

SPIROCYCLIC MTA-COOPERATIVE PRMT5 INHIBITOR**FIELD OF THE INVENTION**

The present invention relates to compounds used as MTA-cooperative inhibitors of protein arginine N-methyl transferase 5 (PRMT5). In particular, the present invention relates to MTA-cooperative PRMT5 inhibitors, including their pharmaceutical compositions comprising the compounds and the methods of use thereof.

BACKGROUND

The protein arginine methyltransferase PRMT5 is crucial for maintaining cellular homeostasis by regulating gene transcription, ribosomal biogenesis, mRNA splicing, protein translation, DNA damage response, and immune functions (Musiani, D. et al., Proteomics profiling of arginine methylation defines PRMT5 substrate specificity. *Sci. Signaling* 2019, 12 (575), eaat8388). PRMT5 is a type II arginine methyltransferase that symmetrically dimethylate histones and non-histone proteins. It catalyzes a methyl group transfer from S-adenosyl-L-methionine (SAM) to an omega-nitrogen of the guanidino function of protein L-arginine residues (omega-monomethylation) and a second methyl group to the other omega-nitrogen, resulting in symmetric dimethylarginine (sDMA) (Gary, J.D., and Clarke, S. *Prog. Nucleic Acid Res. Mol. Biol* 1998, RNA and protein interactions modulated by protein arginine methylation. 61, 65–131).

Due to multiple functions involved with PRMT5, complete inactivation of PRMT5 is lethal in most cell lines. Therefore, PRMT5 is considered as an essential gene for cell viability (McDonald, E. R., et al., Project DRIVE: A Compendium of Cancer Dependencies and Synthetic Lethal Relationships Uncovered by Large-Scale, Deep RNAi Screening. *Cell* 2017, 170 (3), 577–592). PRMT5 is an attractive drug target in the field of oncology. Several potent and selective inhibitors targeting the catalytic pocket of PRMT5 have been developed. However, given the essential role of PRMT5 in normal tissue homeostasis, solely inhibiting PRMT5 may cause the toxicity and lead to a limited therapeutic window.

Methylthioadenosine (MTA) is an endogenous competitor of SAM and partially inhibits PRMT5 without inhibiting PRMT family members other than PRMT5. Studies have shown that inhibition of PRMT5 by MTA will reduce the methylation activity and sensitize cells to PRMT5 inhibitors. MTA is a substrate of methylthioadenosine phosphorylase (MTAP) and can be converted into 5-methylthioribose 1-phosphate (MTR-1-P) by MTAP. Therefore, MTA will not be accumulated in the wild type cells to reduce PRMT5 activity. On the contrary, cells

with homozygous deletion of MTAP will cause MTA to be accumulated in the cells, resulting in decreased PRMT5 activity (Kryukov, G. V. et al., MTAP deletion confers enhanced dependency on the arginine methyltransferase PRMT5 in human cancer cells. *Science* 2016, 351 (6278), 1214–1218). Therefore, MTA-cooperated inhibition of PRMT5 will selectively inhibit PRMT5 activity in cells with homozygous deletion of MTAP.

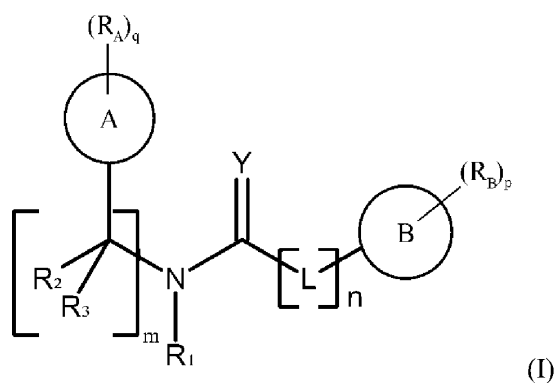
Homozygous deletions of MTAP are relatively common in cancers with about 15% incidence rate. Higher incidence rates were noticed in glioblastoma, bladder cancer, non-small cell lung cancer, and pancreatic cancer. This loss is due to its proximity to the P16/CDKN2A tumor suppressor locus. Homozygous deletions of p16/CDKN2a commonly involve the co-deletion of adjacent genes, such as MTAP (Mavrakis, K. J. et al., Disordered methionine metabolism in MTAP/CDKN2A-deleted cancers leads to dependence on PRMT5. *Science* 2016, 351 (6278), 1208–1213).

We realized that MTA-cooperative inhibition of PRMT5 activity in MTAP-deficient cancers will provide therapeutic benefit for a wide range of cancers. Thus, there is a need to develop new MTA-cooperative PRMT5 inhibitors that are capable of inhibiting PRMT5 activity in the MTAP-deficient cells.

SUMMARY OF THE INVENTION

The compounds of the present invention provide this therapeutic benefit as MTA-cooperative inhibitors of PRMT5 that negatively modulate the activity of MTA-bound PRMT5 in a cell, particularly an MTAP-deficient cell, or for treating various forms of MTAP-associated cancer.

One aspect of the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled:



wherein ring A, ring B, Y, L, R^1 , R^2 , R^3 , R^A , R^B , m, n, p and q are defined as follows:

Ring A is selected from 5-11 membered monocyclic or fused bicyclic aryl, 5-11 membered monocyclic or fused bicyclic heteroaryl;

Ring B is selected from 6 membered monocyclic heteroaryl, 8-11 membered fused bicyclic heteroaryl, 8-11 membered fused bicyclic heterocyclyl, 10-15 membered fused tricyclic heteroaryl and 10-15 membered fused tricyclic heterocyclyl;

Y is O or S;

L is $\#-C(=O)-NH-\$$, wherein # is connected to  and \$ is connected to ring B;

R_1 is C_1-C_5 alkyl or C_1-C_5 alkoxy; wherein the C_1-C_5 alkyl or C_1-C_5 alkoxy is optionally substituted by 1-3 groups selected from the following: deuterium, halogen, oxo, -CN, -OH, -NH₂, C_1-C_6 alkyl optionally substituted by 1-3 R_z , C_1-C_6 alkoxy optionally substituted by 1-3 R_z , C_1-C_6 haloalkyl optionally substituted by 1-3 R_z , C_1-C_6 haloalkoxy optionally substituted by 1-3 R_z , C_3-C_6 cycloalkyl optionally substituted by 1-3 R_z , -NH(C_1-C_6 alkyl) optionally substituted by 1-3 R_z , -N(C_1-C_6 alkyl)(C_1-C_6 alkyl) optionally substituted by 1-3 R_z , C_3-C_6 cycloalkyl optionally substituted by 1-3 R_z , 5-15 membered monocyclic or fused bicyclic or fused tricyclic heterocyclic group optionally substituted by 1-3 R_z , 5-15 membered monocyclic or fused bicyclic or fused tricyclic aryl optionally substituted by 1-3 R_z , or 5-15 membered monocyclic or fused bicyclic or fused tricyclic heteroaryl;

R_2 and R_3 are independently hydrogen, deuterium, halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy;

wherein R_1 , the nitrogen atom to which R_1 is connected, the carbon atom to which R_2 and R_3 are connected, and one atom of the ring A form a ring group, wherein the ring group and the ring A are connected in the form of sharing the one atom to form a spiro ring structure;

R_A is deuterium, halogen, hydroxyl, oxo, cyano, nitro, amine, C_1-C_6 alkyl, cyano C_1-C_6 alkyl, C_1-C_6 alkoxy, - C_1-C_6 alkyl- C_1-C_6 alkoxy, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl).

alkyl), C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, -O-(C₁-C₆ haloalkyl), -NH-(C₁-C₆ haloalkyl), -N(C₁-C₆ haloalkyl)(C₁-C₆ haloalkyl), pentafluorosulfur (-SF₅), C₁-C₆ haloalkoxy or halocycloalkyl, -S(O)₂-(C₁-C₆ alkyl), -S(=O)(C₁-C₆ alkyl)NR_z, -S(=O)(=NR_z)(C₁-C₆ alkyl), -P(=O)(C₁-C₆ alkyl)₂, a 4-8 membered heterocyclyl optionally substituted by 1-3 R_z, a 5-8 membered heteroaryl optionally substituted by 1-3 R_z, a 6-10 membered aryl optionally substituted by 1-3 R_z, a C₃-C₆ cycloalkyl optionally substituted by 1-3 R_z, or

two R_A connected to the same carbon atom form an oxo group, or

two R_A connected to the same carbon atom together with the carbon atom to which they are connected form a C₃-C₈ cycloalkyl;

R_B is deuterium, halogen, hydroxyl, oxo, thioketone, cyano, nitro, amine, C₁-C₆ alkyl, C₁-C₆ alkoxy, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-OH, C₃-C₈ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy or C₃-C₈ halocycloalkyl, or

two R_B connected to the same carbon atom together with the carbon atom to which they are connected form a C₃-C₈ cycloalkyl or 6-7 membered heterocyclyl, or

two R_B connected to different carbon atoms are connected to form a 6-7 membered ring;

R_z is independently selected from deuterium, halogen, C₁-C₆ alkyl, -CN, -OH, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₃-C₆ cycloalkyl, -NH₂, -NH(C₁-C₆ alkyl) or -N(C₁-C₆ alkyl)(C₁-C₆ alkyl), (C₁-C₆ alkyl)C(O)NH-, (C₁-C₆ alkyl)C(O)-, phenyl, pentafluorosulfur, 5-6 membered heteroaryl or 4-6 membered heterocyclyl, or

two R_z connected to the same carbon atom form an oxo group, or

two R_z connected to the same carbon atom together with the carbon atom to which they are connected form a C₃-C₈ cycloalkyl group;

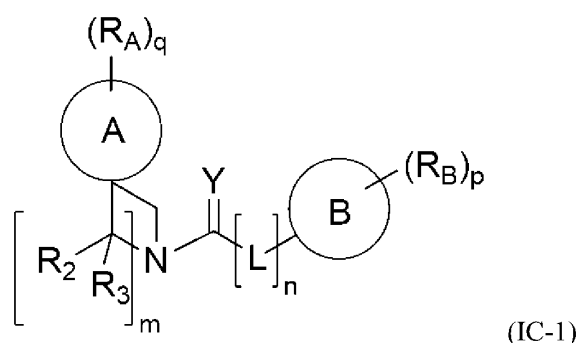
m is 1 or 2;

n is 0 or 1;

p is 0, 1, 2, 3 or 4; and

q is 0, 1, 2, 3, 4 or 5.

One aspect of the present invention provides a compound of formula (IC-1) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled:



wherein ring A, ring B, Y, L, R₂, R₃, R_A, R_B, m, n, p and q are defined as follows:

Ring A is selected from 8-11 membered fused bicyclic aryl and 8-11 membered fused bicyclic heteroaryl;

m is 1 or 2;

Ring B is selected from 6-membered monocyclic heteroaryl, 8-11-membered fused bicyclic heteroaryl, 8-11-membered fused bicyclic heterocyclyl, 10-15-membered fused tricyclic heteroaryl and 10-15-membered fused tricyclic heterocyclyl;

Y is O or S;

L is #-C(=O)-NH-\$, wherein # is connected to  and \$ is connected to ring B;

n is 0 or 1;

each R₂ and each R₃ are independently hydrogen, deuterium, halogen, C₁-C₆ alkyl or C₁-C₆ alkoxy;

R_A is deuterium, halogen, hydroxyl, oxo, cyano, nitro, amine, C₁-C₆ alkyl, cyano C₁-C₆ alkyl, C₁-C₆ alkoxy, -C₁-C₆ alkyl-C₁-C₆ alkoxy, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)(C₁-C₆ alkyl), C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, -O-(C₁-C₆ haloalkyl), -NH-(C₁-C₆ haloalkyl), -N(C₁-C₆ haloalkyl)(C₁-C₆ haloalkyl), pentafluorosulfur, C₁-C₆ haloalkoxy or C₃-C₆ halocycloalkyl, -S(O)₂-(C₁-C₆ alkyl), -S(=O)(=NR₂)(C₁-C₆ alkyl), -P(=O)(C₁-C₆ alkyl)₂, 4-8 membered heterocyclic group optionally substituted by 1-3 R_z, 5-8 membered heteroaryl group optionally substituted by 1-3 R_z, 6-10 membered aryl group optionally substituted by 1-3 R_z, C₃-C₆ cycloalkyl group optionally substituted by 1-3 R_z, or,

two R_A attached to the same carbon atom form an oxo group, or,

two R_A connected to the same carbon atom and the carbon atom to which they are connected form a C₃-C₈ cycloalkyl group;

R_B is deuterium, halogen, hydroxyl, oxo, thioketone, cyano, nitro, amine, C₁-C₆ alkyl, C₁-C₆ alkoxy, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-OH, C₃-C₈

cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy or C₃-C₈ halocycloalkyl, or,

two R_B connected to the same carbon atom and the carbon atom to which they are connected form a C₃-C₈ cycloalkyl group or 6-7 membered heterocyclyl, or,

two R_B connected to different carbon atoms are connected to form a 6-7 membered ring;

R_Z is independently selected from deuterium, halogen, C₁-C₆ alkyl, -CN, -OH, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₃-C₆ cycloalkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)(C₁-C₆ alkyl), (C₁-C₆ alkyl)C(O)NH-, (C₁-C₆ alkyl)C(O)-, phenyl, pentafluorosulfur, 5-6 membered heteroaryl or 4-6 membered heterocyclic group, or

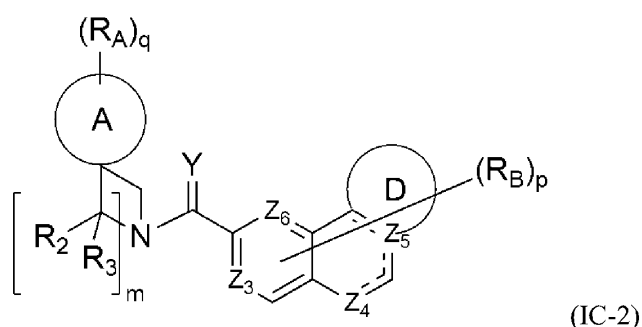
two R_Z connected to the same carbon atom form an oxo group, or

two R_Z connected to the same carbon atom and the carbon atom to which they are connected form a C₃-C₈ cycloalkyl group;

p is 0, 1, 2, 3 or 4; and

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

One aspect of the present invention provides a compound of formula (IC-2) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled:



wherein ring A, ring D, Y, Z₃, Z₄, Z₅, Z₆, R₂, R₃, R_A, R_B, m, p and q are defined as follows:

Z₃ and Z₆ are N or CR_e; Z₄ and Z₅ are N, NH, NR_e or CR_e, and at least one of Z₄ and Z₅ is N or NH; wherein is a single bond or a double bond, and the position of the double bond changes when Z₄ or Z₅ is N or NH;

R_e is hydrogen, deuterium, halogen, hydroxyl, cyano, -NH₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, -NH(C₁-C₆ alkyl) or -N(C₁-C₆ alkyl)(C₁-C₆ alkyl);

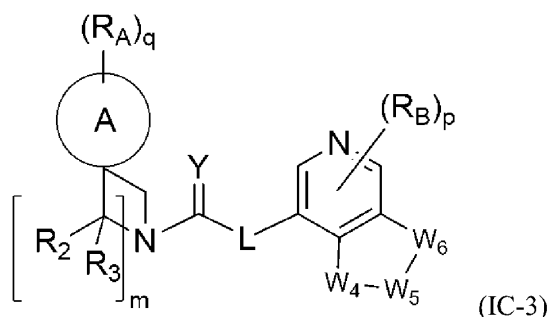
Ring D is a 5-6 membered cycloalkyl, a 5-6 membered heterocyclyl, a 5-6 membered aryl, or a 5-6 membered heteroaryl which is fused to a 10 membered ring, or is absent;

m is 1 or 2;

Ring A is defined as above; and

Y, R₂, R₃, R_A, R_B, p, q are defined as above.

One aspect of the present invention provides a compound of formula (IC-3) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled:



wherein ring A, W₄, W₅, W₆, Y, L, R₂, R₃, R_A, R_B, m, p and q are defined as follows:

-W₄-W₅-W₆- is any one of (1)-CR_f=N-NR_f-, (2) -NR_f-N=CR_f-, (3)-CR_fR_g-O-CR_fR_g-, (4)-S-N=NR_f-, (5)-CR_f=N-S-, (6)-CR_fR_g-CR_fR_g-NR_f-, and (7) non-existence;

R_f and R_g are independently hydrogen, deuterium, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or two R_f and R_g connected to the same carbon atom form an oxo group, or two R_f and R_g connected to the same carbon atom and the carbon atom to which they are connected together form a C₃-C₈ cycloalkyl group, or R_f and R_B are connected to form a 6-7 membered ring;

m is 1 or 2;

Ring A is defined as above;

Y, L, R₂, R₃, R_A, R_B, p, q are defined as above.

Another aspect of the invention is to provide a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I), formula (IC-1), formula (IC-2), or formula (IC-3) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled, and one or more pharmaceutically acceptable carriers or excipients. The pharmaceutical composition of the present invention is used as an MTA-cooperative PRMT5 inhibitor.

Another aspect of the invention is to provide the use of a compound of formula (I), formula (IC-1), formula (IC-2), or formula (IC-3) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the

foregoing being isotope-labeled, in the manufacture of drugs or a medicament for MTA-cooperative PRMT5 inhibitors.

Another aspect of the invention is to provide a method for treating cancer comprising administering a therapeutically effective amount of a compound of formula (I), formula (IC-1), formula (IC-2), or formula (IC-3) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled to a subject in need so that the growth of the cancer in the subject is inhibited. Another aspect of the invention is to provide a compound of formula (I), formula (IC-1), formula (IC-2), or formula (IC-3) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled, for use in treating cancer. The compounds of formula (I), formula (IC-1), formula (IC-2) or formula (IC-3), a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled may be used alone or in combination with another therapeutic agent and/or treatment method.

Another aspect of the invention is to provide a method for preparing a compound of formula (I), formula (IC-1), formula (IC-2), or formula (IC-3) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled.

Embodiments

The present invention can be understood easily by referring to the following detailed description of various embodiments of the invention, the examples, and the tables with their relevant descriptions. Unless otherwise defined, all terms used herein (including technical and scientific terms) have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. It will be further understood that terms such as those defined in commonly used dictionaries should be interpreted consistently with their meaning in the context of the relevant art and will not be interpreted in an idealized or overly formal sense unless expressly so defined herein. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

definition

The definitions set forth in this section are intended to clarify terms used throughout this application. The term "herein" means the entire application.

It must be noted that, as used herein, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, unless otherwise required by context, singular terms shall include the plural and plural terms shall include the singular.

Usually, ranges are expressed herein as from "about" one particular value and/or to "about" another particular value. When such a range is expressed, an embodiment includes the range from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the word "about," it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to and independently of the other endpoint. As used herein, the term "about" refers to $\pm 20\%$, preferably $\pm 10\%$, and even more preferably $\pm 5\%$.

As used herein, the phrase "optionally substituted" means that substitution is optional. In the event a substitution is desired, such substitution means that any number of hydrogens on the designated atom are replaced with a selection from the indicated group, provided that the normal valence of the designated atom is not exceeded, and that the substitution results in a stable compound. For example, when a substituent is keto (i.e., =O), 2 hydrogens on the atom are replaced. Examples of substituents for a "substituted" group are those found in the exemplary compounds and embodiments disclosed herein and can include, but are not limited to, halogen, cyano, alkyl, alkoxy, haloalkyl, alkylamino, aminoalkyl, dialkylamino, hydroxyalkyl, alkoxyalkyl, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, alkylaminoalkoxy, alkylaminoalkyl and the like.

As used herein, the term "halogen" includes fluorine, chlorine, bromine and iodine. "Halo," used as a prefix of a group, means one or more hydrogens on the group are replaced with one or more halogens.

The term "alkyl" used herein refers to a monovalent, saturated, straight or branched hydrocarbon group containing 1 to 12 carbon atoms. Preferably, the alkyl is a C1-C8 alkyl group. More preferably, the alkyl is a C1-C6 alkyl group. The alkyl can be unsubstituted or substituted with one or more substituents. Examples of a C1-C6 alkyl group include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl (including all isomeric forms), and hexyl (including all isomeric forms), heptyl (including all isomeric forms), octyl (including all isomeric forms) and the like.

