl 4-[4-(2-{[2-(dioxo{4-[4-(trifluoromethyl)pyridin-2-yl] piperazin-1-yl}-λ6-sulfanyl)ethyl]oxy}ethyl) hexahydropyridin-1-yl]benzoate (200 mg, 0.319 mmol) in DCM (0.5 mL). After stirred 4h at rt, the reaction mixture was concentrated to give 4-(4-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl) sulfonyl)ethoxy) ethyl)piperidin-1-yl)benzoic acid (180 mg, 98.85%).

[612] **Step-6**: DIEA (0.219 mL, 1.260 mmol) and HATU (179.66 mg, 0.473 mmol) was added to a solution of 4-[4-(2-{[2-(dioxo{4-[4-(trifluoromethyl) pyridin-2-yl] piperazin-1-yl}-λ6-sulfanyl)ethyl]oxy}ethyl) hexahydropyridin-1-yl]benzoic acid (180 mg, 0.315 mmol) and 4-{[(1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutyl]oxy}- 2-methoxybenzene-1-carbonitrile (172.85 mg, 0.630 mmol) in DMF (2 mL). After stirred 3h at rt, water (20 ml) was added and the mixture was extracted with EA (10 ml×3). The organic layers were washed with H_2O (10ml), concentrated and purified by flash column chromatography to get N-((1r,3r)-3-(4-cyano-3- methoxyphenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(2-((4-(4-(trifluoromethyl)pyridin-2-yl) piperazine -1-yl)sulfonyl)ethoxy)ethyl)piperidin-1-yl)benzamide (**Compound 99**, 84 mg, 30.33%). ESI-MS = 827.2, [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.26 (d, J = 3.9 Hz, 1H), 7.82 (d, J = 9.9 Hz, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.68-7.62 (m, 2H), 7.49-7.40 (m, 1H), 7.08-7.02 (m, 2H), 6.95 (d, J = 1.9 Hz, 1H), 6.82 (dd, J = 8.6, 2.4 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 4.45-4.21 (m, 1H), 3.97 -3.90 (m, 1H), 3.92 (s, 2H), 3.72 (d, J = 5.1 Hz, 1H), 3.73-3.66 (m, 3H), 3.64 (dd, J = 6.4, 5.4 Hz, 2H), 3.48-3.37 (m, 6H), 3.13-3.15 (m, 4H), 3.11-3.02 (m, 2H), 1.82-1.50 (m, 8H), 1.12 (t, J = 1.4 Hz, 6H), 1.07 (t, J = 1.4 Hz, 6H).

Example S91

Synthesis of N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)methyl)piperidin-1-yl)pyridazine-3-carboxamide (Compound 100)



[613] **Step-1**: Ethanesulfonyl chloride (823.99 mg, 6.409 mmol) was added to a solution of 2-methylpropan- 2-yl-3-hydroxytetrahydropyrrole-1-carboxylate (1000 mg, 5.341 mmol) and TEA (1.114 ml, 8.011 mmol) in DCM (10 ml). The mixture was stirred at 0°C for 30 min and then kept at room temperature for another 2h. H_2O (10 mL) was added and the mixture was extracted by DCM (10 mL×3). The organic layers were washed by aqueous NaCl, dried in Na_2SO_4 and concentrated to afford 1-{[(2-methylprop-2-yl)oxy]carbonyl}tetrahydropyrrole-3-yl ethanesulfonate (1490 mg, 99.87%).

[614] **Step-2**: Potassium thioacetate (921.76 mg, 8.001 mmol) was added to a solution of 1-{[(2-methylprop-2-yl)oxy]carbonyl}tetrahydropyrrole-3-yl ethanesulfonate (1490 mg, 5.334 mmol) in DMF (5 ml). After stirred 3h at 70°C, H_2O (10 ml) was added and the mixture was extracted by DCM (10 ml×3). The organic layers were washed by aqueous NaCl, dried in Na_2SO_4 and concentrated to afford 2-methylpropan-2-yl-3-(acetylsulfanyl)tetrahydropyrrole-1-carboxylate (1300 mg, crude).

[615] **Step-3**: NCS (816.40 mg, 6.114 mmol), 1M HCl (2.038 mL, 2.038 mmol) was added to a solution of 2-methylpropan-2-yl-3-(acetylsulfanyl)tetrahydropyrrole-1-carboxylate (500 mg, 2.038 mmol) in ACN (20 mL) at 0°C. After stirred 1h at rt, H_2O (10 mL) was added and the mixture was extracted by DCM (10 ml×3). The organic layers were washed by aqueous NaCl, dried in Na_2SO_4 and concentrated to afford 2-methylpropan-2-yl -3-(chlorodioxo-λ6-sulfanyl)tetrahydropyrrole-1-carboxylate (502 mg, crude).

[616] **Step-4**: Et_3N (670mg,6.64mmol) and 2-methylpropan-2-yl -3-(chlorodioxo-λ6-sulfanyl)tetrahydropyrrole -1-carboxylate (502 mg, crude) was slowly added to a solution of 1-(4-(trifluoromethyl)pyridin-2-yl) piperazine hydrochloride (442 mg, 1.66 mmol) in DCM (10 ml) at 0°C. Then the reaction was stirred at room temperature for 4 h. H_2O (10 mL) was added and the mixture was extracted by DCM (10mL×3). The organic layers were washed by aqueous NaCl, dried in Na_2SO_4 and concentrated to afford benzyl 3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl) sulfonyl) pyrrolidine-1-carboxylate (372 mg, 45%).

[617] **Step-5**: 10% Pd/C (40 mg) was added to a solution of benzyl 3-((4-(4-(trifluoromethyl)pyridin-2-yl) piperazin-1-yl)sulfonyl)pyrrolidine-1-carboxylate (372 mg, 0.74 mmol) in MeOH (6 ml), The suspension was degassed under vacuum and purged with H_2 for four times and stirred at rt overnight. The reaction mixture was filtered and the filtrate was concentrated to get 1-(pyrrolidin-3-ylsulfonyl)-4- (4-(trifluoromethyl)pyridin-2-yl)piperazine (250 mg, 92.9%), which was labelled as intermediate G.

[618] **Step-6**: HCl (3 ml, 4 mol/L in ethyl acetate) was added to a solution of 2-methylpropan-2-yl 4-(hydroxymethyl)hexahydropyridine-1-carboxylate (1.0 g, 4.645 mmol) in ethyl acetate (10 ml). After stirred 12 h at rt, the reaction mixture was concentrated to afford piperidin-4-ylmethanol hydrochloride (630 mg, 89%).