Unless the number of rings is specified otherwise, the term "cycloalkyl" used herein refers to a saturated, monovalent hydrocarbon group having cyclic configurations, including monocyclic, bicyclic, tricyclic, and higher polycyclic alkyl groups (and, when multicyclic,

including fused and bridged bicyclic and spirocyclic moieties) wherein each cyclic moiety has from 3 to 12 carbon atoms. Preferably, the cycloalkyl has from 3 to 8 carbon atoms. More preferably, the cycloalkyl has from 3 to 6 carbon atoms. When cycloalkyl contains more than one ring, the rings may be fused or unfused and include bicyclic groups. Fused rings generally refer to at least two rings sharing two atoms therebetween. Such cycloalkyl groups include, for example, monocyclic structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1-methylcyclopropyl, 2-methylcyclopentyl, 2-methylcyclooctyl and the like, or bicyclic, polycyclic or bridged ring structures, such as adamantyl and the like.

Unless the number of rings is specified otherwise, the term "heterocyclyl" means a saturated or partially unsaturated monovalent monocyclic group of 3 to 9 ring atoms or a saturated or partially unsaturated monovalent fused bicyclic group of 5 to 12 ring atoms, wherein one or more, such as one, two, three or four ring heteroatoms are independently selected from the following: -O-, -S(O)_x- (x is 0, 1 or 2), -N=, -N(R^y)- (where R^y is hydrogen, alkyl, hydroxyl, alkoxy, acyl or alkylsulfonyl) and the remaining ring atoms are carbon. One or two ring carbon atoms may be replaced by -C(O)-, -C(S)- or -C(=NH)- groups. Fused bicyclic groups include bridged ring systems. Unless otherwise stated, the valency of a group may be on any atom of any ring within the group as long as the valency rules permit it. Specifically, R^y is absent when the valence position is on the nitrogen atom. More specifically, the term "heterocyclyl" includes, but is not limited to: piperidinyl, pyrimidinyl, morpholinyl, piperazinyl, azetidiny, pyrrolidinyl, 2-oxopyrrolidinyl, 2,5-dihydro-1H-pyrrolyl, 4-piperidinonyl, 2-oxopiperazinyl, tetrahydropyranyl, 2-oxopiperidinyl, thiomorpholinyl, perhydroazepinyl, pyrazolidinyl, dihydroimidazolyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, oxazoliny, oxazolidinyl, isoxazoliny, thiazoliny, thiazolidinyl, quinuclidinyl, isothiazolidinyl, octahydroindolyl, octahydroisoindolyl, decahydroisoquinolyl, tetrahydrofuranyl and tetrahydropyranyl, and their derivatives, or N-oxide or its protected derivatives.

The term "ring" as used herein refers to "cycloalkyl," "aryl," "heteroaryl" and "heterocyclyl" which do not exist in the form of a radical.

Unless the number of rings is otherwise specified, the term "aryl" means a monovalent 6-14 membered mono- or bicyclic ring, such as an 8-11 membered mono- or bicyclic ring, wherein at least one of the rings in the bicyclic ring is a carbon aromatic ring. Representative examples include, but are not limited to, phenyl, biphenyl, naphthyl, indenyl, and the like. In an aryl group containing a bicyclic ring, any non-aromatic ring contained therein may be a cycloalkyl or heterocyclic group as described above, as long as the total number of ring atoms

meets the definition of aryl herein. In one embodiment of aryl, a fused bicyclic ring comprises a cycloalkyl and an aryl or a fused bicyclic ring comprises a heterocyclic ring and an aryl, wherein one or two ring carbon atoms of the cycloalkyl or heterocyclic ring may be replaced by -C(O)-, -C(S)-, or -C(=NH)- groups, and wherein the heteroalkyl group comprises one or two ring heteroatoms independently selected from the following: -O-, -S(O)_x- (x is 0, 1 or 2), -N=, -N(R^y)- (wherein R^y is hydrogen, alkyl, hydroxyl, alkoxy, acyl or alkylsulfonyl), and the remaining ring atoms are carbon. Fused bicyclic groups include bridged ring systems. Unless otherwise specified, the valences may be located on any atom of any ring of the aryl group as long as the valency rules allow it.

Unless the number of rings is otherwise specified, "heteroaryl" means a monocyclic, fused bicyclic or fused tricyclic monovalent group of 5 to 14 ring atoms, which contains one or more, for example one, two, three or four, ring heteroatom moieties independently selected from the following: -O-, -S(O)_n- (n is 0, 1 or 2), -N-, -N(R^x)- (R^x is hydrogen, alkyl, hydroxyl, alkoxy, acyl or alkylsulfonyl), and the remaining ring atoms are carbon, wherein at least one of the fused rings containing the bicyclic or tricyclic group is an aromatic ring containing a ring heteroatom. In the heteroaryl containing bicyclic or tricyclic group, any non-aromatic ring contained therein may be a cycloalkyl or heterocyclic group as described above, as long as the total number of ring atoms meets the definition of heteroaryl herein. In one embodiment of heteroaryl, a fused bicyclic ring comprises a cycloalkyl group and a heteroaryl group or a fused bicyclic ring comprises a heterocyclic group and a heteroaryl group, wherein one or two ring carbon atoms of the cycloalkyl group or the heterocyclic group may be replaced by a -C(O)-, -C(S)- or -C(=NH)- group, and wherein the heteroalkyl group comprises one or two ring heteroatoms independently selected from the following: -O-, -S(O)_x- (x is 0, 1 or 2), -N=, -N(R^y)- (wherein R^y is hydrogen, alkyl, hydroxyl, alkoxy, acyl or alkylsulfonyl), and the remaining ring atoms are carbon. A fused bicyclic group includes bridged ring systems. Unless stated otherwise, the valency may be located on any atom of any ring of the heteroaryl group as long as the valency rules permit it. In particular, when the point of valency is located on the nitrogen, R_x is absent. More specifically, the term heteroaryl includes, but is not limited to, benzocyclopentanyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrofuro[3,2-b]pyridine, 2,3-dihydrofuro[3,2-c]pyridine, 6,7-dihydro-5H-cyclopenta[b]pyridine, chromanyl, isochromanyl, 3,4-dihydro-2H-pyrano[2,3-b]pyridine, 5,8-dihydro-6H-pyrano[3,4-b]pyridine, 1,3,4,5-tetrahydrobenzo[c]oxazepine, indanyl, phthalyl, indolyl, 1,2,4-triazolyl, 1,3,5-triazolyl, phthalimidyl, pyridyl, pyrrolyl, imidazolyl, thienyl, furanyl, indolyl, 2,3-dihydro-1H-indolyl (including, for example, 2,3-dihydro-1H-indol-2-yl or 2,3-dihydro-1H-indol-5-yl, and the

like), isoindolyl, indolyl, isoindolyl, benzimidazolyl, benzodioxol-4-yl, benzofuranyl, cinnolyl, indolizyl, naphthyridin-3-yl, phthalazin-3-yl, phthalazin-4-yl, pyridinyl, purinyl, quinazolyl, quinoxaline, tetrazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, diazinyl, oxazolyl, isoxazolyl, oxadiazolyl, benzoxazolyl, quinolyl, isoquinolyl, tetrahydroisoquinolyl (including, for example, tetrahydroisoquinolin-4-yl or tetrahydroisoquinolin-6-yl, and the like), pyrrolo[3,2-c]pyridinyl (including, for example, pyrrolo[3,2-c]pyridin-2-yl or pyrrolo[3,2-c]pyridin-7-yl, and the like), benzopyranyl, thiazolyl, isothiazolyl, thiadiazolyl, benzothiazolyl, benzothieryl, tetrahydrofuropyridyl, pyridotetrahydrofuryl, tetrahydropyranopyridyl, pyridotetrahydropyranyl, tetrahydropyranophenyl or chromanyl, pyridinoxazolyl, oxazolopyridyl, pyridopyrrolyl, pyrrolopyridyl, diazophenyl, benzodiazolyl, benzoxazolyl, oxazolophenyl, and their derivatives, or N-oxide or its protected derivatives.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making pharmaceutically acceptable acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. Suitable non-toxic acids include, but are not limited to, inorganic and organic acids such as acetic acid, alginic acid, anthranilic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethanesulfonic acid, formic acid, fumaric acid, furoic acid, galacturonic acid, gluconic acid, glucuronic acid, glutamic acid, glycolic acid, hydrobromic acid, hydrochloric acid, isethionic acid, lactic acid, maleic acid, malic acid, phenylglycolic acid, methanesulfonic acid, mucic acid, nitric acid, pamoic acid, pantothenic acid, phenylacetic acid, phosphoric acid, propionic acid, salicylic acid, stearic acid, succinic acid, p-aminobenzenesulfonic acid, sulfuric acid, tartaric acid and p-toluenesulfonic acid. Non-limiting examples of salts of compounds of the present invention include, but are not limited to: hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, 2-hydroxyethanesulfonate, phosphate, hydrogen phosphate, acetate, adipate, alginate, aspartate, benzoate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, glycerolphosphate, hemisulfate, enanthate, caproate, formate, succinate, malonate, fumarate, maleate, methanesulfonate, mesitylenesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, trimethylacetate, propionate, trichloroacetate, trifluoroacetate, glutamate, bicarbonate, undecanoate, lactate, citrate, tartrate,

glucose Sugar salts, benzenesulfonates and p-toluenesulfonates.

As used herein, the term "geometric isomers" includes, but is not limited to, cis and trans; E- and Z-forms; c-, t-, and r-forms; internal and external; R-, S- and meso; boat, chair, twist, envelope and semi-chair; and combinations thereof.

As used herein, the term "enantiomers" refers to a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a racemic mixture. The term "enantiomers" is used where appropriate to refer to racemic mixtures. A "diastereomer" is a stereoisomer having at least two atoms that are asymmetric but are not mirror images of each other. Absolute stereochemistry can be assigned according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer, the stereochemistry at each chiral carbon can be designated by R or S. Resolved compounds can be represented as (+) or (-) depending on the direction (dextral or levorotary) which they rotate plane polarized light at the wavelength of the sodium D line. Certain compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be in the E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration.

As used herein, "prodrugs" are intended to include any covalently bonded carriers that release the active parent drug according to formula (I) through in vivo physiological action, such as hydrolysis, metabolism and the like, when such prodrug is administered to a subject. The suitability and techniques involved in making and using prodrugs are well known by a person of ordinary skill in the art. Prodrugs of the compounds of formula (I) (parent compounds) can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. "Prodrugs" include the compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrugs are administered to a subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, derivatives and metabolites of the compounds of formula (I) that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates,

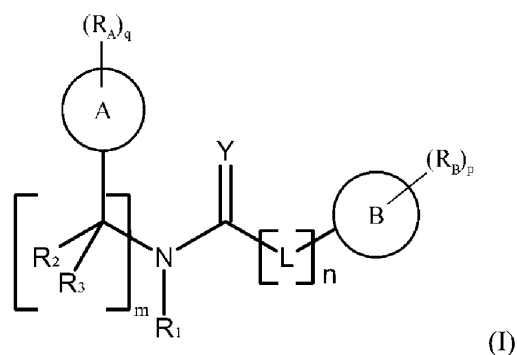
biohydrolyzable ureides, and biohydrolyzable phosphate analogues. In certain embodiments, prodrugs of the compounds of formula (I) with carboxyl functional groups are the lower alkyl (e.g., C1-C6) esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule.

The present invention also includes all pharmaceutically acceptable isotopically labeled compounds identical to those of the present invention except that one or more atoms are replaced by atoms with the same atomic number but different atomic masses or mass numbers from those that predominate in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include, but are not limited to, isotopes of hydrogen (e.g., deuterium (D, 2H), tritium (T, 3H)); isotopes of carbon (e.g., 11C, 13C, and 14C); isotopes of chlorine (e.g., 36Cl); isotopes of fluorine (e.g., 18F); isotopes of iodine (e.g., 123I and 125I); isotopes of nitrogen (e.g., 13N and 15N); isotopes of oxygen (e.g., 15O, 17O and 18O); isotopes of phosphorus (e.g., 32P); and isotopes of sulfur (e.g., 35S). Certain isotopically labeled compounds of the present invention (e.g., those incorporating radioactive isotopes) may be used in drug and/or substrate tissue distribution studies (e.g., assays). The radioactive isotopes tritium (i.e., 3H) and carbon-14 (i.e., 14C) are particularly useful for this purpose because they are easy to incorporate and detect. Substitution with positron-emitting isotopes such as 11C, 18F, 15O, and 13N can be used to examine substrate receptor occupancy in positron emission tomography (PET) studies. Isotopically labeled compounds of the invention may be prepared by methods analogous to those described in the accompanying Schemes and/or Examples and Preparations by using appropriate isotopically labeled reagents in place of the previously employed non-labeled reagents. Pharmaceutically acceptable solvates of the invention include those in which the crystallization solvent may be isotopically substituted, for example, D₂O, acetone-d₆ or DMSO-d₆.

As used herein, the term "solvate" means a compound or a pharmaceutically acceptable salt thereof that further includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. If the solvent is water, the solvate may be suitably called a "hydrate," such as hemi-hydrate, mono-hydrate, sesqui-hydrate, di-hydrate, tri-hydrate, etc.

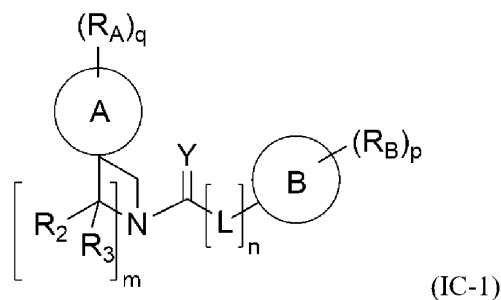
Compounds

The invention provides a compound of formula (I) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled:



wherein the groups are defined as above. are defined as above.

The invention provides a compound of formula (IC-1) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled:



wherein the groups are defined as above.

In one embodiment, in formula (I) or formula (IC-1), Ring B is selected from 8-11 membered fused bicyclic heteroaryl and 10-15 membered fused tricyclic heteroaryl.

In one embodiment, in formula (I) or formula (IC-1), Ring B is selected from 8-11 membered fused bicyclic heteroaryl and 8-11 membered fused bicyclic heterocyclyl, preferably 8-11 membered fused bicyclic heteroaryl.

In one embodiment, in formula (I) or formula (IC-1), Ring B is selected from 10-15 membered fused tricyclic heteroaryl and 10-15 membered fused tricyclic heterocyclyl, preferably a 10-15 membered fused tricyclic heteroaryl.

In the preceding embodiments, in formula (I) or formula (IC-1), n is 0.

In the preceding embodiments, in formula (I) or formula (IC-1), n is 1, preferably ring B is 9-10 membered fused bicyclic heteroaryl, and more preferably ring B is 9 membered fused bicyclic heteroaryl.

In the preceding embodiments, in formula (I) or formula (IC-1), n is 1, preferably ring B is 10-15 membered fused tricyclic heteroaryl, and more preferably ring B is 12-13 membered

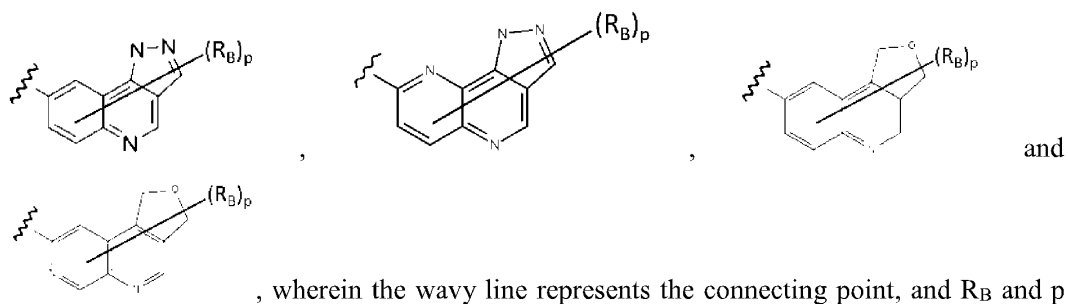
fused tricyclic heteroaryl.

In the preceding embodiments, in Formula (I) or Formula (IC-1), m is 1.

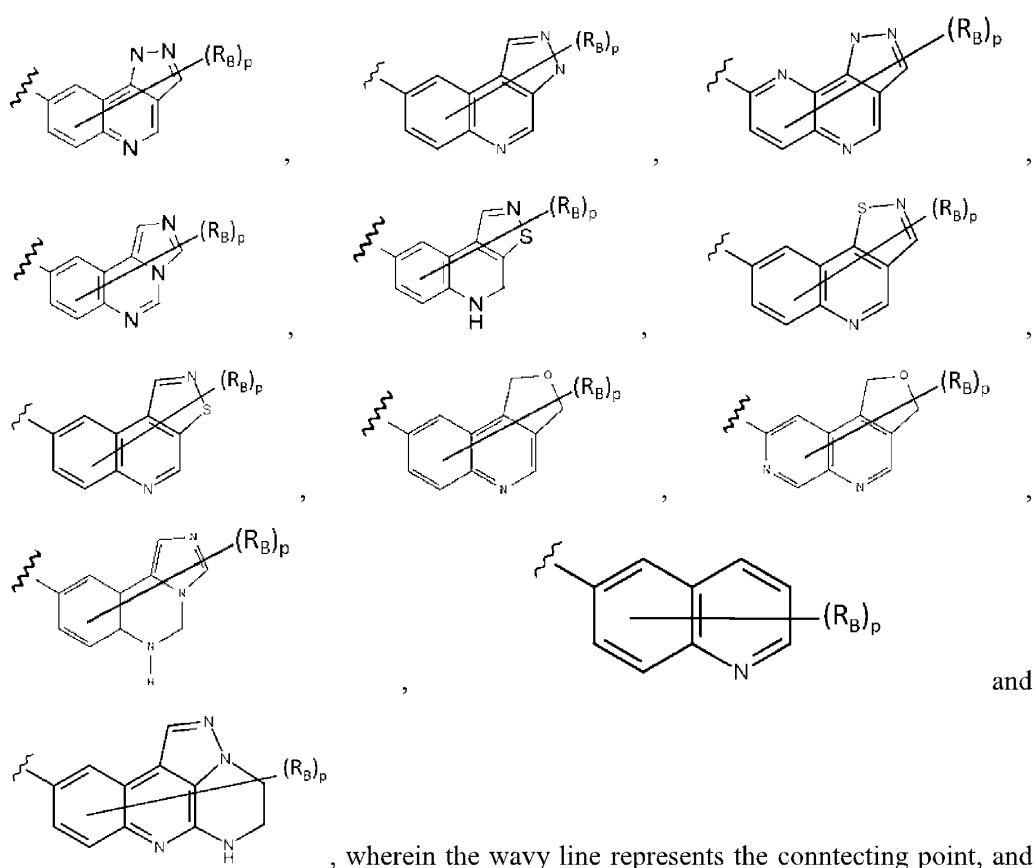
In the preceding embodiments, in formula (I) or formula (IC-1), m is 0.

In the preceding embodiments, in formula (I) or formula (IC-1), ring B is 10-15 membered fused tricyclic heteroaryl, preferably ring B is 12-13 membered fused tricyclic heteroaryl.