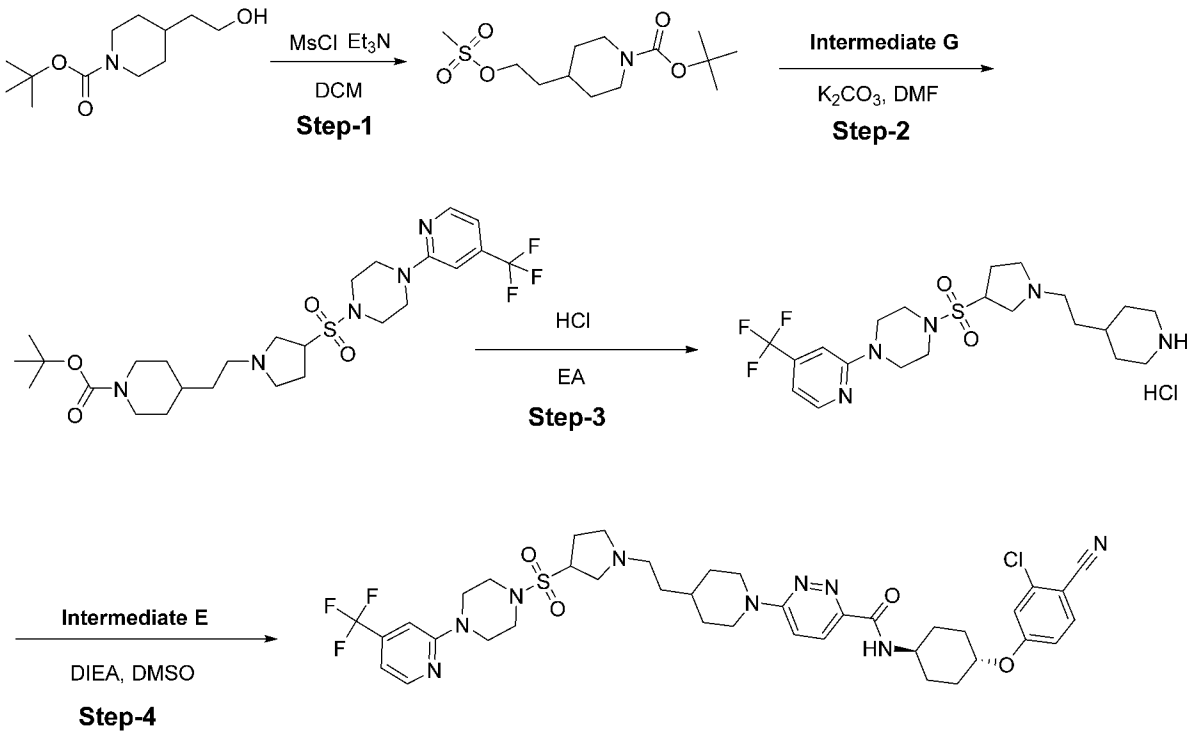
[619] **Step-7**: DIPEA (895.99 mg, 6.946 mmol) was added to a solution of hexahydropyridin-4-ylmethanol (200 mg, 1.736 mmol) and 2-methylpropan-2-yl 4-fluorobenzoate (340.72 mg, 1.736 mmol) in DMSO (2 mL). After stirred 16 h at 110°C, H_2O (10 ml) was added and the mixture was extracted by EA (10 ml×3). The organic layers were washed by aqueous NaCl, dried in Na_2SO_4 and concentrated to afford N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(hydroxymethyl)piperidin-1-yl)pyridazine-3-carboxamide (212 mg, 44 %).

[620] **Step-8**: Dess-Martin periodinane (104.69 mg, 0.247 mmol) was slowly added to a solution of 6-[4-(hydroxymethyl)hexahydropyridin-1-yl]-N-[(1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy]cyclohexyl]-1,2-diazine-3-carboxamide (58 mg, 0.123 mmol) in DCM (10 mL). After stirred 2h at rt, saturated sodium bicarbonate aqueous solution (10ml) was added to the reaction and stirred for 30 min. The mixture was extracted by DCM (10 ml×3). The organic layers were washed by aqueous NaCl, dried in Na_2SO_4 and concentrated to afford 6-(4-formylhexahydropyridin-1-yl)- N-[(1r,4r)-4- [(3-chloro-4-cyanophenyl)oxy]cyclohexyl]-1,2-diazine-3-carboxamide(57 mg, 98%).

[621] **Step-9**: $NaBH(OAc)_3$ (54.35 mg, 0.256 mmol) was added to a solution of 6-(4-formylhexahydropyridin -1-yl)-N-[(1r,4r)-4-[(3-chloro-4-cyanophenyl)oxy] cyclohexyl]-1,2-diazine-3-carboxamide (60 mg, 0.128 mmol) and 1-(pyrrolidin -3- ylsulfonyl)-4-(4-(trifluoromethyl)pyridin-2-yl)piperazine (Intermediate G,46.72 mg, 0.128 mmol) in DCE (2 mL). After stirred 12h at rt, saturated sodium bicarbonate aqueous solution (10 ml) was added to the reaction and extracted by DCM (10 ml×3), The organic layers were washed by aqueous NaCl, dried in Na_2SO_4, concentrated and purified by silica gel chromatography to afford N-((1r,4r) -4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)methyl)piperidin-1-yl)pyridazine-3-carboxamide (**Compound 100**, 48.0 mg,60 %). ESI-MS = 816.3, [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.26 (d, J = 3.9 Hz, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.86 (d, J = 9.7 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.49 (dd, J = 3.8, 2.2 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 6.97- 6.92 (m, 2H), 4.00-3.90 (m, 3H), 3.87-3.73 (m, 3H), 3.71 (dd, J = 7.5, 4.6 Hz, 2H), 3.64 (dd, J = 7.5, 4.8 Hz, 2H), 3.28 -3.11 (m, 6H), 2.90-2.79 (m, 2H), 2.68-2.59 (m, 1H), 2.57-2.51 (m, 1H), 2.48 (dd, J = 11.4, 5.3 Hz, 1H), 2.21-2.11 (m, 1H), 2.10-2.01 (m, 1H), 2.03-1.64 (m, 14H).

Example S92

Synthesis of N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(2-((R)-3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)ethyl)piperidin-1-yl)pyridazine-3-carboxamide (Compound 101)



[622] **Step-1**: Methanesulfonyl chloride (299.69 mg, 2.616 mmol) was added to a stirred solution of 2-methylpropan -2-yl 4-(2-hydroxyethyl)hexahydropyridine-1-carboxylate (500 mg, 2.180 mmol) and Et_3N (0.909 mL, 6.541 mmol) in DCM (5 mL) at 0°C. And then the reaction was stirred at rt for 2h. H_2O (10 mL) was added and the mixture was extracted by EA (10 ml × 3). The organic layers were washed by aqueous NaCl, dried in Na_2SO_4 and concentrated to afford tert-butyl 4-(2-((methylsulfonyl)oxy)ethyl) piperidine-1-carboxylate (690 mg, crude).