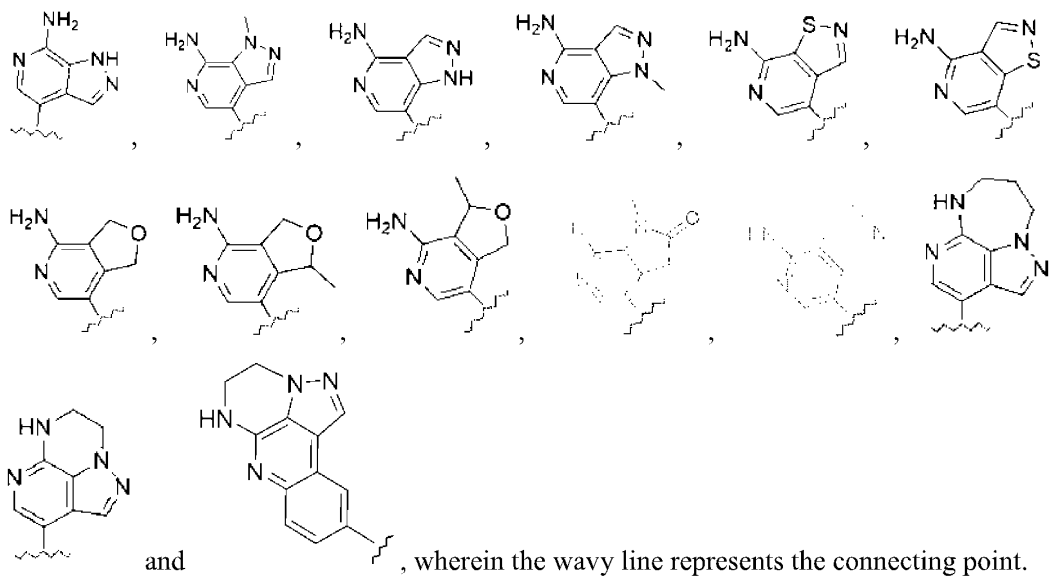
In the preceding embodiments, in formula (I) or formula (IC-1), ring B is selected from



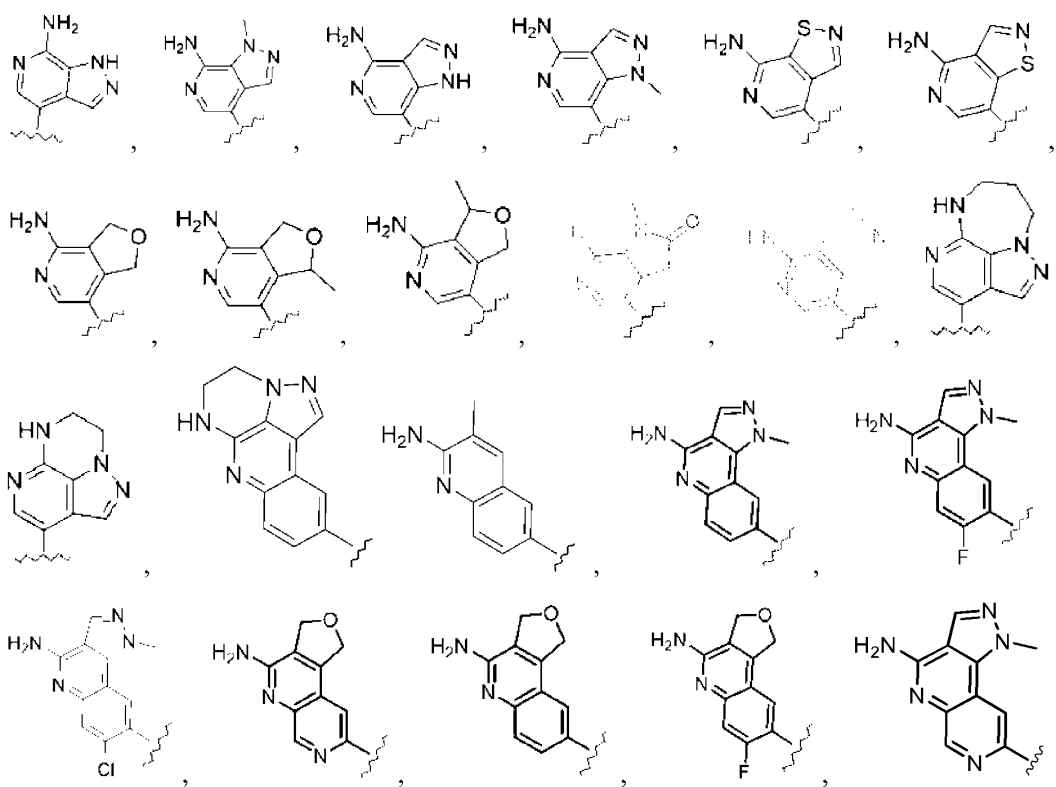
In the preceding embodiments, in formula (I) or formula (IC-1), ring B is selected from

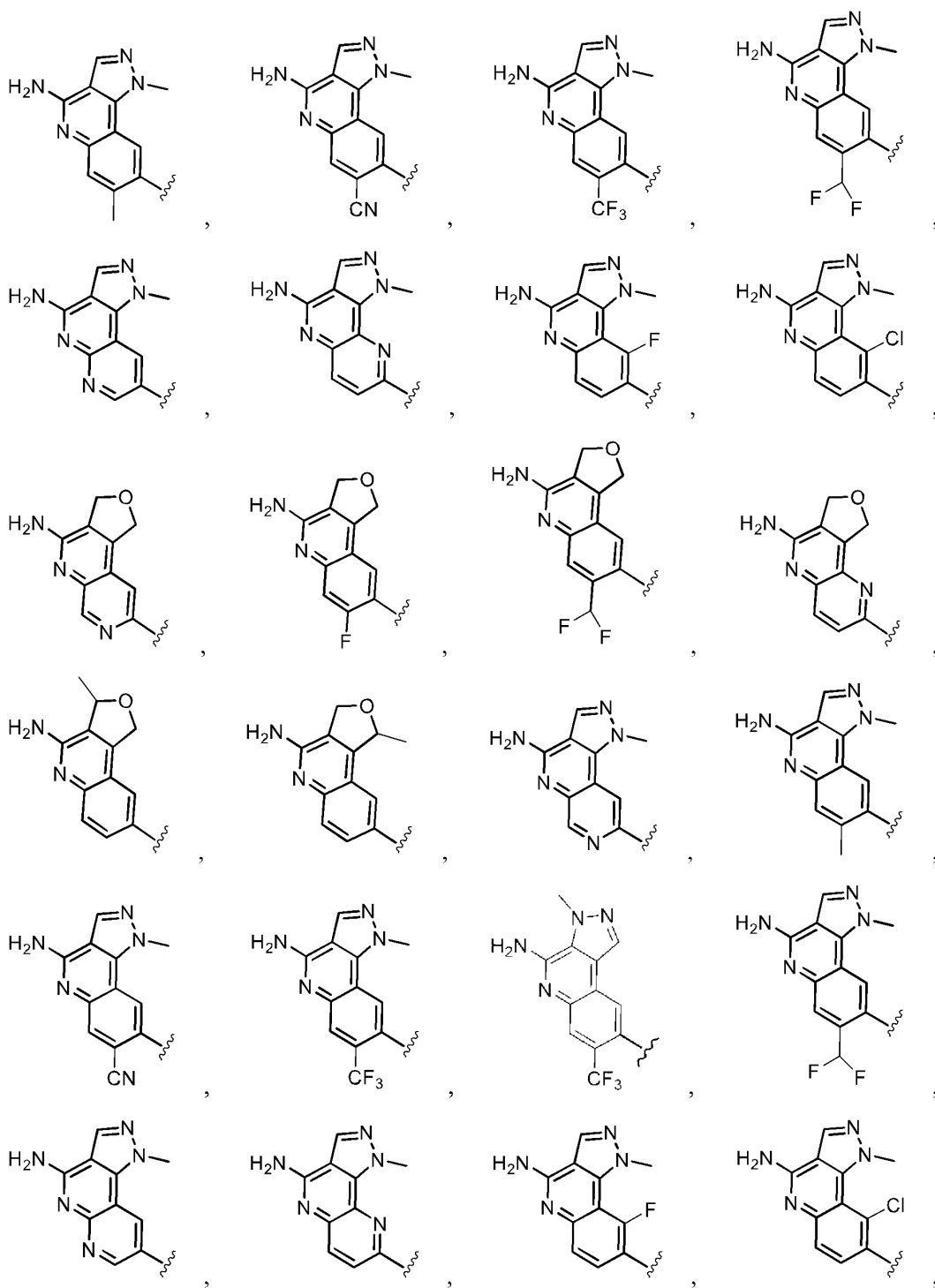


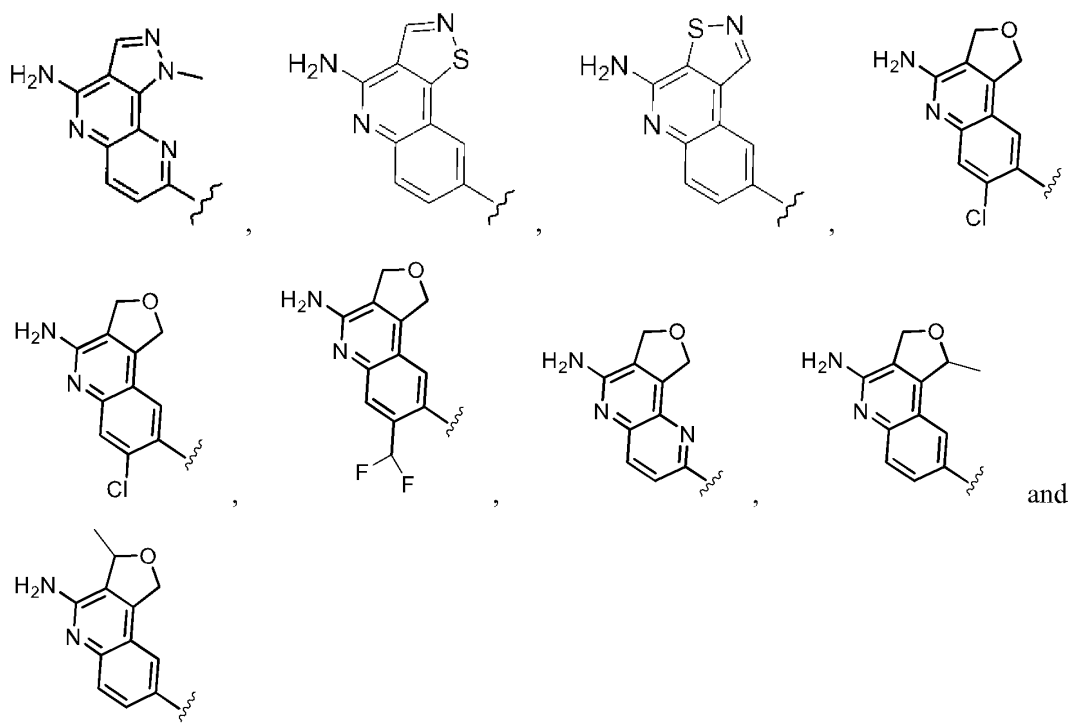
In the preceding embodiments, in formula (I) or formula (IC-1), ring B is selected from



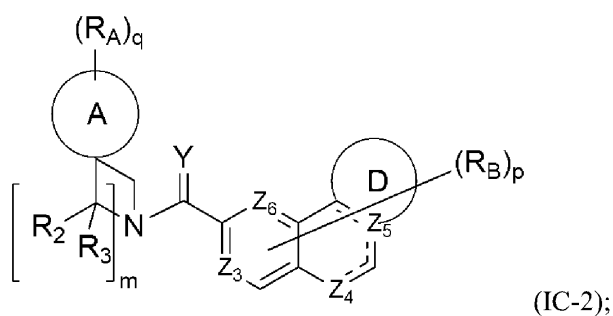
In the preceding embodiments, in formula (I) or formula (IC-1), ring B is selected from







In one embodiment, the invention provides a compound of formula (IC-2) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled:



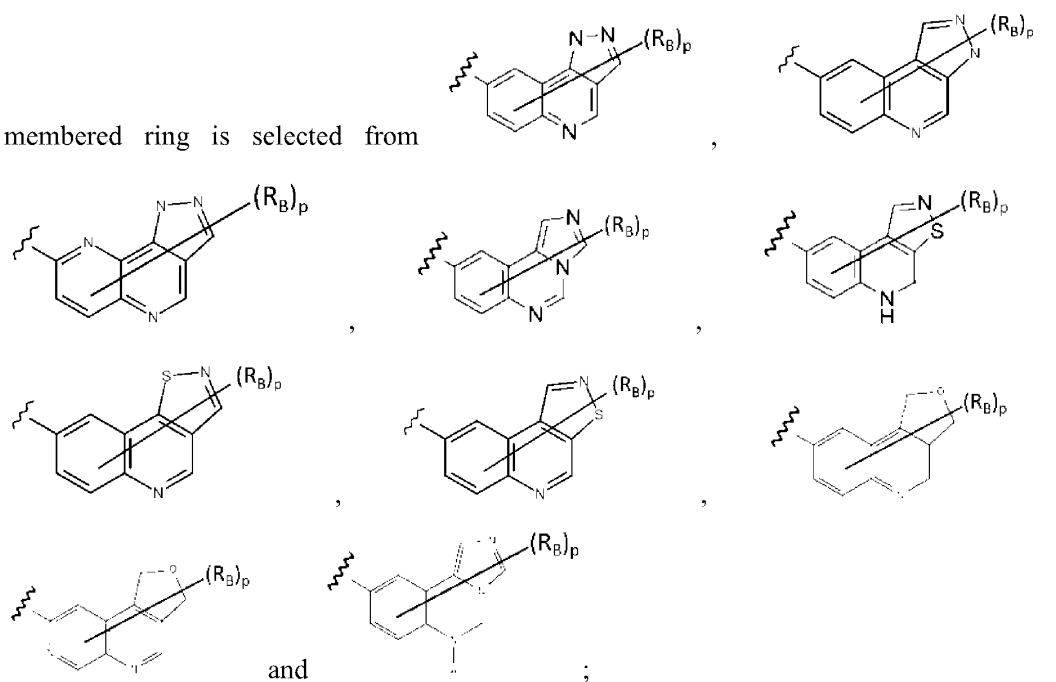
wherein the groups are defined as above.

In one embodiment, in formula (IC-2), one of Z_3 and Z_6 is N and the other is CR_e ; and Z_4 is N, NH or NR_e and Z_5 is CR_e .

In one embodiment, in formula (IC-2), Z_3 and Z_6 are each independently CR_e ; and wherein Z_4 is N, NH or NR_e and Z_5 is CR_e .

In one embodiment, in formula (IC-2), the moiety formed by Ring D fused with the 10-

membered ring is selected from

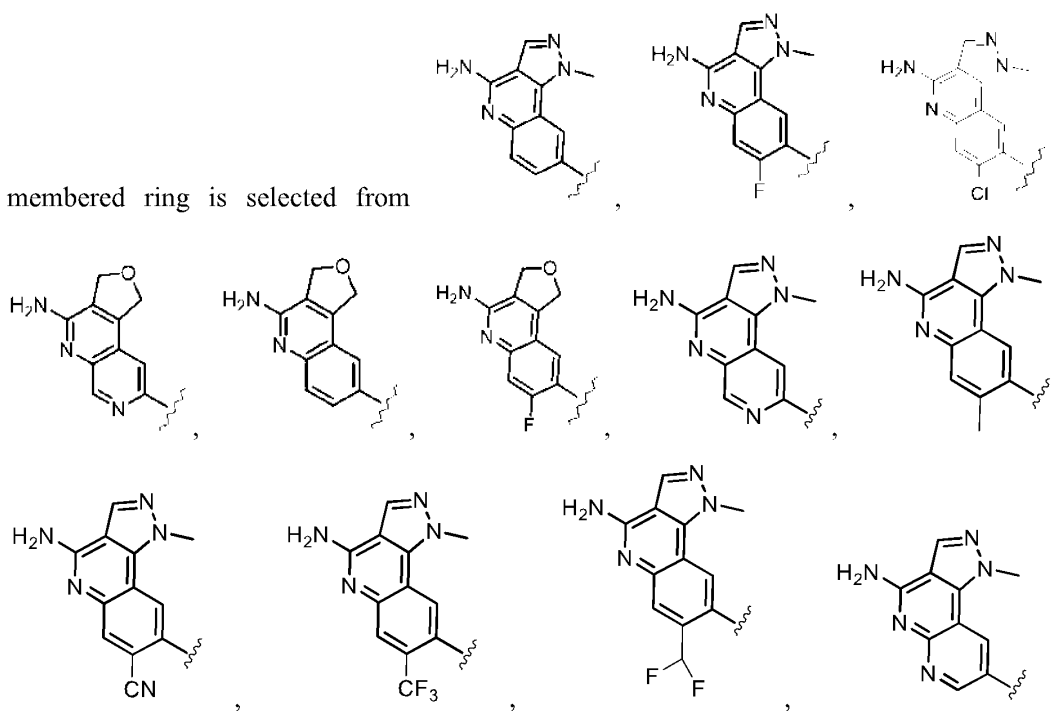


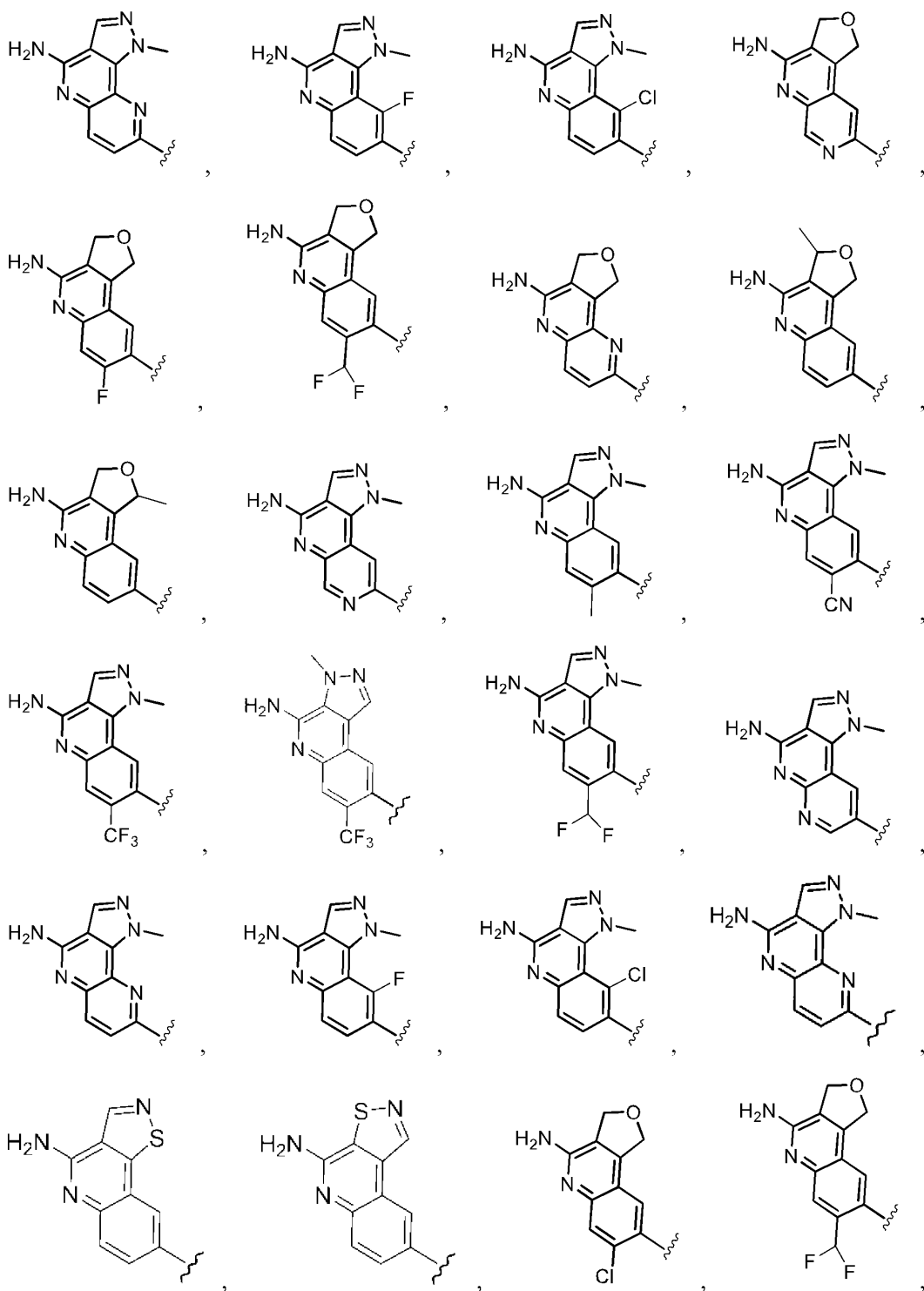
R_B and p are as defined in the preceding embodiments.

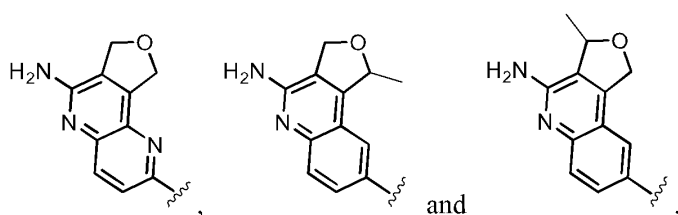
In one embodiment, in formula (IC-2), Ring D is absent.