[623] **Step-2**: K_2CO_3 (74.93 mg, 0.542 mmol) was added to a solution of tert-butyl 4-(2-((methyl sulfonyl) oxy)ethyl)piperidine-1-carboxylate (350 mg, 1.139 mmol) and 1-{dioxo[tetrahydro-1H- pyrrol -3-yl] -λ6-sulfanyl}-4-[4-(trifluoromethyl)pyridin-2-yl]piperazine (Intermediate G, 276.59 mg, 0.759 mmol) in DMF (5 mL). After stirred 12h at 110°C. H_2O (10 mL) was added and the mixture was extracted by EA (10 mL×3). The organic layers were washed by aqueous NaCl, dried in Na_2SO_4, concentrated and purified by silica gel chromatography to afford tert-butyl 4-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl) piperazin-1-yl) sulfonyl)pyrrolidin-1-yl)ethyl)piperidine-1-carboxylate (106 mg, 24.2%).

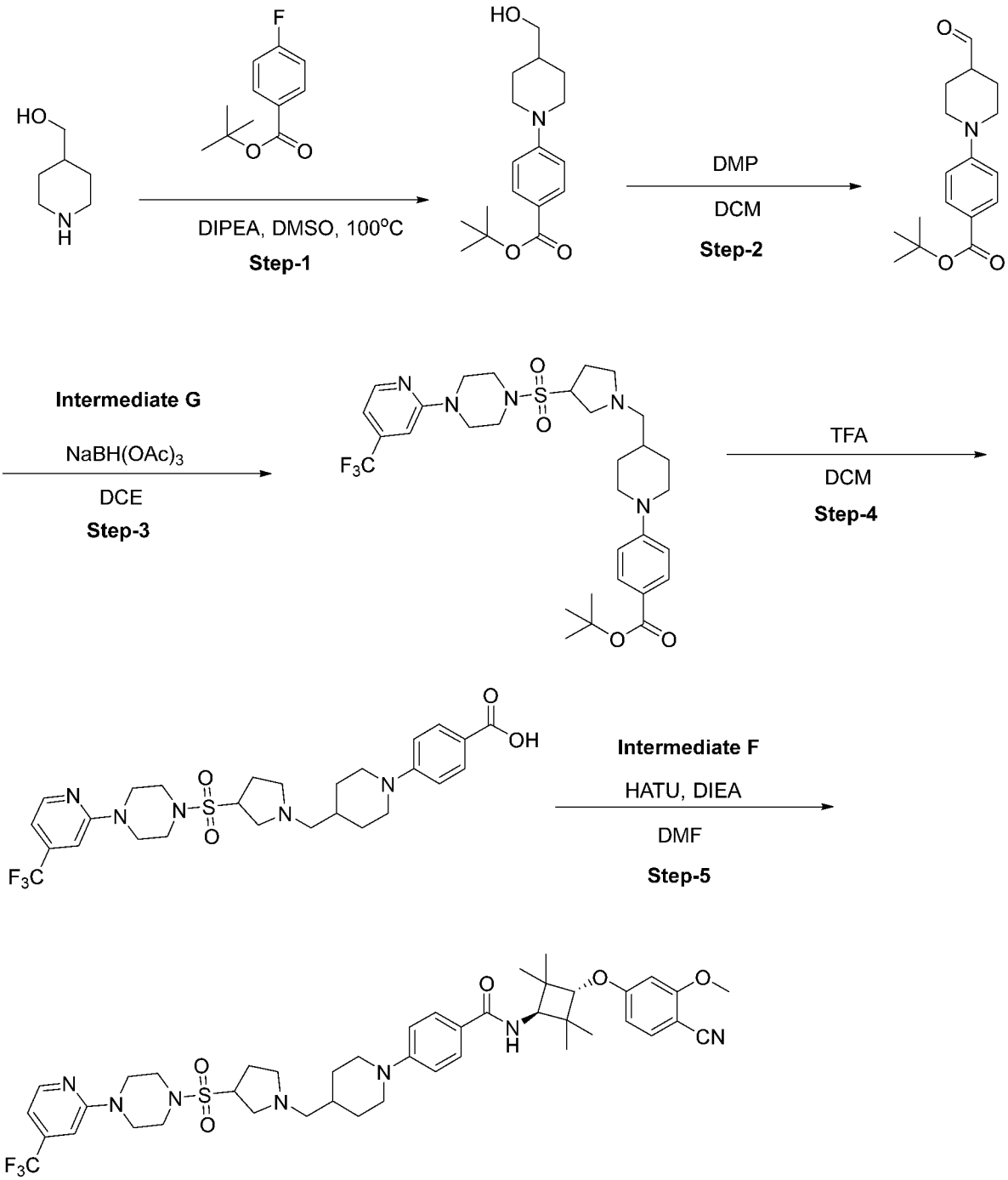
[624] **Step-3**: HCl (0.3 ml, 4 mol/L in ethyl acetate) was added to a solution of 2-methylpropan-2-yl 4-{2-[3- (dioxo4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-λ6-sulfanyl)tetrahydro-1H-pyrrol-1-yl]ethyl}hexahydropyridine-1-carboxylate (67 mg, 0.116 mmol) in ethyl acetate (2 ml). After stirred 12 h at rt, the reaction solution was concentrated to afford 1-((1-(2-(piperidin-4-yl)ethyl)pyrrolidin-3-yl) sulfonyl)-4- (4-(trifluoromethyl)pyridin-2-yl)piperazine hydrochloride (58.7 mg, 98.5%).

[625] **Step-4**: DIPEA (0.068 mL, 0.391 mmol) was added to a solution of 1-{[1-[2-(hexahydropyridin -4-yl)ethyl]tetrahydro-1H-pyrrol-3-yl]dioxo-λ6-sulfanyl}-4-[4-(trifluoromethyl)pyridin-

2-yl]piperazine (58.7 mg, 0.115 mmol) and 6-chloro-N-[(1r,4r)-4-[(3-chloro-4-cyanophenyl) oxy]cyclohexyl]-1,2-diazine -3-carboxamide (Intermediate E, 38.15 mg, 0.098 mmol) in DMSO (1 mL). After stirred 16h at 110°C, H_2O (10 ml) was added and the mixture was extracted by EA (10 ml×3). The organic layers were washed by aqueous NaCl, dried in Na_2SO_4, concentrated and purified by silica gel chromatography to afford N-((1r,4r)-4- (3-chloro-4-cyanophenoxy)cyclohexyl) -6-(4-(2-(3-((4-(4-(trifluoromethyl)pyridin-2-yl) piperazin-1-yl) sulfonyl) pyrrolidin-1-yl)ethyl)piperidin-1-yl)pyridazine-3-carboxamide (**Compound 101**, 35 mg ,42.3%). ESI-MS = 830.3, [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.43 (d, J = 4.0 Hz, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.86 (d, J = 9.7 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.49 (dd, J = 3.8, 1.8 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.16 (d, J = 2.2 Hz, 1H), 6.98-6.92 (m, 2H), 3.97-3.84 (m, 3H), 3.82-3.73 (m, 1H), 3.71 (dd, J = 7.5, 4.6 Hz, 2H), 3.64 (dd, J = 7.5, 4.8 Hz, 2H), 3.53-3.45 (m, 2H), 3.29-3.23 (m, 1H), 3.21-3.11 (m, 5H), 2.91- 2.82 (m, 2H), 2.70-2.68 (m, 1H), 2.47 (d, J = 15.9 Hz, 1H), 2.16-2.10 (m, 1H), 2.07-1.98 (m, 1H), 2.02-1.95 (m, 1H), 1.97-1.92 (m, 1H), 1.95-1.86 (m, 1H), 1.89-1.82 (m, 3H), 1.85-1.80 (m, 1H), 1.81 (t, J = 2.2 Hz, 1H), 1.82-1.69 (m, 4H), 1.72-1.65 (m, 2H), 1.60-1.50 (m,1H), 1.48-1.40 (m, 2H).

Example S93

Synthesis of N-((1r,3r)-3-(4-cyano-3-methoxyphenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((3-((4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)methyl)piperidin-1-yl)benzamide (Compound 102)



[626] **Step-1**: DIPEA (895.99 mg, 6.946 mmol) was added to a solution of hexahydropyridin-4-ylmethanol (200 mg, 1.736 mmol) and 2-methylpropan-2-yl 4-fluorobenzoate (340.72 mg, 1.736 mmol) in DMSO (2 mL). After stirred 16h at 120°C, H_2O (10 ml) was added and the mixture was extracted by EA (10 ml×3). The organic layers were washed by aqueous NaCl, dried in Na_2SO_4, concentrated and purified by silica gel chromatography to afford tert-butyl 4-(4-(hydroxymethyl)piperidin-1-yl)benzoate (106 mg, 20 %).

[627] **Step-2**: DMP (145.56 mg, 0.343 mmol) was added to a solution of 2-methylpropan-2-yl 4-[4-(hydroxy methyl)hexahydropyridin-1-yl]benzoate (50 mg, 0.172 mmol) in DCM (1 mL). After stirred

2h at rt, saturated sodium bicarbonate aqueous solution (10 ml) was added to the reaction and the mixture was extracted by DCM (10 ml×3).The organic layers were washed by aqueous NaCl, dried in Na_2SO_4, concentrated to afford tert-butyl 4-(4-formylpiperidin-1-yl)benzoate (49 mg, 98%).

[628] **Step-3:** $NaBH(OAc)_3$ (71.77 mg, 0.339 mmol) was added to a solution of 4-[dioxo(tetrahydro-1H-pyrrol- 3-yl -λ6-sulfanyl]-1-[4-(trifluoromethyl)pyridin-2-yl]piperazine (Intermediate G, 80.21 mg, 0.220 mmol) and 2-methylpropan-2-yl 4-(4-formylhexahydropyridin-1-yl)benzoate (49 mg, 0.169 mmol) in DCE (2 mL). After stirred 3h at rt, saturated sodium bicarbonate aqueous solution (10ml) was added to the reaction and the mixture was extracted by DCM (10 ml × 3). The organic layers were washed by aqueous NaCl, dried in Na_2SO_4, concentrated and purified by silica gel chromatography to afford tert-butyl 4-(4-((3-((4-(4- (trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyrrolidin-1-yl)methyl)piperidin-1-yl)benzoate (99 mg, 92 %).

[629] **Step-4:** 2,2,2-trifluoroacetic acid (1 mL, 13.059 mmol) was added to a solution of methylpropan -2-yl-4-(4- {[3-(dioxo{4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-λ6-sulfanyl)tetrahydro-1H-pyrrol-1-yl]methyl}hexahydropyridin-1-yl)benzoate (99 mg, 0.155 mmol) in DCM (2 ml). After stirred 6 h at rt, the reaction was concentrated to dryness to give 4-(4-((3-((4-(4-(trifluoromethyl)pyridin-2-yl) piperazin-1-yl)sulfonyl) pyrrolidin-1-yl)methyl)piperidin-1-yl)benzoic acid (50 mg, 55 %).

[630] **Step-5:** DIPEA (33.27 mg, 0.258 mmol) and HATU (49.03 mg, 0.129 mmol) were added to a solution of 5-(4-{[3-(dioxo{4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-λ6-sulfanyl)tetrahydro-1H-pyrrol-1 -yl]methyl}hexahydropyridin-1-yl)benzoic acid (50 mg, 0.086 mmol) and 4-{[(1r,3r)-3-amino-2,2,4,4- tetramethylcyclobutyl]oxy}-2-methoxybenzene-1-carbonitrile (Intermediate F, 28.30 mg, 0.103 mmol) in DMF(2 mL). After stirred 2 h at rt, H_2O (10ml) was added to the reaction and the mixture was extracted by DCM (10 ml×3). The organic layers were washed by aqueous NaCl, dried in Na_2SO_4, concentrated and purified by silica gel chromatography to afford (**Compound 102**, 15 mg, 74 %). ESI-MS = 838.2, [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.43 (d, J = 3.9 Hz, 1H), 7.82 (d, J = 9.9 Hz, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.68-7.62 (m, 2H), 7.49 -7.46 (m, 1H), 7.08-7.02 (m, 2H), 6.95 (d, J = 1.9 Hz, 1H), 6.82-6.80 (m, 1H), 6.68 (d, J = 2.4 Hz, 1H), 4.45-4.35 (m, 1H), 3.96-3.93 (m, 1H), 3.92 (s, 2H), 3.71 (dd, J = 7.5, 4.6 Hz, 2H), 3.64 (dd, J = 7.5, 4.8 Hz, 2H), 3.42-3.35 (m, 2H), 3.23-3.19 (m, 1H), 3.18 (d, J = 4.7 Hz, 1H), 3.19 – 3.11 (m, 4H), 3.09-3.01 (m, 2H), 2.90-2.79 (m, 2H), 2.68-2.64 (m, 1H), 2.53 (dd, J = 11.4, 5.1 Hz, 1H), 2.48 (dd, J = 11.4, 5.1 Hz, 1H), 2.16-2.14 (m, J = 12.6, 7.1, 5.8 Hz, 1H), 2.10-2.00 (m, 1H), 1.85-1.78 (m, 1H), 1.78 (dd, J = 5.9, 3.8 Hz, 1H), 1.78-1.72 (m, 2H), 1.75-1.68 (m, 1H), 1.12 (t, J = 1.4 Hz, 6H), 1.07 (t, J = 1.4 Hz, 6H).

BIOLOGICAL EXAMPLES

[631] A variety of assays can be used to evaluate the activity of compounds in multiple cancer cell lines.