In one embodiment, in formula (IC-2), the moiety formed by ring D fused with the 10

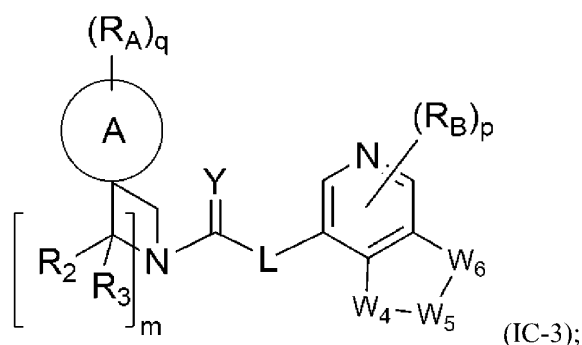
membered ring is selected from





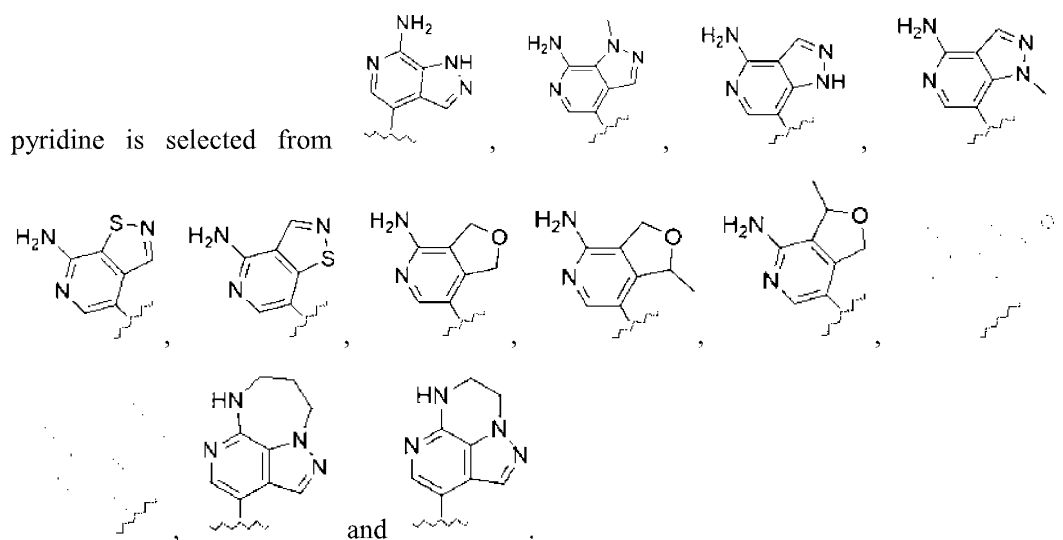


In one embodiment, the invention provides a compound of formula (IC-3) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled:

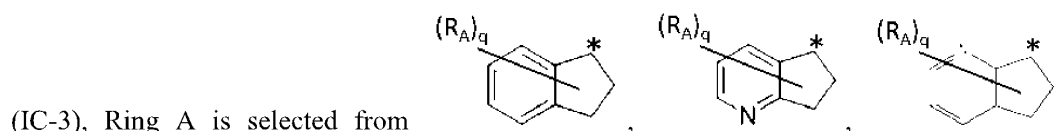


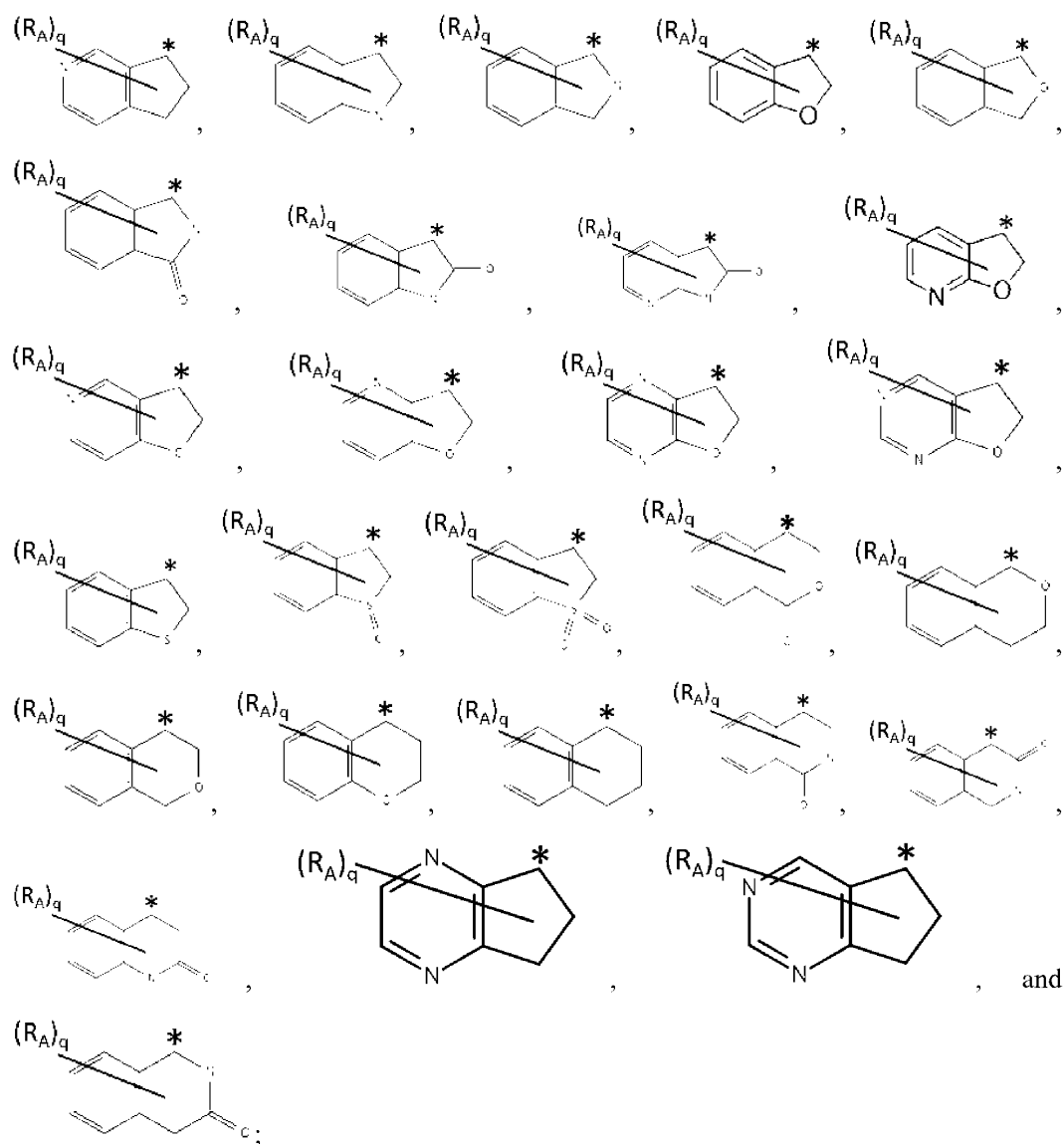
wherein the groups are as defined in the preceding embodiments.

In one embodiment, in formula (IC-3), the moiety formed by -W₄-W₅-W₆- fused with the



In the preceding embodiments, in formula (I), formula (IC-1), formula (IC-2) or formula



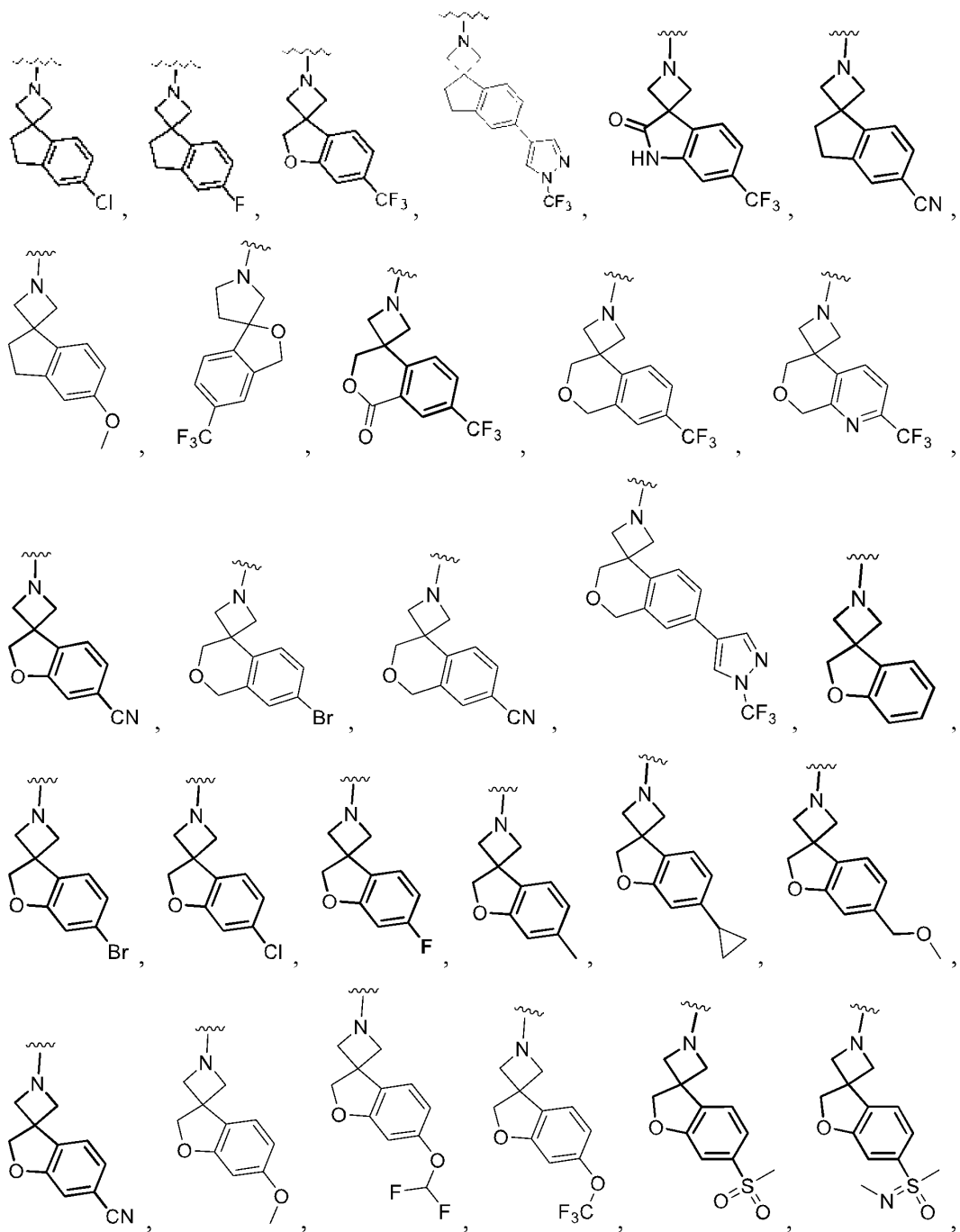
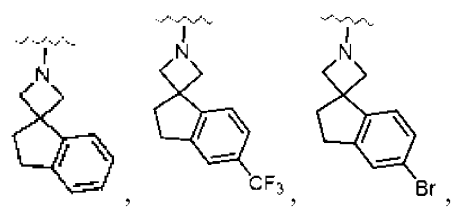


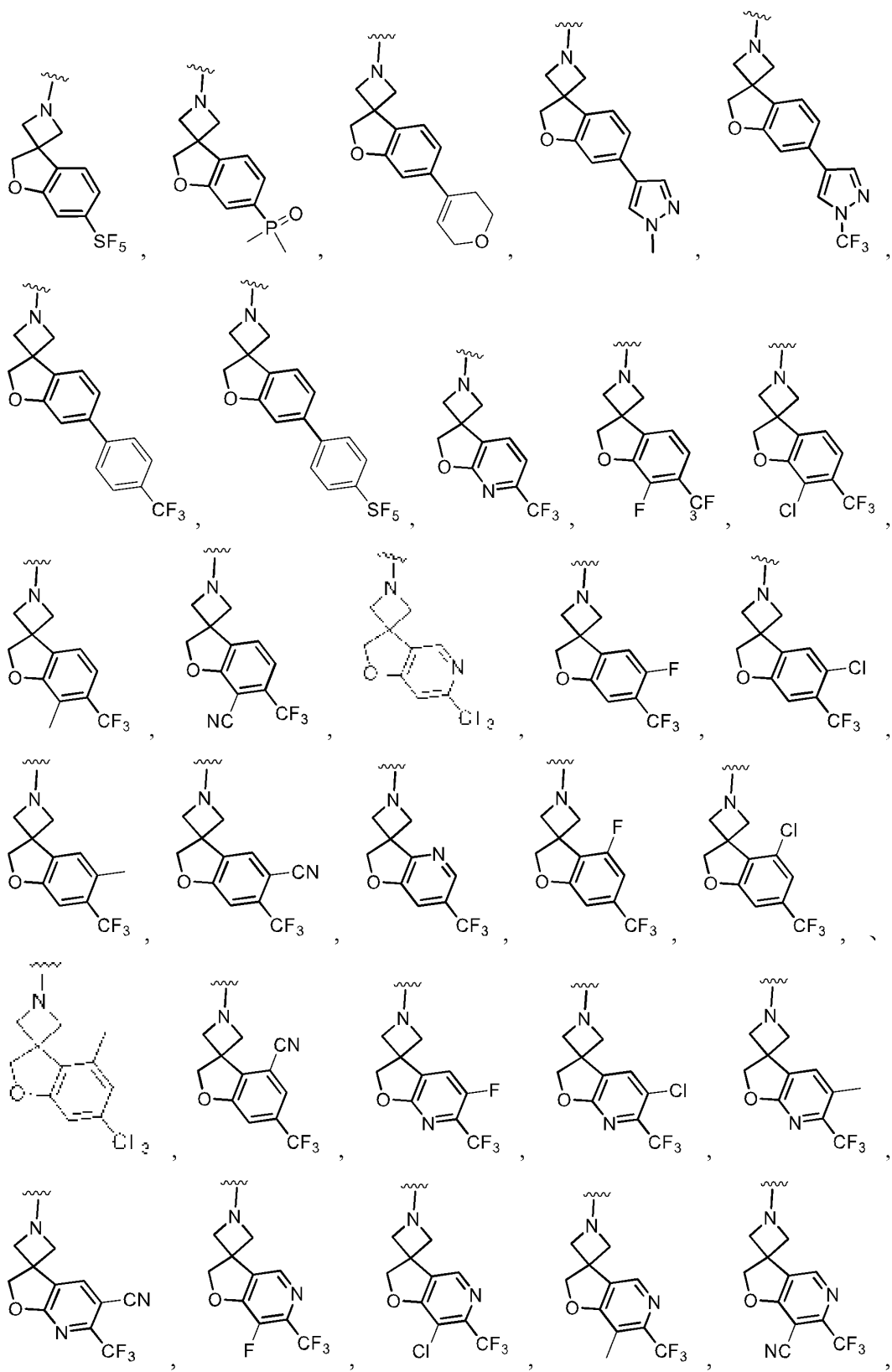
wherein * indicates the connecting point of spiral ring; and

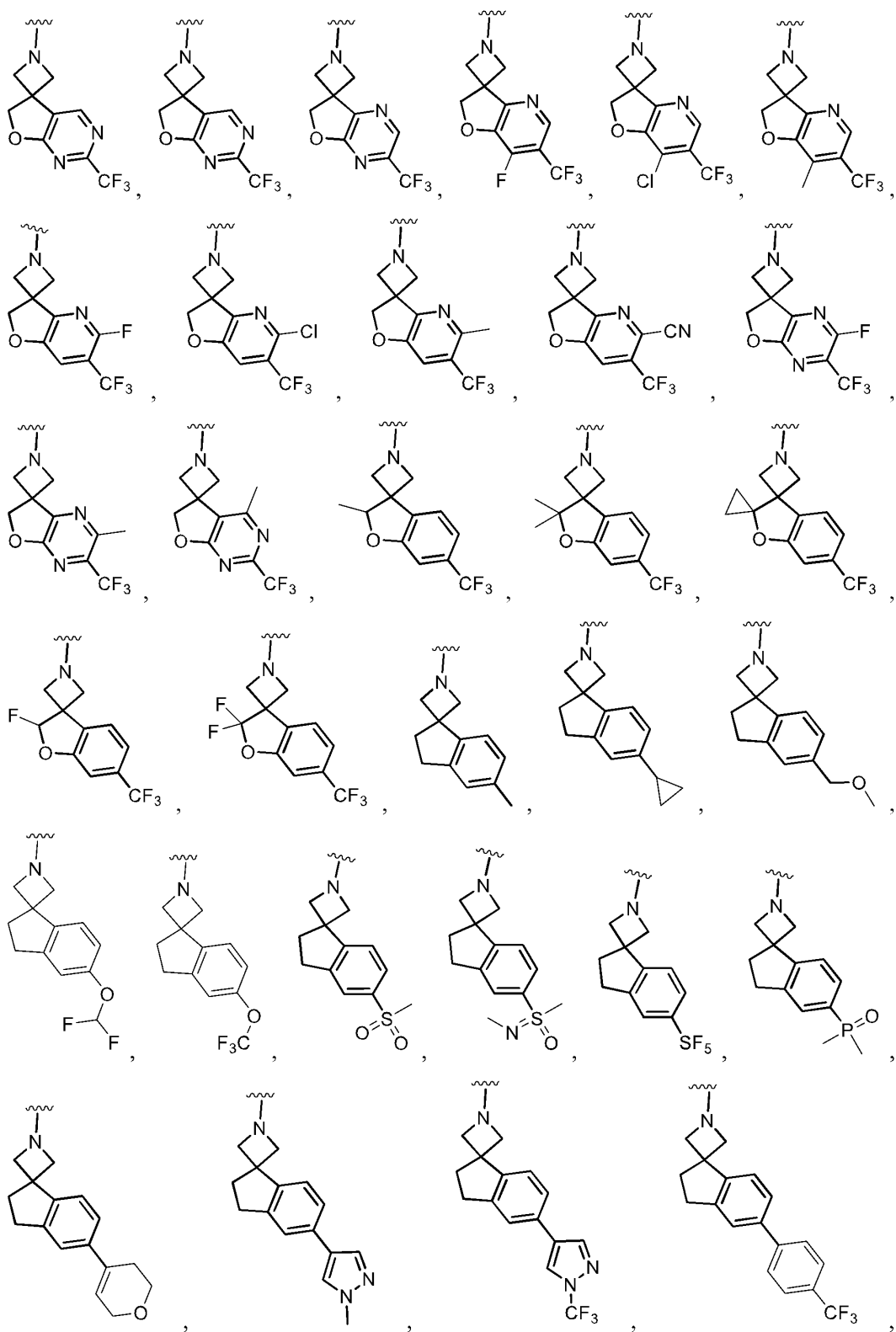
R_A and q are as defined in the preceding embodiments.