Example B1: Determination of compound activity in VCap cells

[632] Dextran-coated charcoal (DCC) was added into Fetal bovine serum (FBS), then rotated at 4 ° C overnight (16 hour). The next day, FBS was filtered three time with with 0.22 μm filter. VCap cells (#CRL_2876, AR-dependent human prostate cancer cells) were seeded in DMEM growth medium supplemented with 10% fetal bovine serum (FBS) treated with DCC and incubated in a humidified incubator at 37 ° C (5% CO_2). After 5 days cell culture with DCC stripped FBS medium, VCap cells were seeded into 96-well transparent plates and allowed to adhere overnight in a humidified incubator at 37 °C (5% CO_2). On the third day, the cells were treated with PROTAC at 6 concentrations (According to 6-point concentration curve, maximum final concentration in the assay was 10 μM, followed by a half log dilution to a minimum concentration of 30 nM). The maxium and minium inhibtion ratio was measured by adding the androgen analogue R1881 (1.7x10e6 molecules/cell) and DMSO control, respectively. Each PROTAC was tested independently on 96-well plates in at least 3 experiments. On the fifth day, 100 μl of medium was removed from each well and CCK8 equilibrated at room temperature was added to the well. After addition, activity was measured using a VARIOSKAN LUX reader (Thermo Scientific, Vantaa, Finland). Each compound was determined in triplicate, and activity was calculated as IC50 using GraphPad Prism software (San Diego, California).

Table B1: Anti-proliferative activity (Vcap)

Compound	IC50 (nM)	Compound	IC50 (nM)	Compound	IC50 (nM)
1	1100	34	542	66	563
2	1209	35	150	67	343
3	>1000	36	242	68	214
4	>1000	37	367	69	252
5	>1000	38	330	70	196
6	>1000	39	281	71	321
7	563	40	>1000	72	139
8	1079	41	1630	73	371
9	>1000	42	340	74	223
10	445	43	>1000	75	336
11	>1000	44	407	76	437
12	509	45	217	77	185

13	402	46	1409	78	109
14	1875	47	901	79	326
15	212	48	855	80	331
16	>1000	49	567	81	684
17	642	50	545	82	122
18	892	51	312	83	321
19	>1000	52	348	84	239
20	>1000	53	418	85	278
21	172	54	>1000	86	261
22	>1000	55	154	87	330
23	336	56	167	88	393
24	524	57	221	89	976
25	463	58	893	90	429
26	>1000	59	571	91	491
27	388	60	739	92	236
28	3472	61	>1000	93	537
29	1449	62	201	94	318
30	698	63	383	95	94.9
32	677	64	295	96	421
33	>1000	65	263	97	310

Example B2: Determination of compound activity based on PC-3 cells

[633] PC-3 cells (#CRL_1435, AR-independent human prostate cancer cells) were seeded into 96-well clear plates in Hams F12K growth medium with 10% fetal bovine serum (FBS) and allowed to adhere overnight (16 hours) in a humidified incubator at 37 ° C (5% CO_2). On the third day, the cells were treated with PROTAC at 6 concentrations (According to 6-point concentration curve, the highest final concentration in the assay was 10μM, followed by a half log dilution to a minimum concentration of 30nM). Each PROTAC was tested independently on 96-well plates in two experiments. On the fifth day, 100μl of medium was removed from each well and CCK8 equilibrated at room temperature was added to the well. After addition, activity was measured using a VARIOSKAN LUX reader (Thermo Scientific, Vantaa, Finland). Each compound was determined in triplicate, and toxicity was calculated as IC50 using GraphPad Prism software (San Diego, California).

Table B2: Anti-proliferative activity (PC-3)

Compound	IC50 (nM)	Compound	IC50 (nM)	Compound	IC50 (nM)

15	1698	60	148	82	197
33	>1000	62	50	83	258
35	252	63	101	84	60
39	152	64	53	85	139
42	1049	65	134	86	598
44	202	68	197	87	80
45	106	70	199	88	546
48	2088	71	53.3	89	207
49	60	72	105	91	96.3
50	397	73	29	92	25.9
51	257	74	22	93	192
52	84	75	74	94	70.8
53	250	76	188	95	13.8
55	221	77	61	96	64.7
56	312	78	69.5	97	48.6
57	386	79	186	100	119
58	368	80	163	101	67
59	274	81	374	102	>1000

Example B3: Determination of compound activity based on 22RV1 cells

[634] Dextran-coated charcoal (DCC) was added into Fetal bovine serum (FBS), then rotated at 4 ° C overnight (16 hour). The next day, FBS was filtered three times with 0.22 μm filter for future use. 22RV1 cells (AR independent human prostate cancer cells) were seeded in RPMI1640 growth medium supplemented with 10% fetal bovine serum (FBS) treated with DCC and incubate in a humidified incubator at 37 ° C (5% CO_2). 22RV1 cells were seeded into 96-well transparent plates and allowed to adhere overnight in a humidified incubator at 37 °C (5% CO_2). On the first day, the cells were treated with PROTAC at 6 concentrations (According to 6-point concentration curve, maximum final concentration in the assay was 10 μM, followed by a half log dilution to a minimum concentration of 30 nM). The maxium and minium inhibtion ratio was measured by AD and DMSO control, respectively. Each PROTAC was tested independently on 96-well plates in at least 3 experiments. On the fifth day, 100 μl of medium was removed from each well and CCK8 equilibrated at room temperature was added to the well. After addition, activity was measured using a VARIOSKAN LUX reader (Thermo Scientific, Vantaa, Finland). Each compound was determined in triplicate, and activity was calculated as IC50 using GraphPad Prism software (San Diego, California).

Table B3: Anti-proliferative activity (22RV1-dcc medium).

Compound	IC50 (nM)	Compound	IC50 (nM)
79	2165	82	969

80	1044	84	>1000
81	>1000	85	1537

[635] 22RV1 cells (AR-independent human prostate cancer cells) were seeded into 96-well clear plates in RPMI1640 growth medium with 10% fetal bovine serum (FBS) and allowed to adhere overnight (16 hours) in a humidified incubator at 37 ° C (5% CO_2). On the third day, the cells were treated with PROTAC at 6 concentrations (According to 6-point concentration curve, the highest final concentration in the assay was 10μM, followed by a half log dilution to a minimum concentration of 30nM). Each PROTAC was tested independently on 96-well plates in two experiments. On the fifth day, 100μl of medium was removed from each well and CCK8 equilibrated at room temperature was added to the well. After addition, activity was measured using a VARIOSKAN LUX reader (Thermo Scientific, Vantaa, Finland). Each compound was determined in triplicate, and toxicity was calculated as IC50 using GraphPad Prism software (San Diego, California).

Table B4: Anti-proliferative activity (22RV1-cm)

Compound	IC50 (nM)	Compound	IC50 (nM)
62	483	94	>10000
72	>1000	95	>10000
73	>1000	96	1018
74	945	97	1016
75	927	98	>10000
77	833	99	>10000
78	868	100	490
91	2476	101	150
92	>10000	102	>10000
93	>10000		

[636] All references throughout, such as publications, patents, patent applications and published patent applications, are incorporated herein by reference in their entireties.