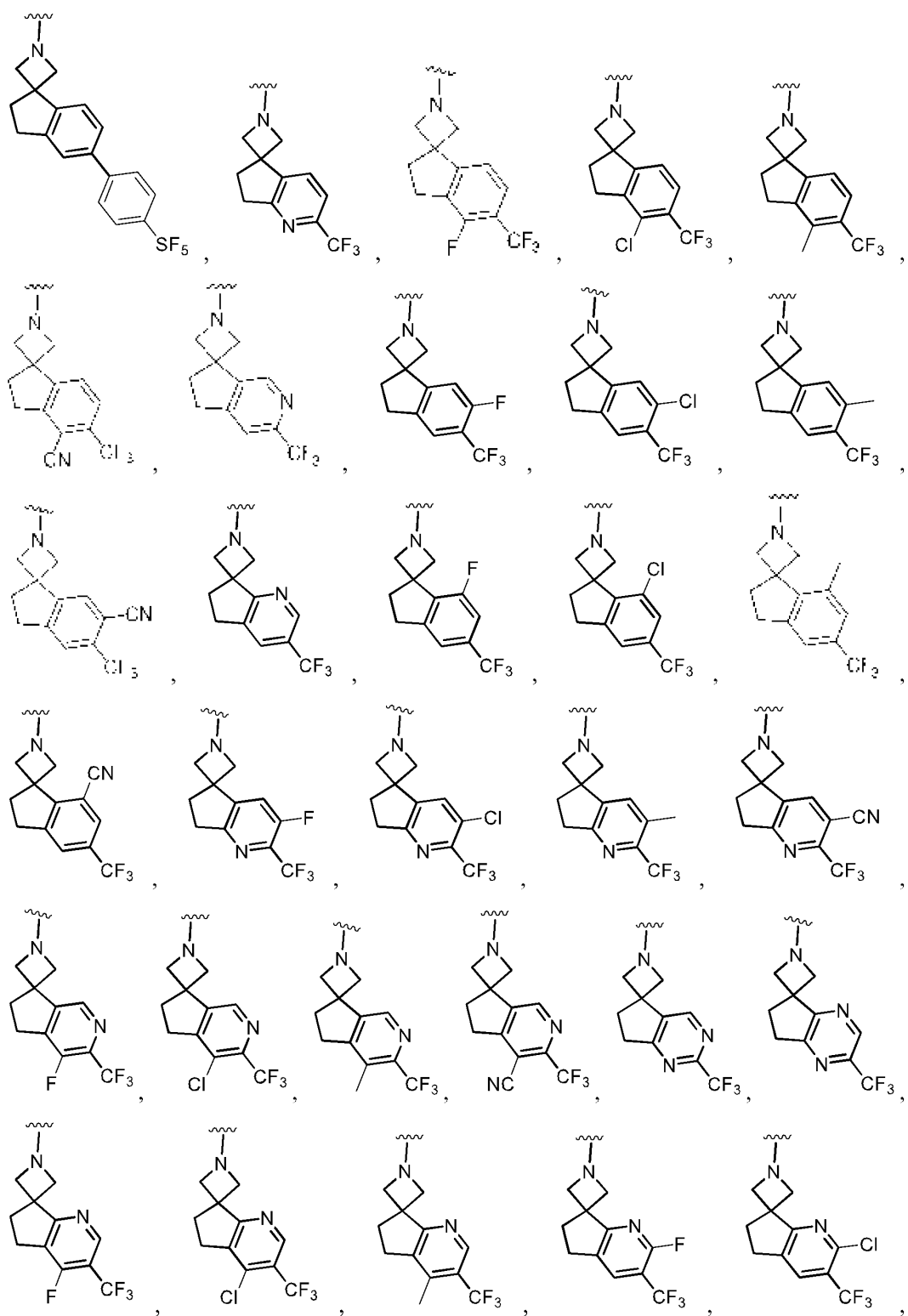
In the preceding embodiments, in formula (I), formula (IC-1), formula (IC-2) or formula (IC-3), wherein (1) R_1 , the nitrogen atom to which R_1 is connected, the carbon atom to which R_2 and R_3 are connected, and one atom of the ring A form a cyclic group, and this cyclic group and the ring A are connected in the form of sharing such atom to form a spirocyclic structure, or (2) the carbon atom to which R_2 and R_3 are connected, the adjacent nitrogen atom, the adjacent methylene group, and one atom of the ring A form a cyclic group, and this cyclic group and the ring A are connected in the form of sharing such one atom to form a spirocyclic

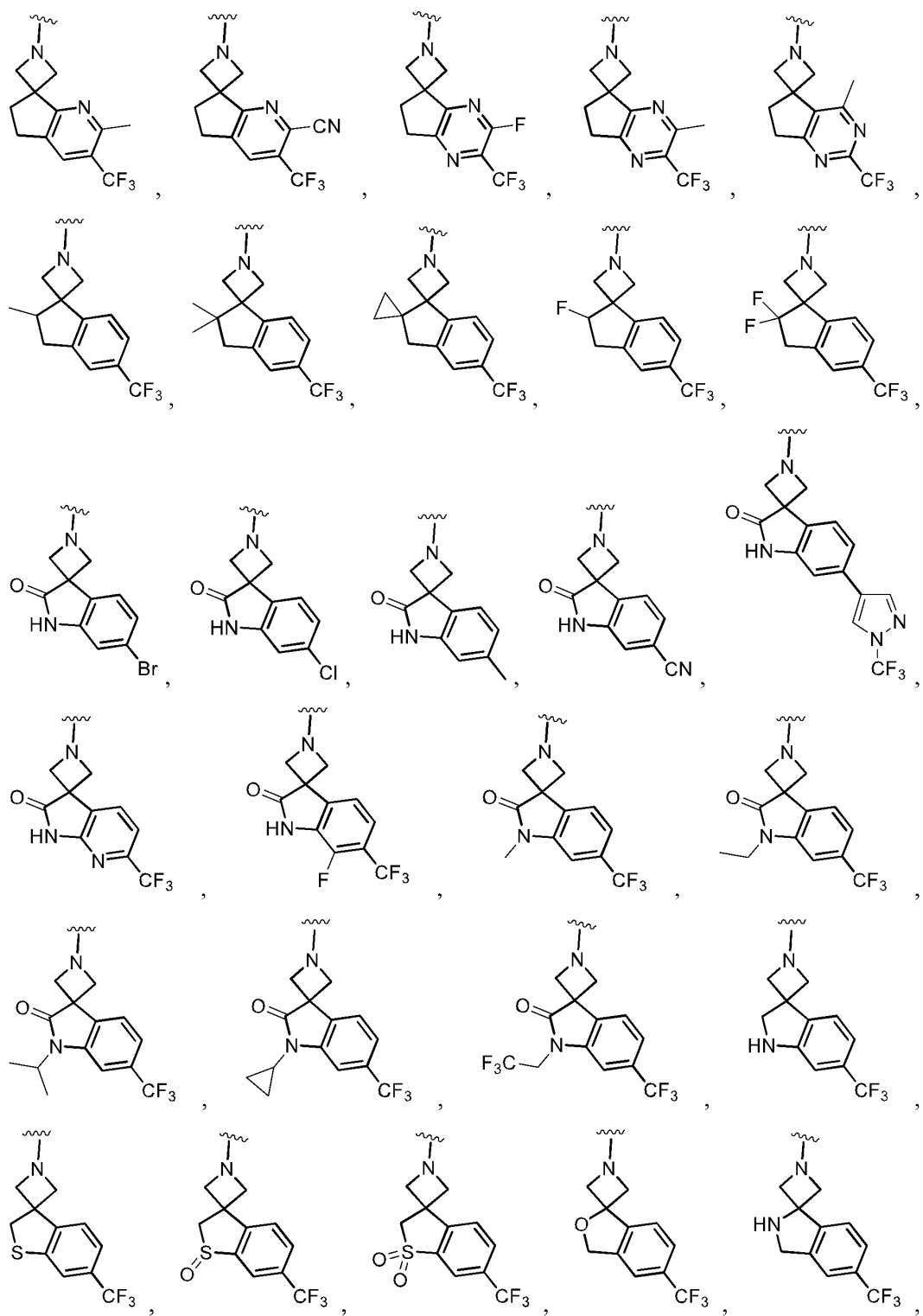
structure, the spirocyclic structure is selected from

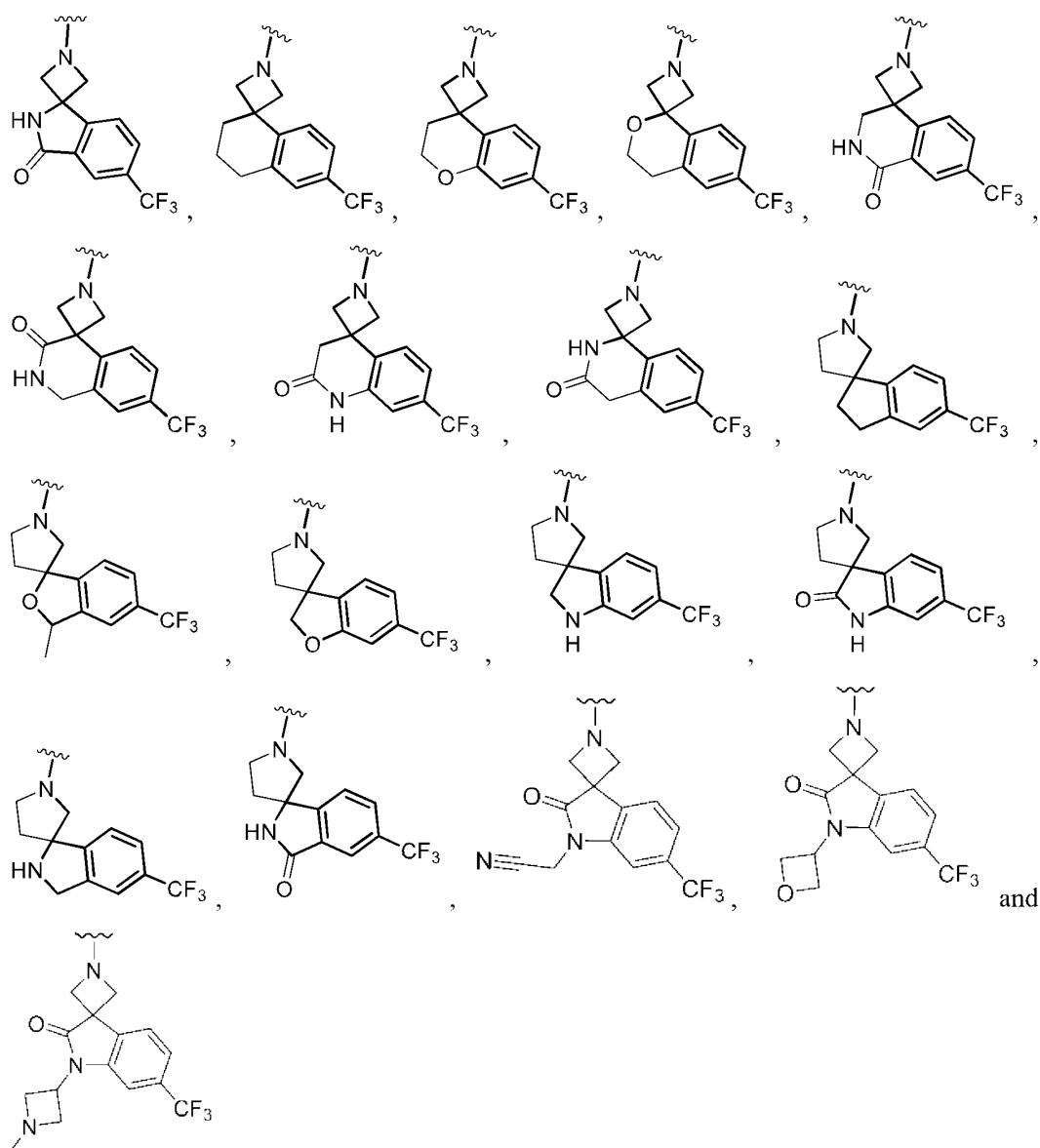






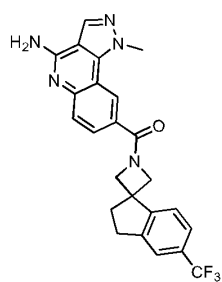




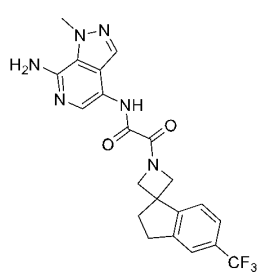


In one embodiment, the compound of formula (I) is a compound of (IC-1), (IC-2), or (IC-3). In one embodiment, the compound of formula (I) is a compound of formula (IC-1). In one embodiment, the compound of (IC-1) is a compound of formula (IC-2). In one embodiment, the compound of formula (IC-1) is a compound of formula (IC-3); or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled.

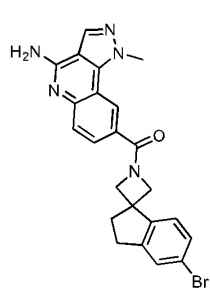
In another preferred embodiment, the present invention provides a compound selected from:



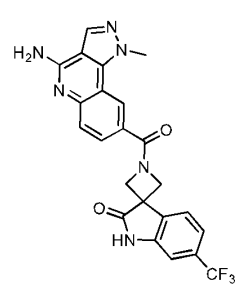
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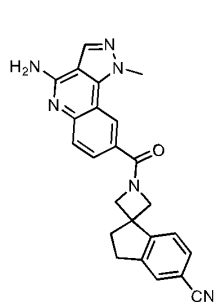
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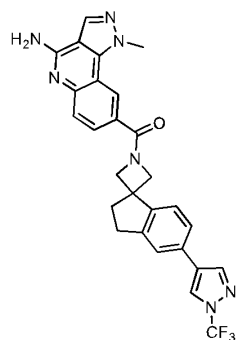
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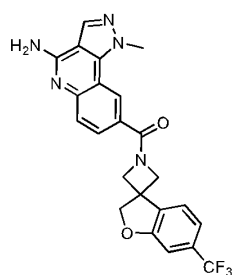
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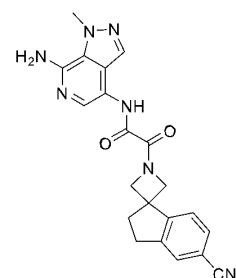
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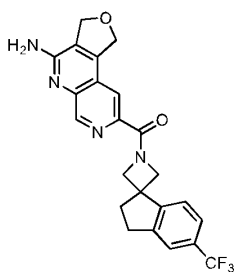
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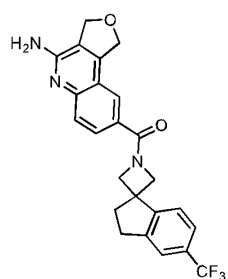
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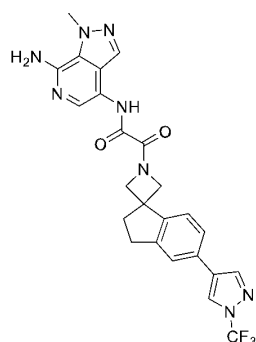
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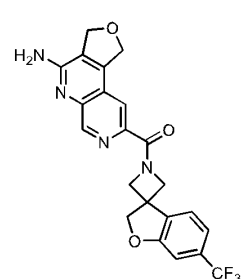
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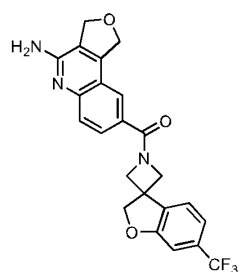
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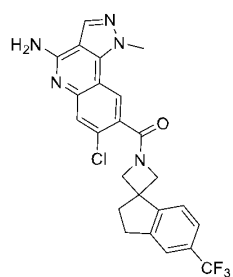
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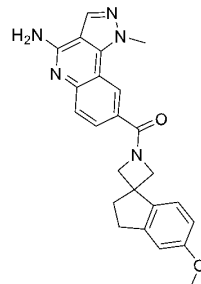
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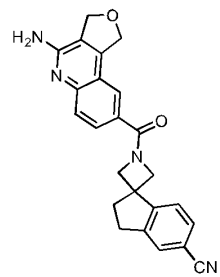
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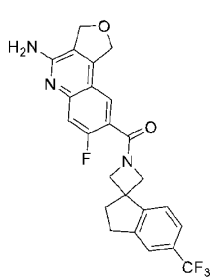
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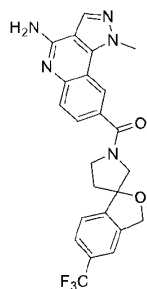
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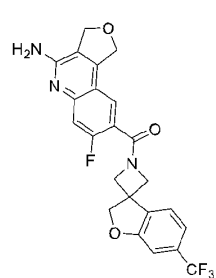
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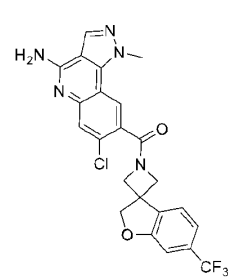
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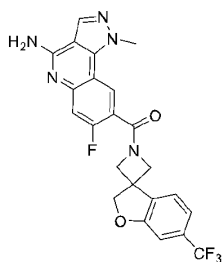
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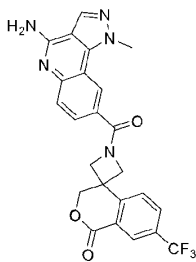
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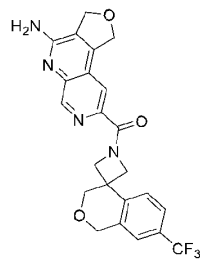
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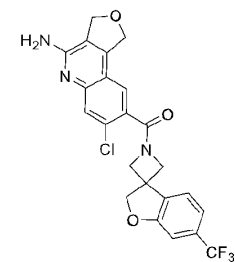
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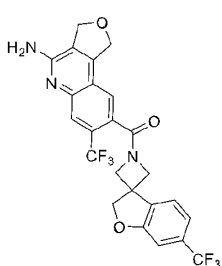
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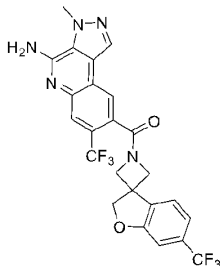
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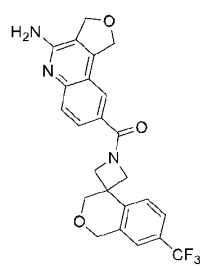
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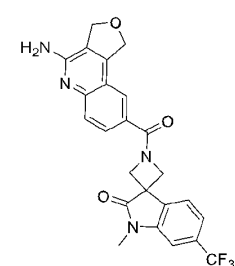
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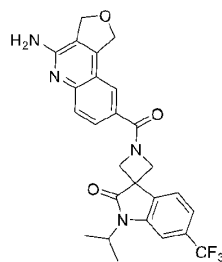
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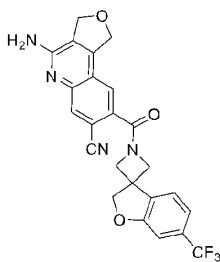
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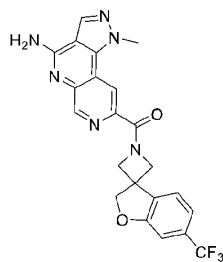
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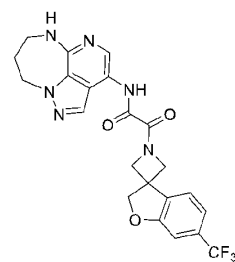
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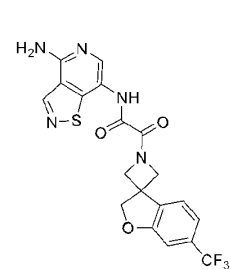
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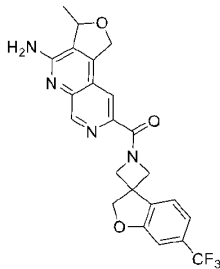
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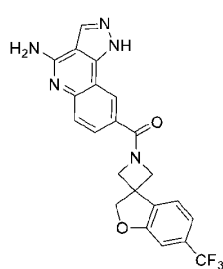
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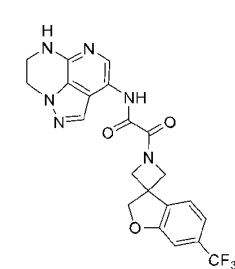
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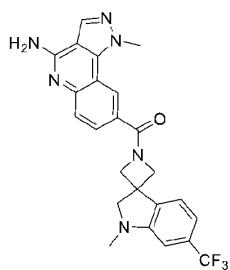
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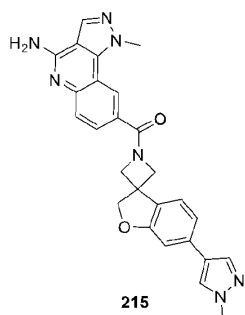
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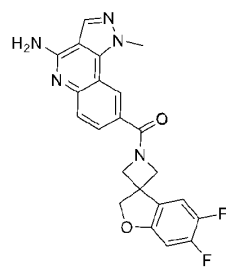
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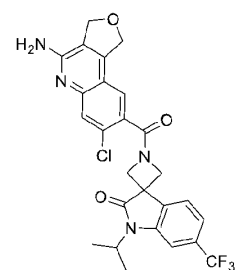
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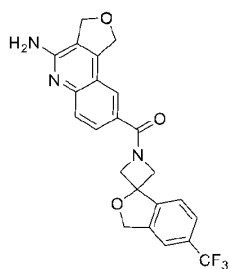
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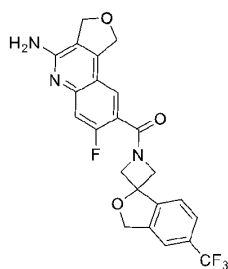
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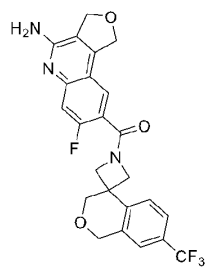
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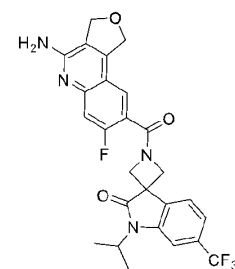
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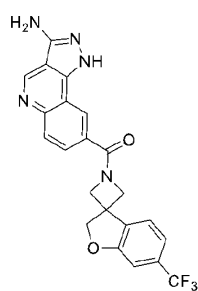
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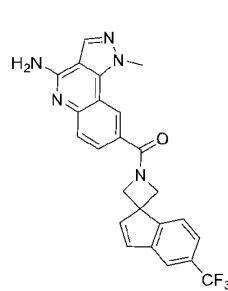
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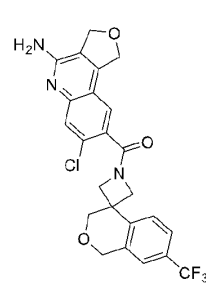
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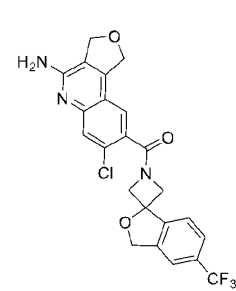
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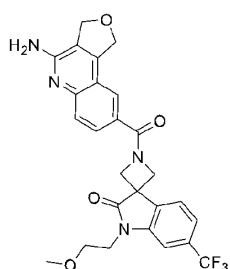
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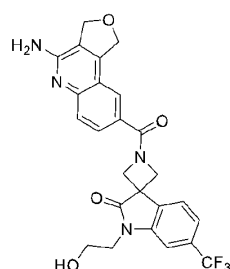
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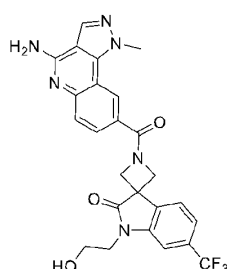
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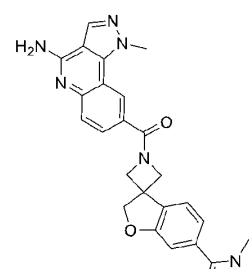
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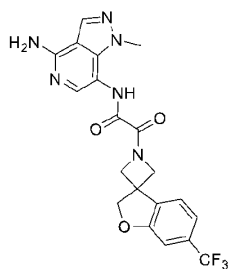
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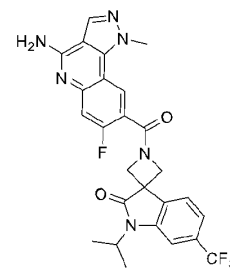
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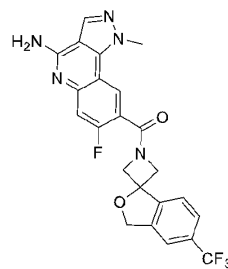
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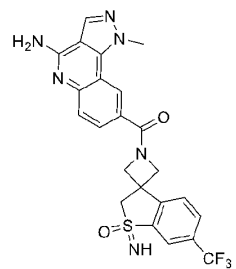
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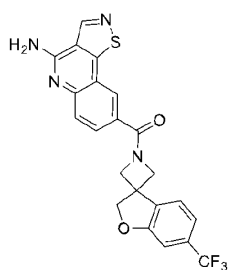
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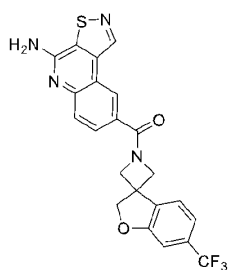
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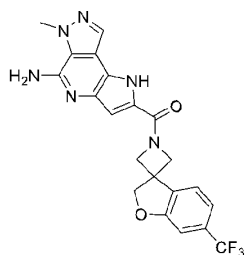
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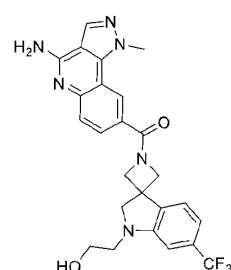
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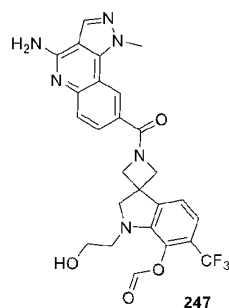
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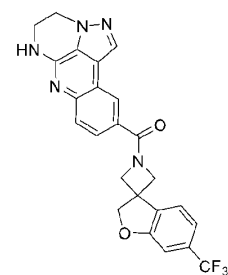
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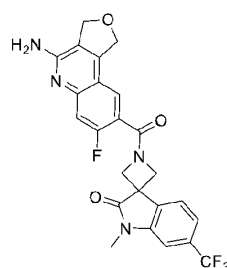
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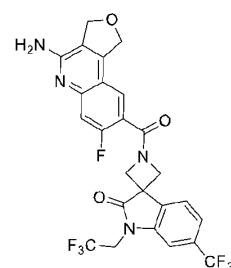
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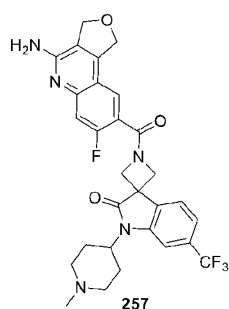
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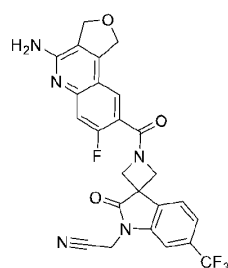
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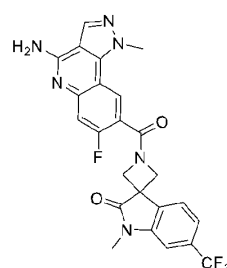
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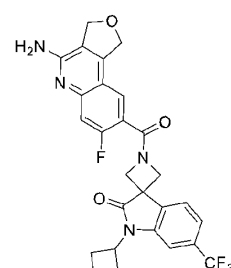
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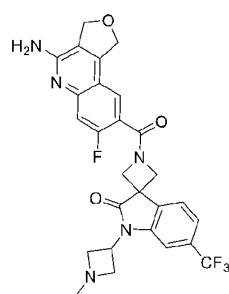
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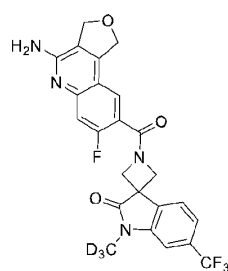
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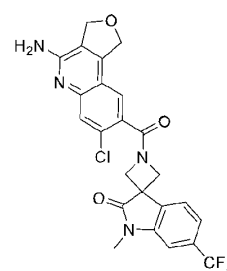
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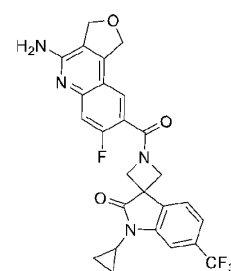
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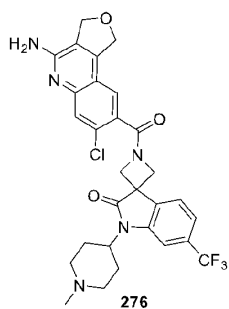
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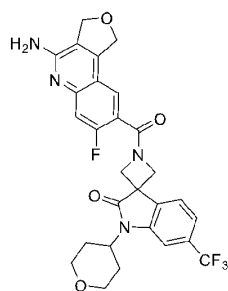
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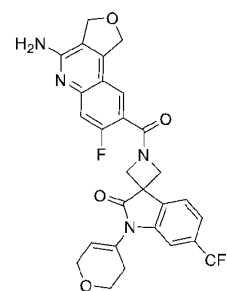
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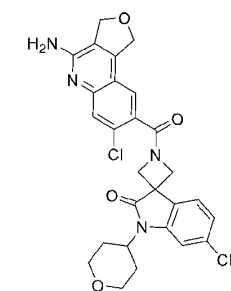
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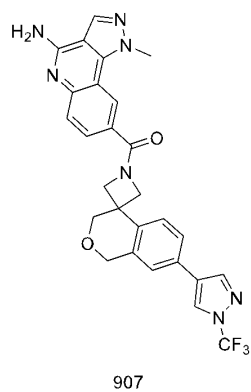
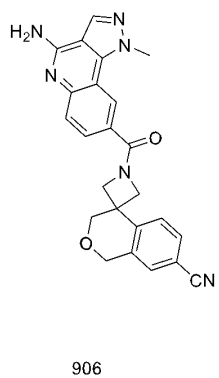
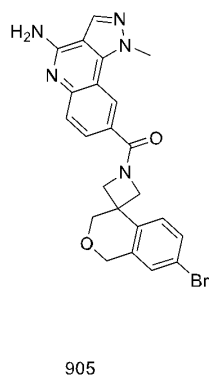
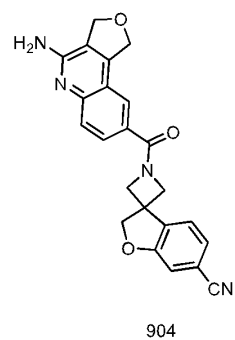
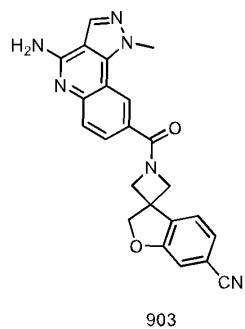
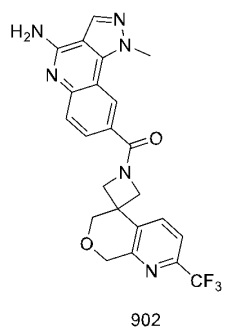
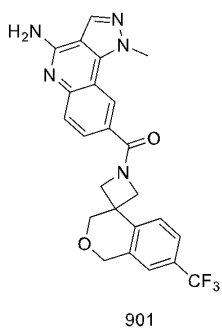
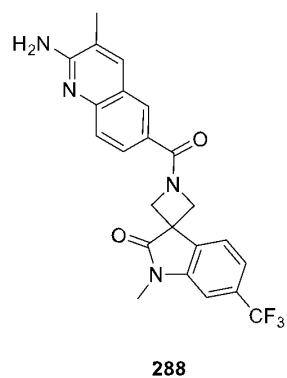
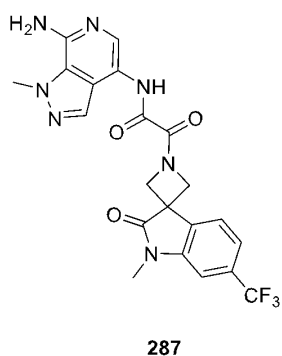
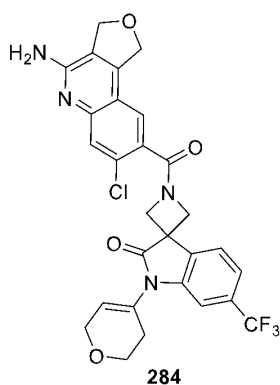
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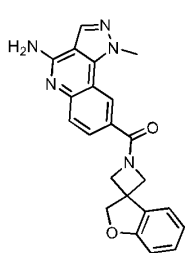


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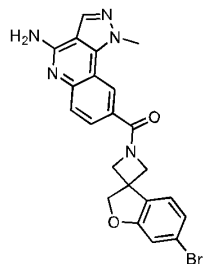


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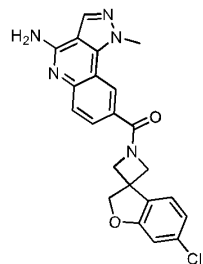




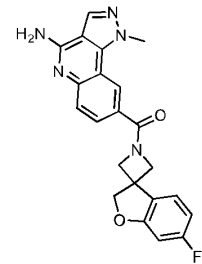
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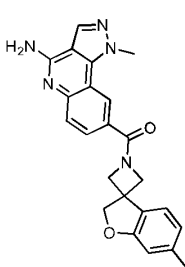
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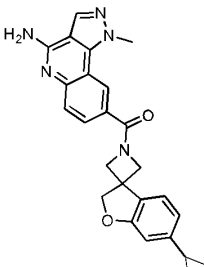
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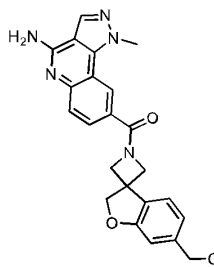
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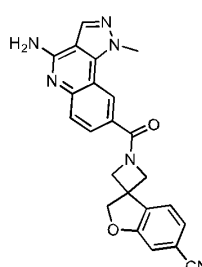
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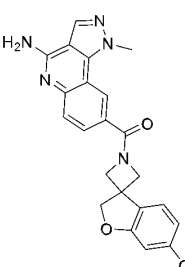
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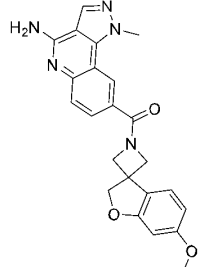
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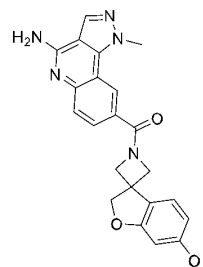
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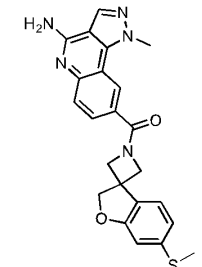
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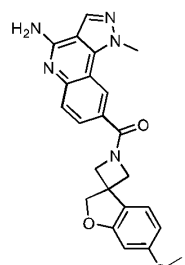
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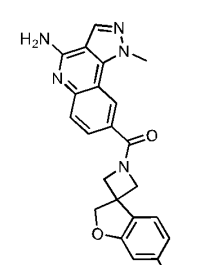
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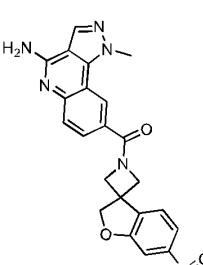
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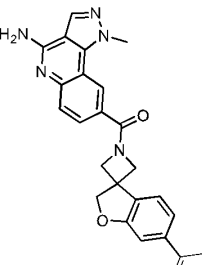
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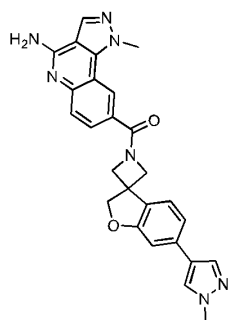
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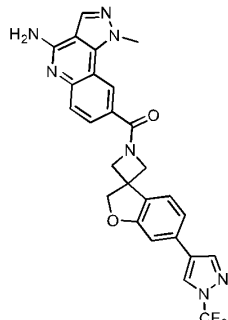
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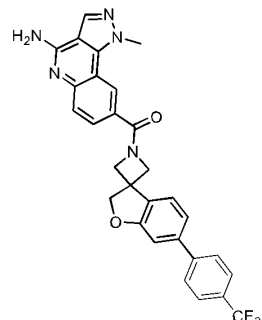
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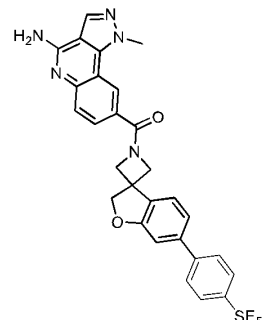
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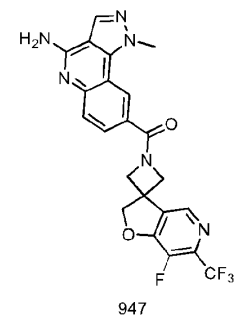
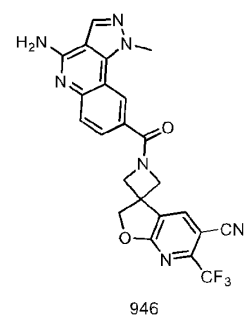
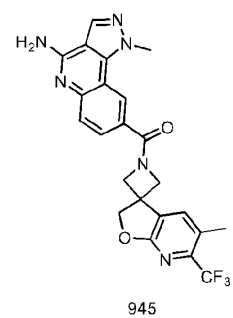
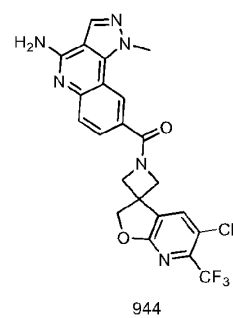
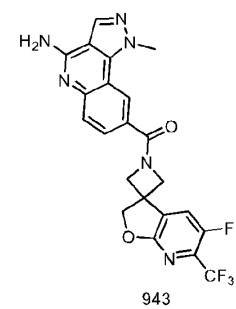
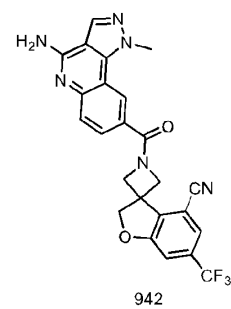
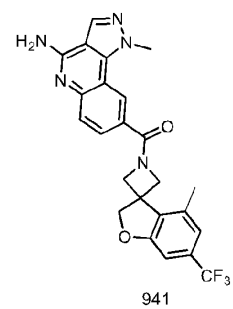
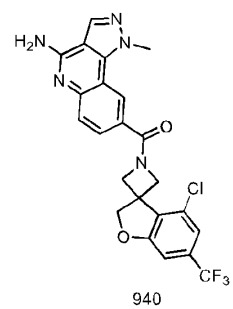
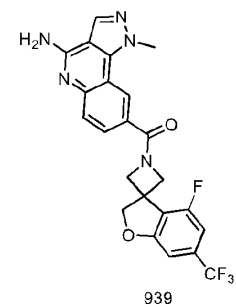
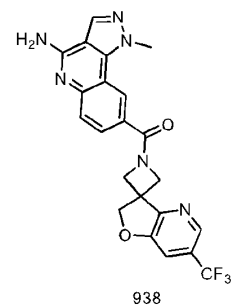
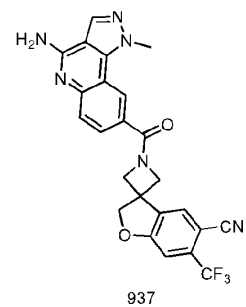
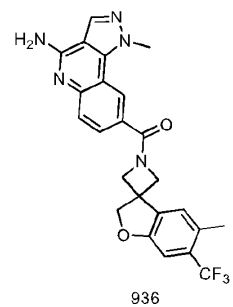
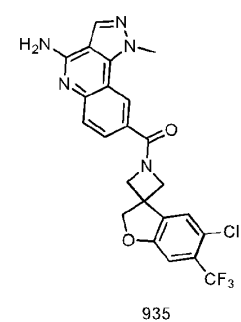
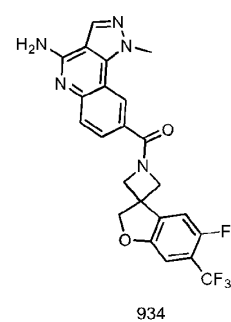
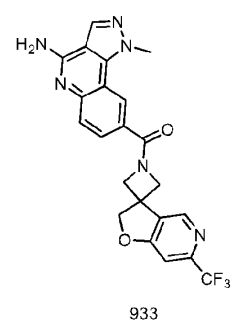
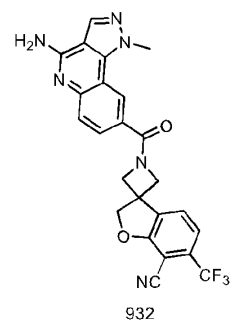
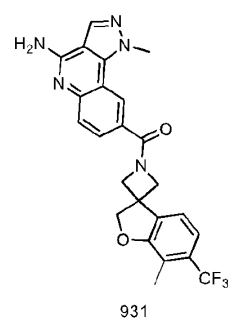
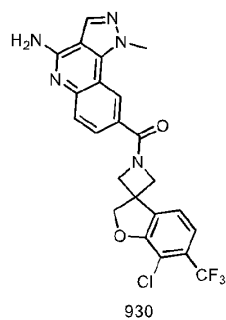
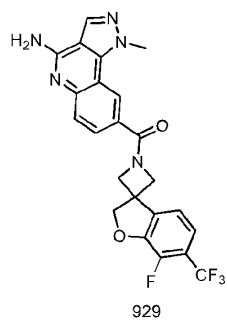
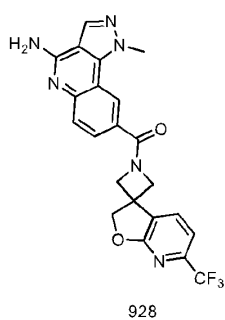
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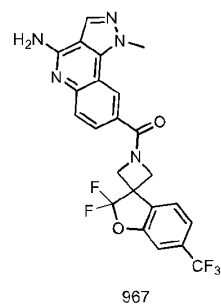
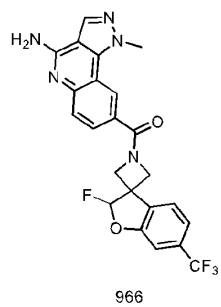
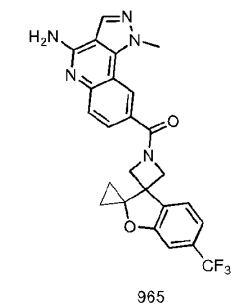
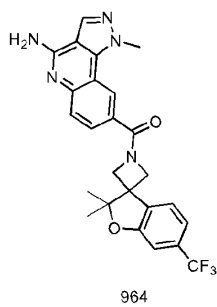
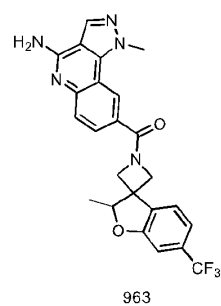
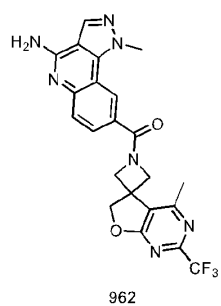
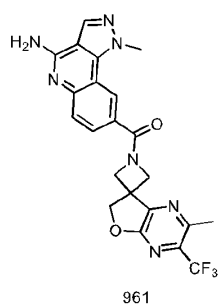
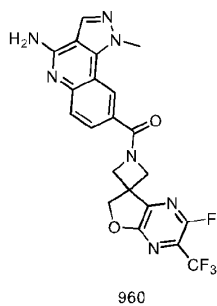
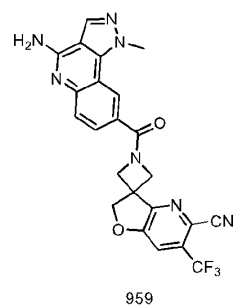
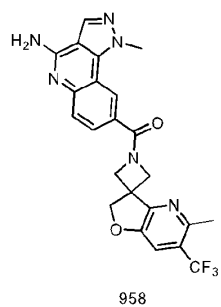
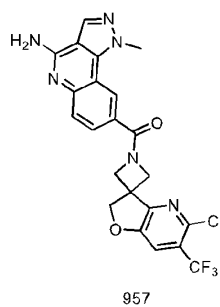
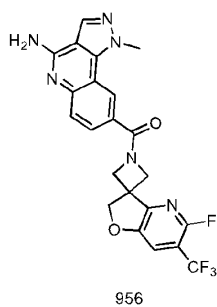
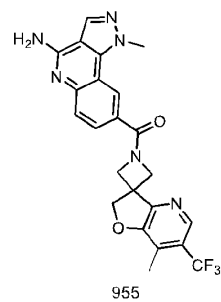
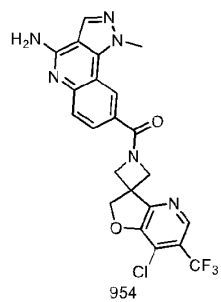
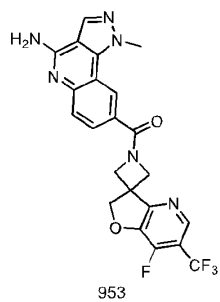
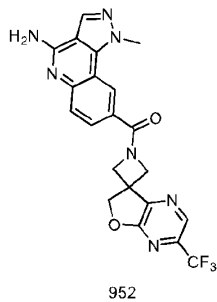
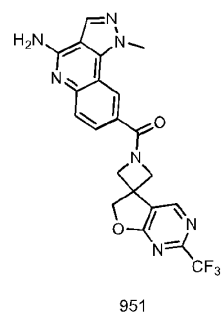
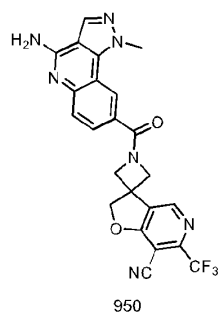
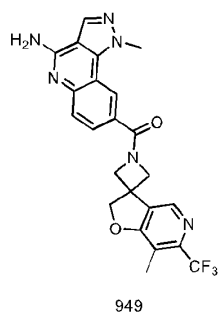
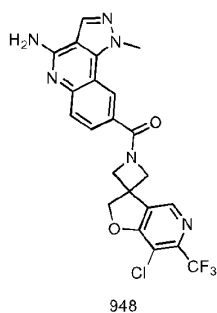