CLAIMS

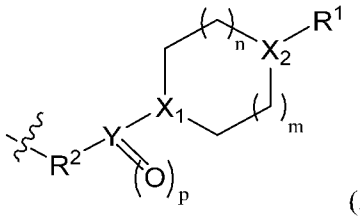
1. A bifunctional compound of formula (I):

PTM-L-ULM (I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

the PTM is a moiety that binds a target protein;

the ULM is an E3 ubiquitin ligase CDC20 (Cell Division Cycle 20) binding moiety of formula (A):



(A)

wherein

R^1 is C_1-C_6 alkyl, C_{6-10} aryl or 5- to 6-membered heteroaryl, each of which is optionally substituted with C_1-C_6 alkyl, halogen, -OH, oxo, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), -NO_2, or -CN;

R^2 is a bond, C_1-C_6 alkylene, C_{3-8} cycloalkylene, 3- to 10- membered heterocyclylene, C_{6-10} arylene, or 5- to 10- membered heteroarylene;

X_1 and X_2 are independently N or CH;

Y is C or S;

m and n are independently 0 1, or 2; and

p is 0, 1 or 2;

and

L is a bond or a chemical linker covalently connecting the PTM and the ULM.

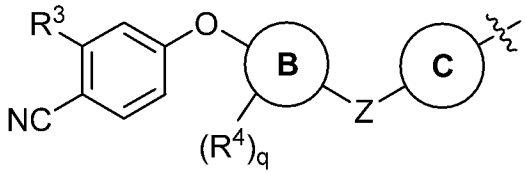
2. The bifunctional compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the ULM target is an E3 ubiquitin ligase CDC20 (Cell Division Cycle 20) that is Anaphase Promoting Complex (APC).

3. The bifunctional compound of claim 1 or 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the target protein is selected from the group consisting of AR, ER, Hsp90, MDM2, BET, HDAC, AAK, ABL, AKT, AURKA, AURKB, BCKSK, BLK, BMP2K, BMPR1A, BTK, BUB1, CAMKK1, CDK, CHEK1, CIT, CLK1, COQ8, CSK, CSNK1, DAPK1, DDR2, EEF2K, EIF2AK, EPHA, EPHB, ERN1, FER, FGFR, FLT1, FYN, GAK,

GSK3, HASPIN, HIPK1, IRAK, ITK, Kras, LATS1, LCK, LIMK, LRRK2, LYN, MAPK, MARK, MAST3, MELK, MINK1, MKNK2, NEK, NLK, NUAK1, PAK4, PDIK1L, PDK, PIK3CG, PIM2, PKMYT1, PKN3, PLK, PRAG1, PRKAA, PRKCI, PKT, RIOK2, RIPK, RPS6KA, RPS6KB, RPS6KC, SBK1, SGK3, SIK, SNRK, SRC, STK, TAOK, TBCK, TBK1, TEC, TESK2, TGFBR1, TNK, TRIB3, TRPM7, TTK, TYK2, UHMK1, ULK, WEE1, YES1, ABCF1, ACHE, ASH1L, BCL2, BRD4, CD147, CYP1B1, GCN5, HDAC, HMACR, H-PGDS, Hsp90, IDO1, IKZF, LYPLA2, MCL1, PARP, PCAF, PDE, Plek2, SLC99A1, SMARCA, STAT3, Tau, TGF-β1, WDR5, AR, AR-V7, ATOX1, CCS, CREPT, EED, ER, EZH2, MLL, MYC, NAMPT, NSD, PRMT5, SHP2, Smad3, SMARCA2, SUZ12, and β-catenin.

4. The bifunctional compound of any one of claims 1-3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the target protein is androgen receptor (AR).

5. The bifunctional compound of any one of claims 1-4, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the PTM is of formula (B):

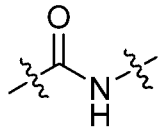
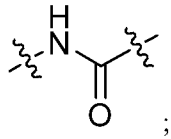


(B)

wherein

Ring B is C_3-C_8 cycloalkyl;

Ring C is C_{6-10} aryl or 5- to 10- membered heteroaryl;

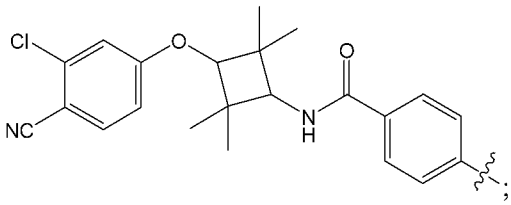
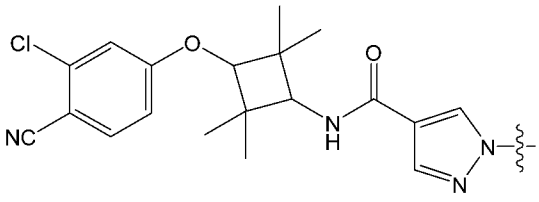
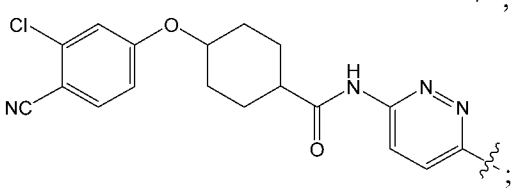
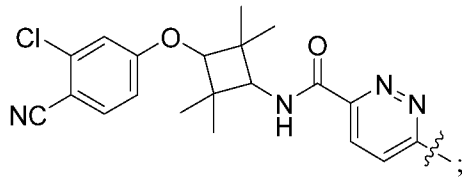
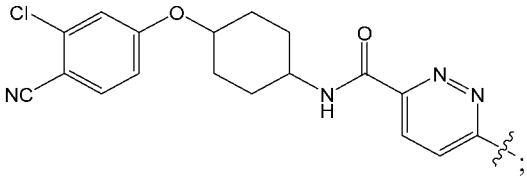
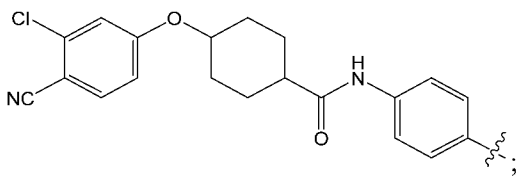
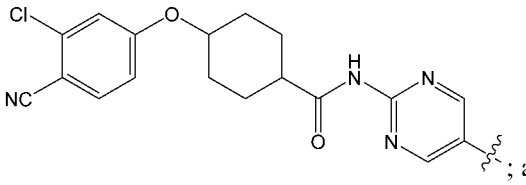
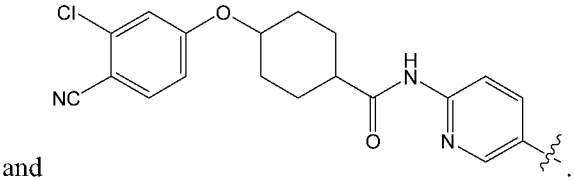
Z is  or ;

R^3 is halogen, or methoxy;

R^4 is C_1-C_6 alkyl; and

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

6. The bifunctional compound of any one of claims 1-5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the PTM is selected from the group consisting of:









; and

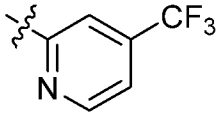
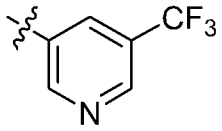
7. The bifunctional compound of any one of claims 1-6, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is C_{6-10} aryl or 5- to 6-membered heteroaryl, each of which is optionally substituted with C_1-C_6 alkyl, halogen, -OH, oxo, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), $-NO_2$, or -CN.