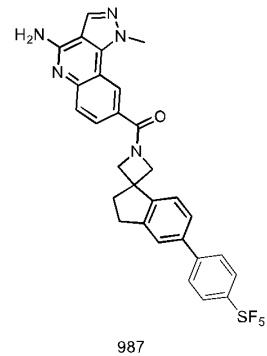
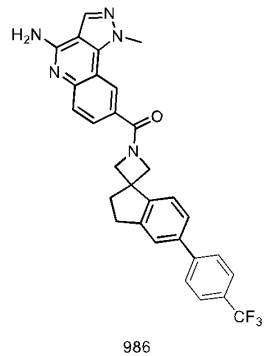
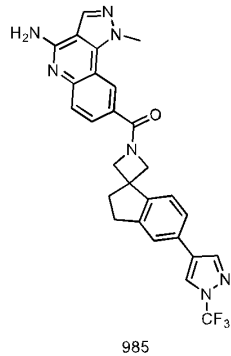
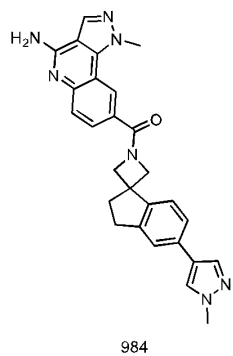
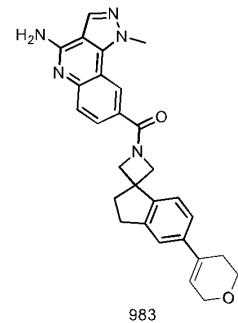
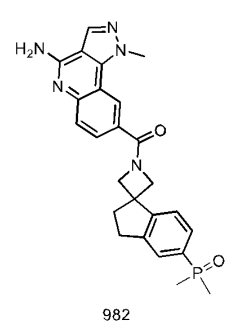
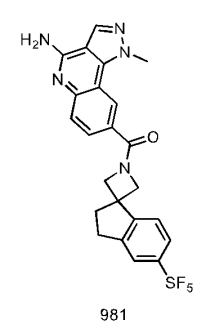
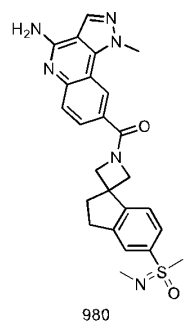
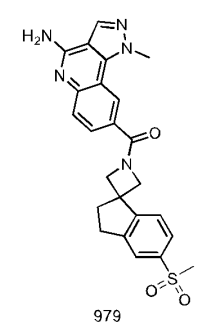
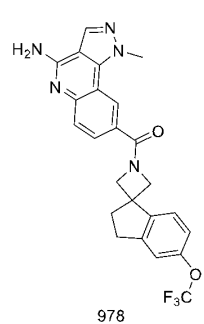
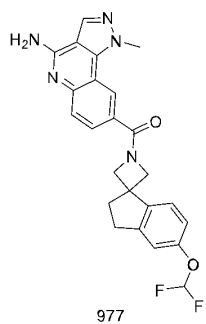
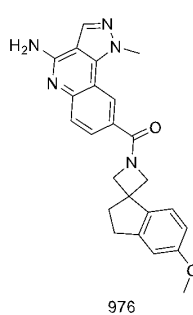
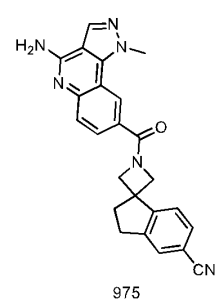
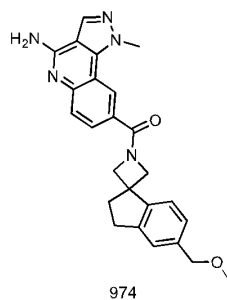
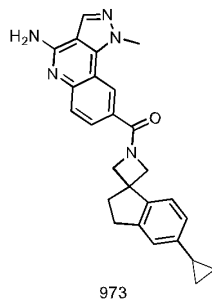
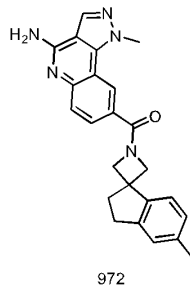
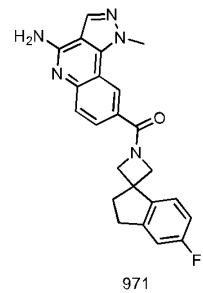
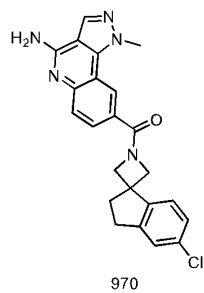
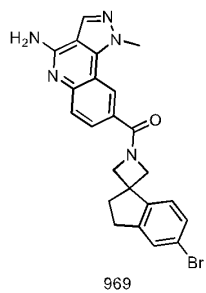
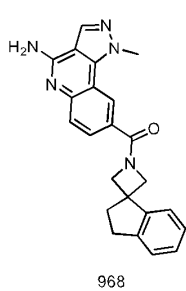
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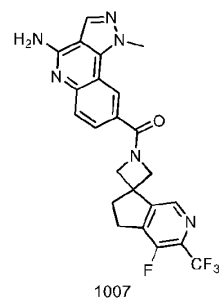
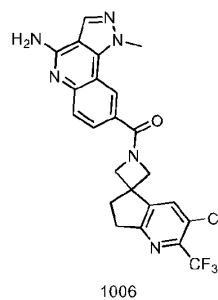
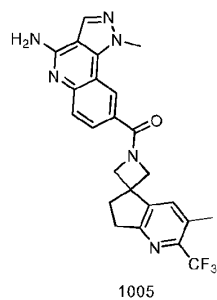
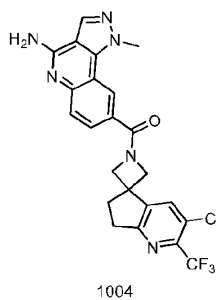
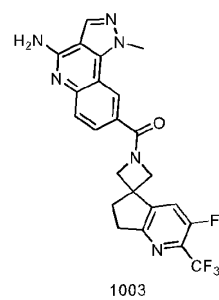
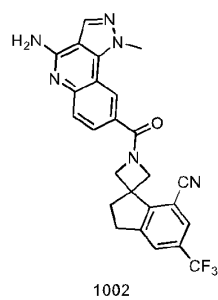
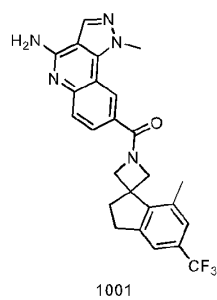
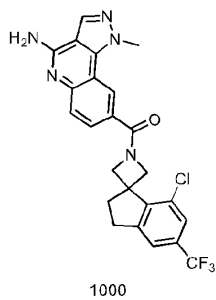
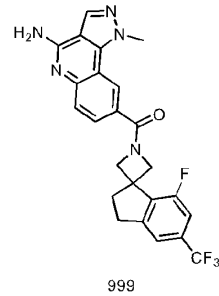
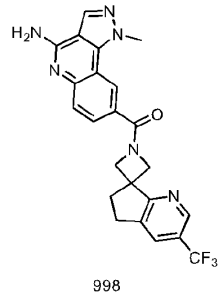
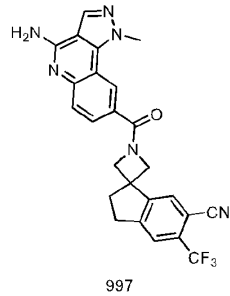
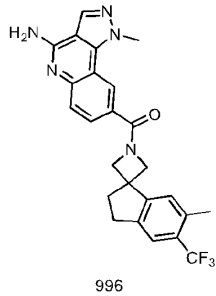
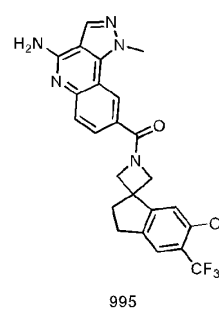
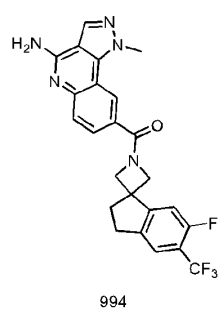
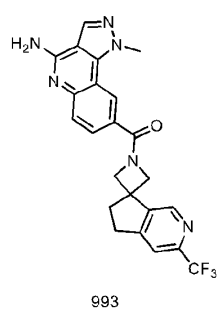
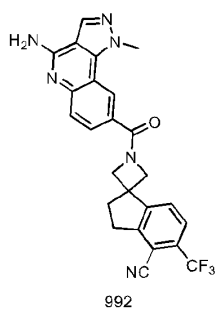
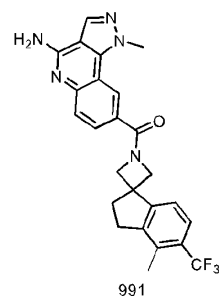
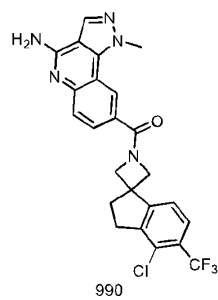
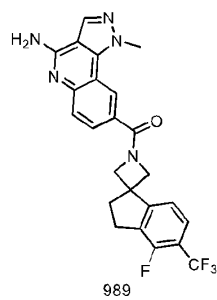
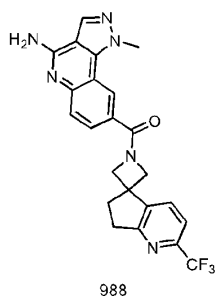


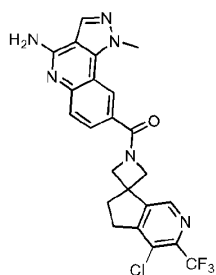
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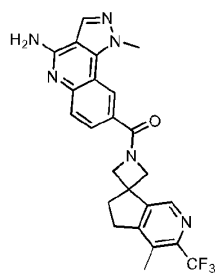