8. The bifunctional compound of any one of claims 1-7, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is 5- to 6-membered heteroaryl optionally substituted with C_1-C_6 alkyl, halogen, -OH, oxo, -COOH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), $-NO_2$, or -CN.

9. The bifunctional compound of any one of claims 1-8, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is optionally substituted with fluoro, chloro, -OH, -COOH, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, $-NO_2$, or -CN.

10. The bifunctional compound of any one of claims 1-9, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is 5- to 6-membered heteroaryl optionally substituted with $-CH_3$ or $-CF_3$.

11. The bifunctional compound of any one of claims 1-10, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is pyridinyl substituted with $-CH_3$ or $-CF_3$.

12. The bifunctional compound of any one of claims 1-11, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is  or .

13. The bifunctional compound of any one of claims 1-12, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a bond or C_1-C_6 alkylene.

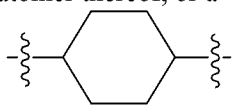
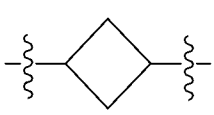
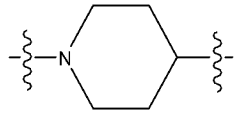
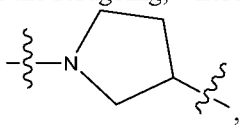
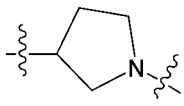
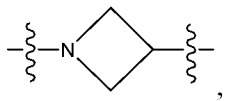
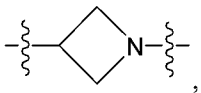
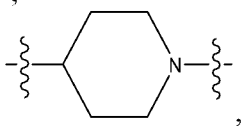
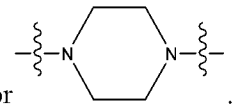
14. The bifunctional compound of any one of claims 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a bond.

15. The bifunctional compound of any one of claims 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_1-C_6 alkylene.

16. The bifunctional compound of any one of claims 1-12, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{6-10} arylene or 5- to 10- membered heteroarylene.

17. The bifunctional compound of claim 16, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is phenylene, pyridinyl, pyridazinyl, or pyrimidinyl.

18. The bifunctional compound of any one of claims 1-12, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{3-8} cycloalkylene or 3- to 10-membered heterocyclylene.

19. The bifunctional compound of claim 18, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is, , , , , , , , , or .

20. The bifunctional compound of any one of claims 1-19, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X_1 and X_2 are each N.

21. The bifunctional compound of any one of claims 1-20, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y is S.

22. The bifunctional compound of any one of claims 1-21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein m and n are each 1.

23. The bifunctional compound of any one of claims 1-22, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein p is 2.

24. The bifunctional compound of any one of claims 1-23, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is *—A^{L1}-A^{L2}-A^{L3}-A^{L4}—**, wherein

* represents the point of attachment to the PTM,

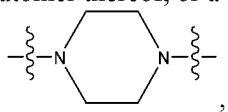
** represents the point of attachment to the ULM,

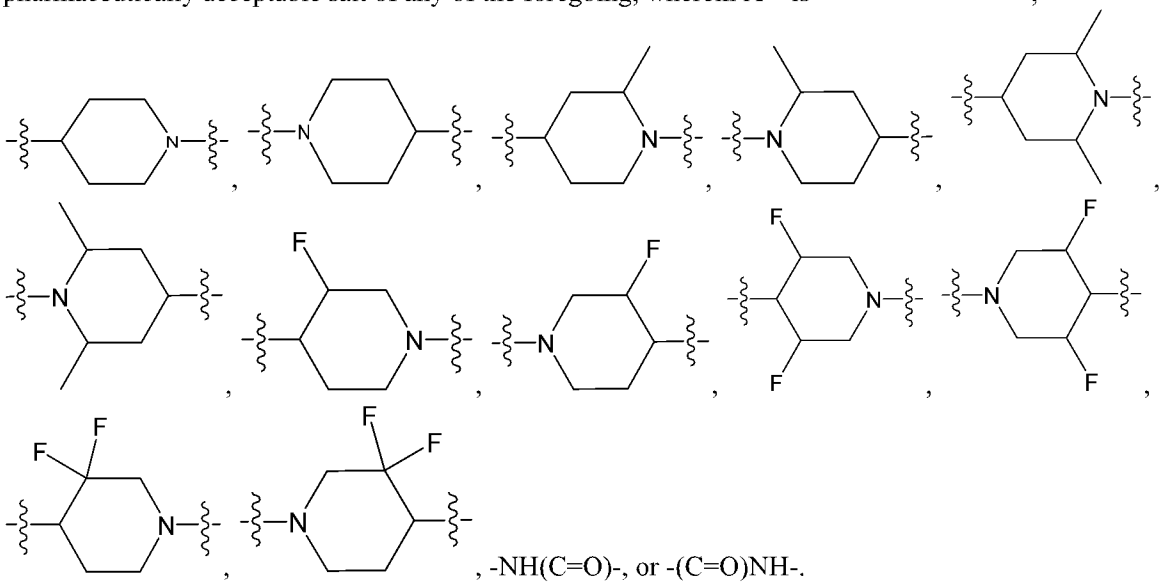
A^{L1} and A^{L4} are each independently a bond, -(C=O)-, -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, or C_{3-8} cycloalkylene;

wherein the -(C=O)NH-, -(C=O)NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH(C=O)-, -NH(C=O)-, -NH-C_{1-3} alkylene, -C_{1-3} alkylene-NH-, 3- to 10- membered heterocyclylene, C_{3-8} cycloalkylene-CH_2-, -CH_2-C_{3-8} cycloalkylene-, 3- to 10- membered heterocyclylene-CH_2-, -CH_2-(3- to 10- membered heterocyclylene)-, and C_{3-8} cycloalkylene of A^{L1} and A^{L4} are each independently and optionally substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen; and

A^{L2} and A^{L3} are each independently a bond, -$(CH_2)_r$-, -$(OCH_2CH_2)_s$-, -$(CH_2CH_2O)_s$-, -$(NHCH_2CH_2)_s$-, -$(CH_2CH_2NH)_s$-, wherein r and s are each an integer between 0 and 10;

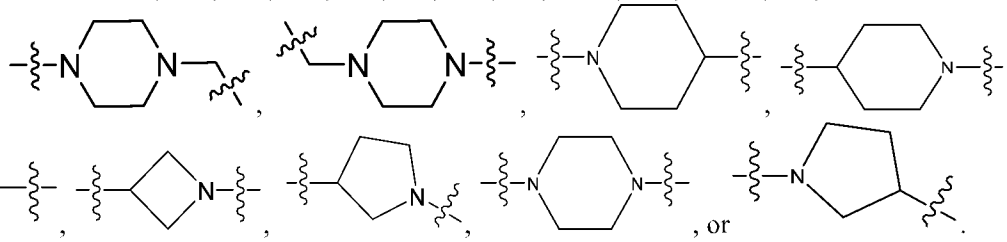
wherein the -$(CH_2)_r$-, -$(OCH_2CH_2)_s$-, -$(CH_2CH_2O)_s$-, -$(NHCH_2CH_2)_s$-, and -$(CH_2CH_2NH)_s$- of A^{L2} and A^{L3} are each independently and optionally substituted with 1-5 independently selected substituents selected from C_1-C_6 alkyl and halogen.

25. The bifunctional compound of claim 24, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein A^{L1} is ,



, -NH(C=O)-, or -(C=O)NH-.

26. The bifunctional compound of claim 24 or 25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein A^{L4} is

-(C=O)$NHCH_2$-, -CH_2-NH(C=O)-, -(C=O)$NH(CH_2)_3$-, -$(CH_2)_3$-NH(C=O)-, -$NH(CH_2)_3$-, -$(CH_2)_3$-NH-, 

, or .

27. The bifunctional compound of any one of claims 24-26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein A^{L2}-A^{L3} is a bond.

28. The bifunctional compound of any one of claims 24-26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein A^{L2}-A^{L3} is $-(CH_2)_r-$.

29. The bifunctional compound of any one of claims 24-26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein A^{L2}-A^{L3} is $-(CH_2CH_2O)_s-(CH_2)_r-$ or $-(CH_2)_r-(CH_2CH_2O)_s-$.

30. A bifunctional compound selected from the compounds in Table 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

31. A pharmaceutical composition comprising at least one bifunctional compound according to any one of claims 1-30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient.

32. A method of treating a disease or disorder in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a bifunctional compound according to any one of claims 1-30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a therapeutically effective amount of a pharmaceutical composition of claim 31.

33. The method of claim 32, wherein disease or disorder is cancer.

34. The method of claim 32 or 33, wherein the compound, the stereoisomer or tautomer thereof, the pharmaceutically acceptable salt, or the pharmaceutical composition is administered in combination with a therapeutically effective amount of one or more additional bioactive agents.

35. The method of claim 34, wherein the additional bioactive agent is an anti-cancer agent.

36. The method of claim 35, wherein the additional bioactive agent is selected from the group consisting of a taxane, a Cox-2 inhibitor, a platinum-based antineoplastic drug, an anthracycline, a pyrimidine analog, a topoisomerase inhibitor, an mTOR inhibitor, an immune-check point inhibitor, and an agent that is used in immune oncology.

37. The method of any one of claims 33-36, further comprising administering radiation.

38. The method any one of claims 33-37, wherein the cancer is selected from the group consisting of pancreatic cancer, breast cancer, kidney cancer, bladder cancer, prostate cancer, testicular cancer, urothelial cancer, endometrial cancer, ovarian cancer, cervical cancer, renal cancer, esophageal cancer, gastrointestinal stromal tumor (GIST), multiple myeloma, cancer of secretory cells, thyroid cancer, gastrointestinal carcinoma, chronic myeloid leukemia, hepatocellular carcinoma, colon cancer, melanoma, malignant glioma, glioblastoma, glioblastoma multiforme, astrocytoma, dysplastic gangliocytoma of the cerebellum, Ewing's sarcoma, rhabdomyosarcoma, ependymoma, medulloblastoma, ductal adenocarcinoma, adenosquamous carcinoma, nephroblastoma, acinar cell carcinoma, lung cancer, non-Hodgkin's lymphoma, Burkitt's lymphoma, chronic lymphocytic leukemia, monoclonal gammopathy of undetermined significance (MGUS), plasmocytoma, lymphoplasmacytic lymphoma, and acute lymphoblastic leukemia.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/076704

A. CLASSIFICATION OF SUBJECT MATTER

C07D401/14(2006.01)i; A61K31/444(2006.01)i; A61P35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC:C07D,A61K,A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNABS;DWPI;CNKI;Web of science;REGISTRY(STN);CAPLUS(STN):AUBRAK,proteolysis,targeting,chimera,ubiquitin,ligase,PTM,cancer,tumor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	CN 116444486 A (YANTAI UNIVERSITY) 18 July 2023 (2023-07-18) claims 1-2,abstract	1-38
A	CN 115175901 A (ARVINAS OPERATIONS, INC.) 11 October 2022 (2022-10-11) abstract,claim1,examples 16-20	1-38
A	CN 114181277 A (JIANGSU ZHEREI MEDICINE CO., LTD.et al.) 15 March 2022 (2022-03-15) abstract,claim 1	1-38
A	CN 107428734 A (ARVINAS INC.) 01 December 2017 (2017-12-01) claims 1-18	1-38
A	WO 2022235698 A1 (NURIX THERAPEUTICS INC. et al.) 10 November 2022 (2022-11-10) the whole document	1-38
A	US 2021047278 A1 (HUTCHINSON FRED CANCER RES. et al.) 18 February 2021 (2021-02-18) the whole document	1-38

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 2024	**25 April 2024**

Name and mailing address of the ISA/CN	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/076704

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PA	CN 117126133 A (OCEAN UNIVERSITY OF CHINA) 28 November 2023 (2023-11-28) the whole document	1-38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/076704

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **32-38**
because they relate to subject matter not required to be searched by this Authority, namely:

The subject matter of claims 32-38 relates to methods of treatment for diseases of the living human or animal body as defined in PCT Rule 39.1(iv). This report is based on the subject matter of the use in manufacture of medicament corresponding to the subject matter of aforementioned claims.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2024/076704

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	116444486	A	18 July 2023	None			
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				WO	2021127443	A1	24 June 2021
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				EP	4077309	A1	26 October 2022
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				AU	2022270089	A1	16 November 2023
				EP	4334302	A1	13 March 2024
US	2021047278	A1	18 February 2021	WO	2019200310	A1	17 October 2019
				EP	3774766	A1	17 February 2021
CN	117126133	A	28 November 2023	None			