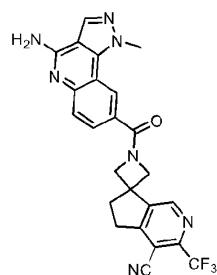




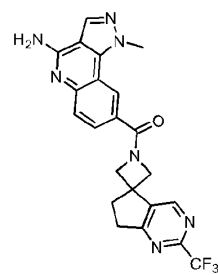
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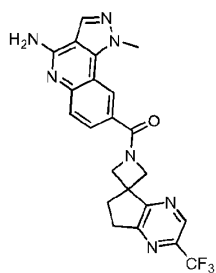
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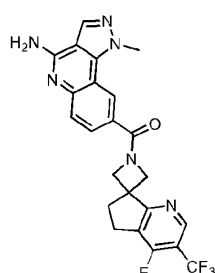
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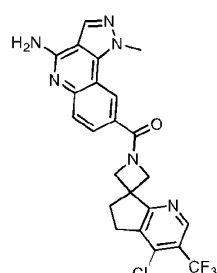
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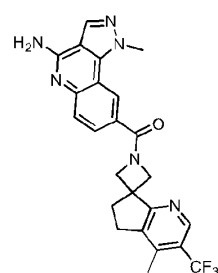
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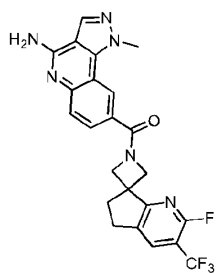
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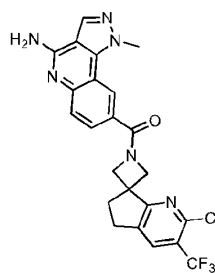
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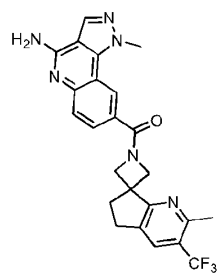
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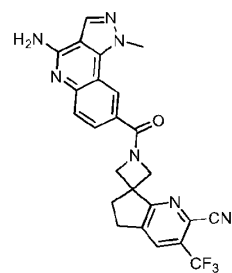
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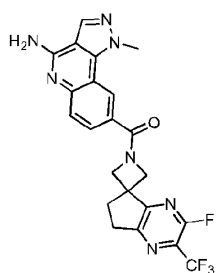
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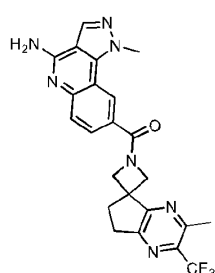
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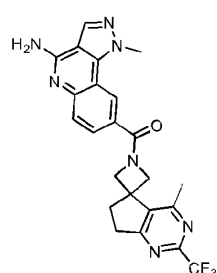
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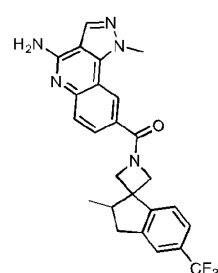
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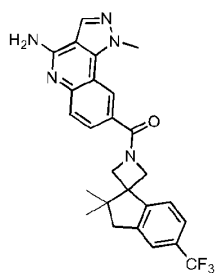
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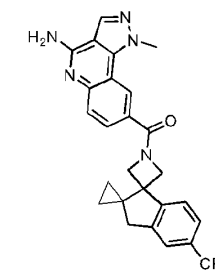
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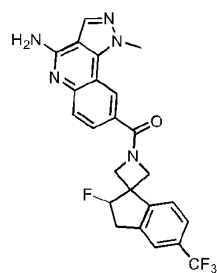
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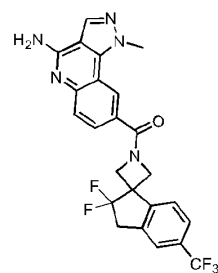
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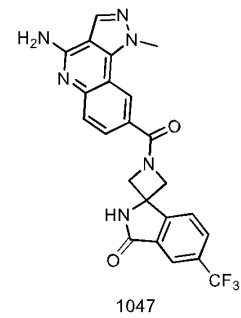
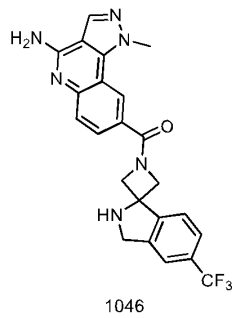
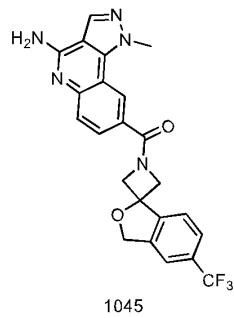
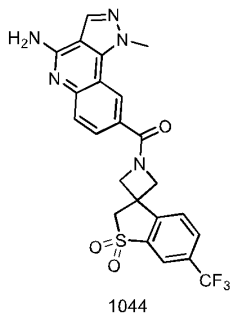
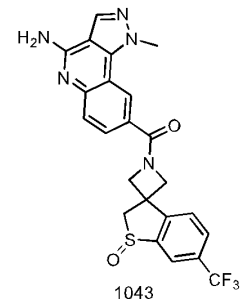
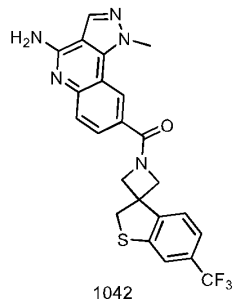
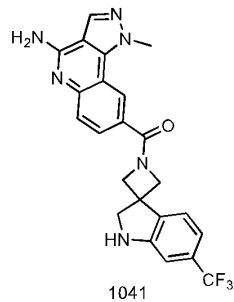
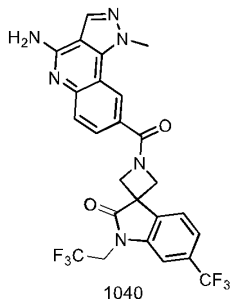
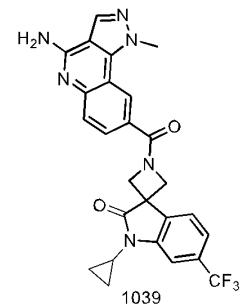
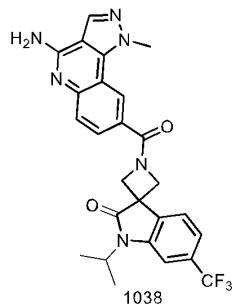
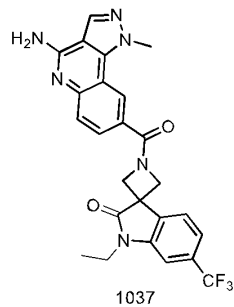
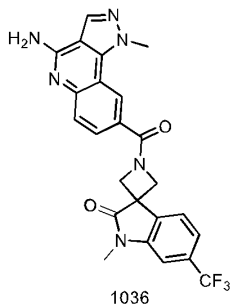
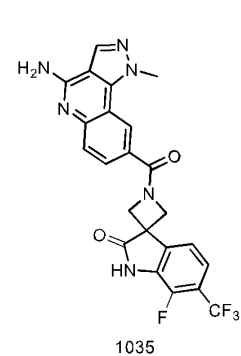
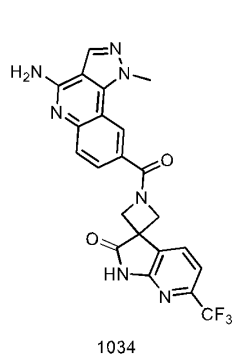
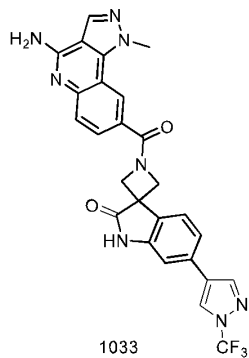
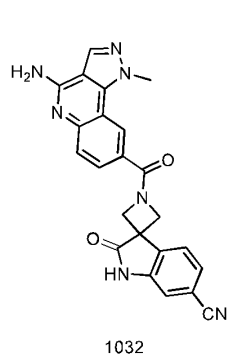
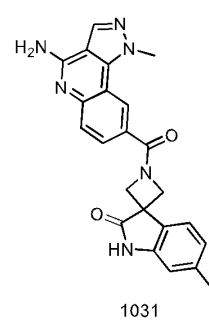
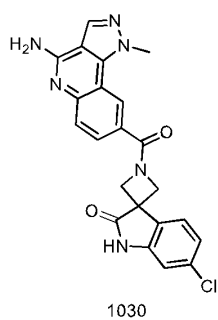
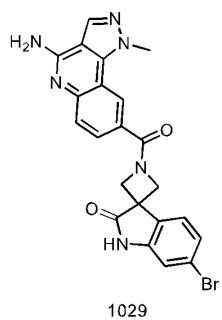
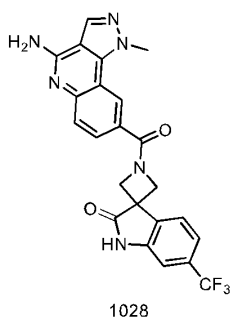
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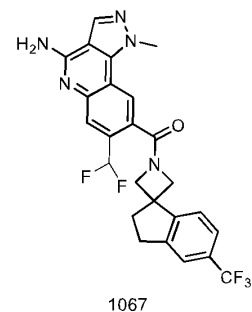
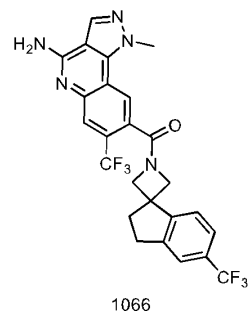
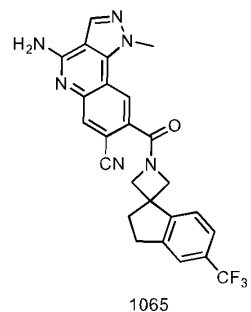
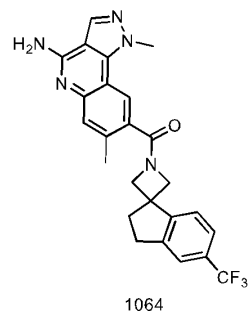
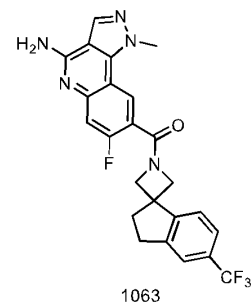
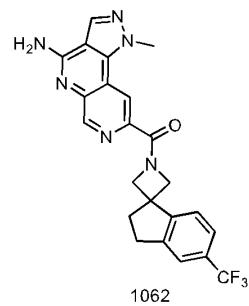
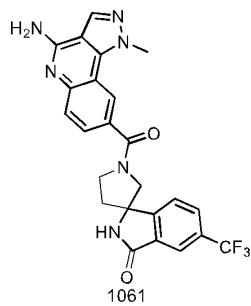
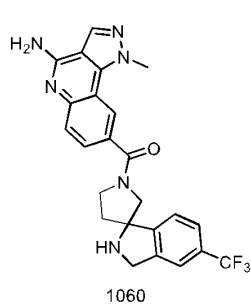
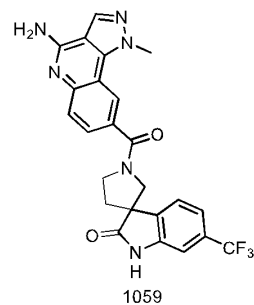
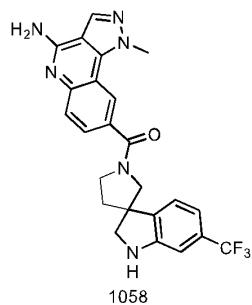
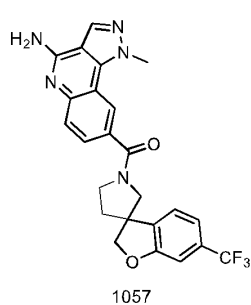
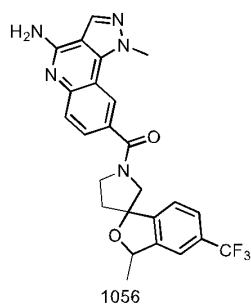
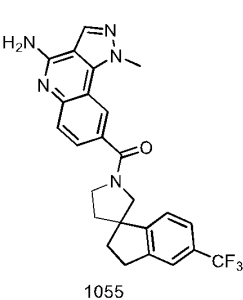
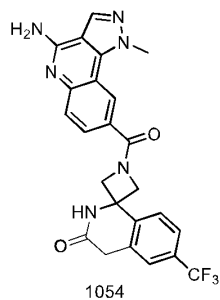
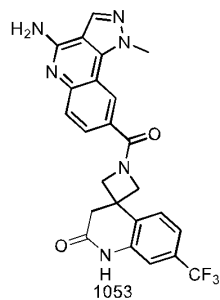
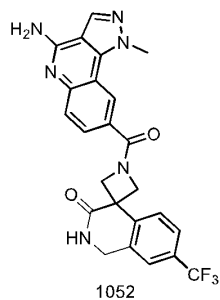
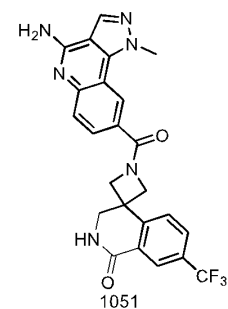
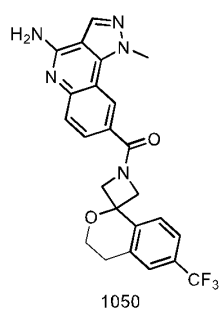
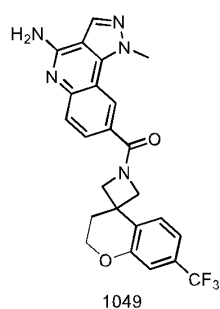
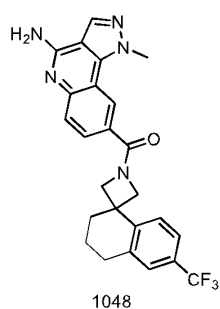


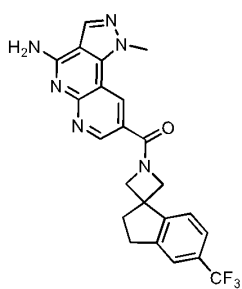
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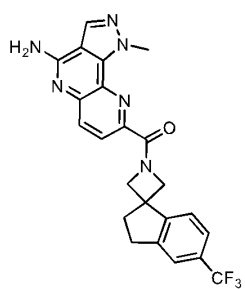
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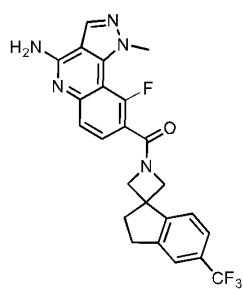




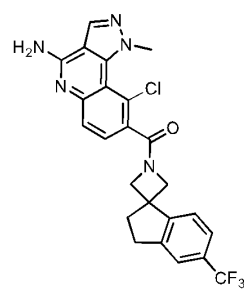
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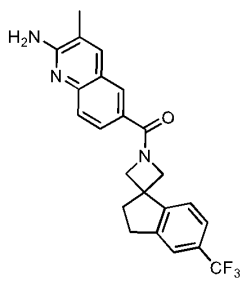
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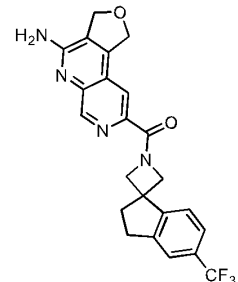
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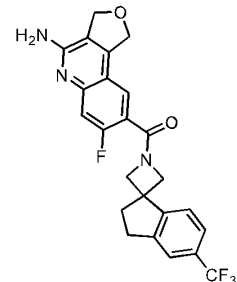
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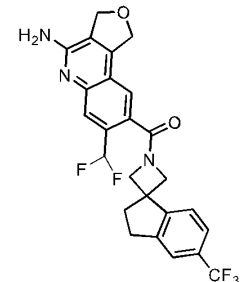
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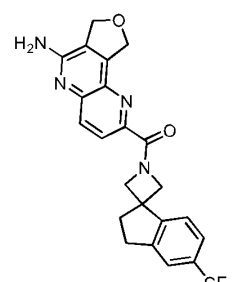
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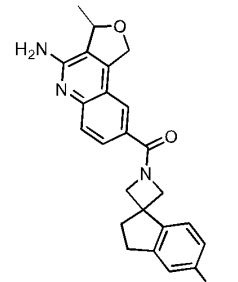
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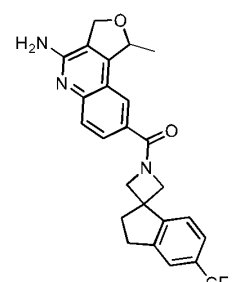
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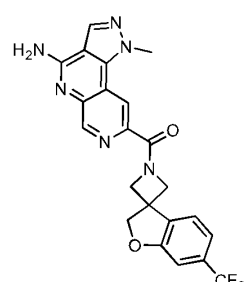
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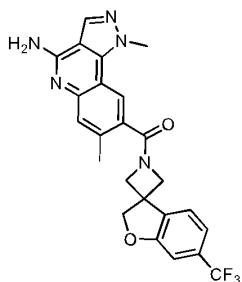
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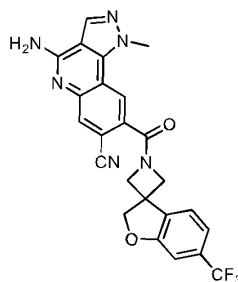
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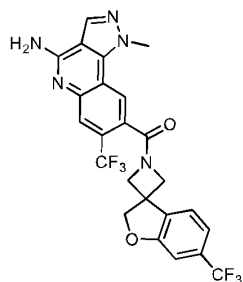
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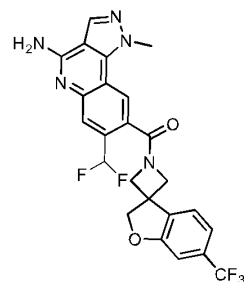
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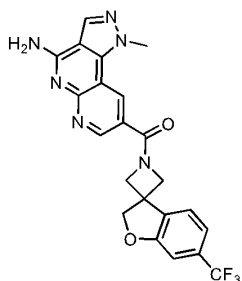
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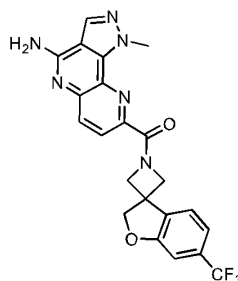
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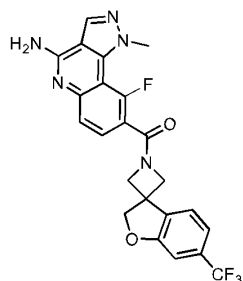
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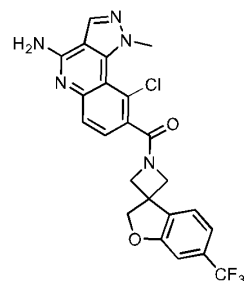
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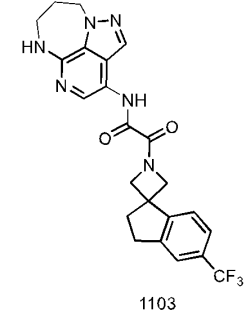
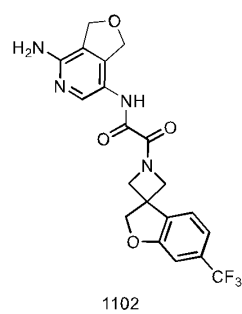
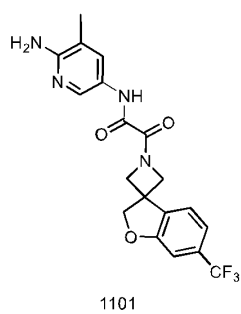
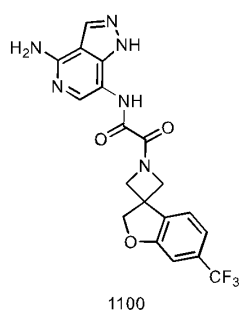
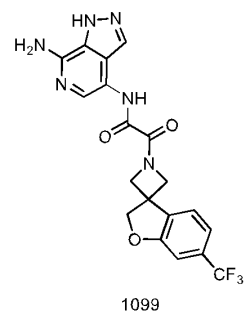
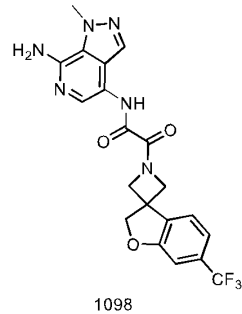
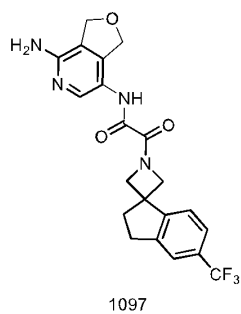
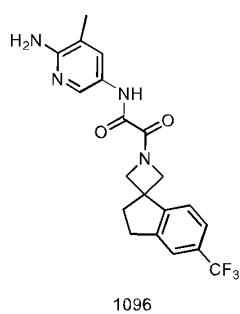
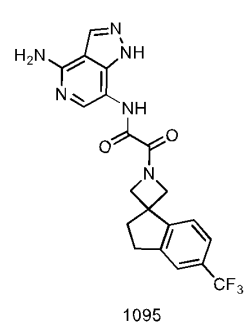
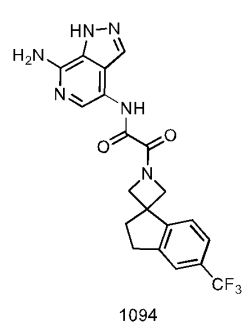
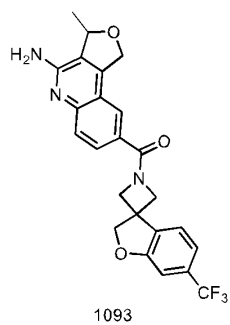
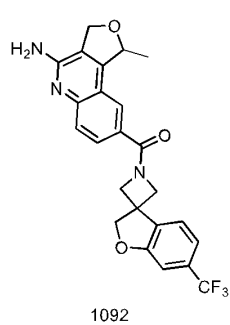
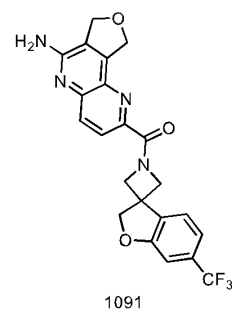
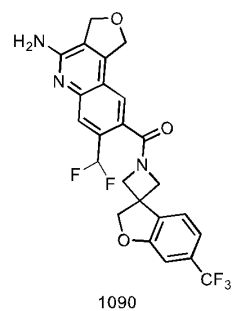
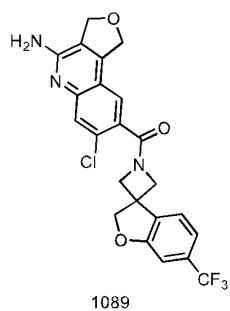
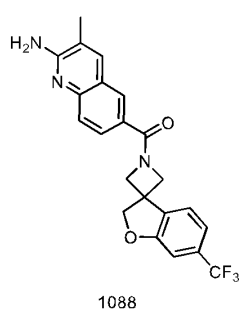
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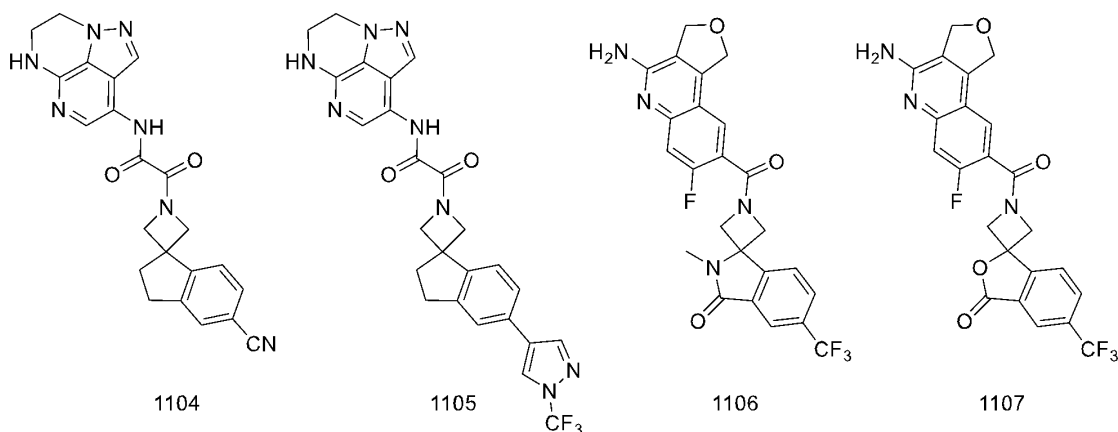


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; or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled.

Pharmaceutical compositions, uses and methods

The compounds or derivatives (such as a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled) of the present invention can be therapeutically administered as the neat chemical, but it may be more beneficial to administer the compounds in a form of a pharmaceutical composition or formulation. Thus, the present invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I), formula (IC-1), formula (IC-2) or , formula (IC-3), or a pharmaceutically acceptable salt, geometric isomer, enantiomer, distereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled, and one or more pharmaceutically acceptable carriers or excipients.

The pharmaceutical compositions can be administered in a variety of dosage forms including, but not being limited to, a solid dosage form, a liquid dosage form, an oral dosage form, a parenteral dosage form, an intranasal dosage form, suppository, lozenge, sugar-coated dosage form, oral administered, a controlled release dosage form, a pulsed release dosage form, an immediate release dosage form, an intravenous solution, suspension or combinations thereof. The compounds can be administered, for example, via oral or parenteral routes, including such as intravenous, intramuscular, intraperitoneal, subcutaneous, transdermal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual) administration.

In one embodiment of the present invention, the compound or derivatives of formula (I) is orally administered. For oral administration, the compounds may generally be provided in

unit dosage form suitable for ingestion by a subject, such as tablets, pills, sugar-coated tablets, lozenges, capsules, powders, granules, aqueous solutions, suspensions, liquids, gels, syrups, slurries and the like. The dosage form may be a tablet or a controlled release dosage form formulated as a tablet. Tablets for oral use may include the active ingredients mixed with one or more pharmaceutically acceptable excipients.

An "excipient" generally refers to a substance, often an inert substance, added to a pharmacological composition or otherwise used as a vehicle to further facilitate administration of a compound. Examples of excipients include, but are not limited to, inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents, preservatives, effervescent mixtures, and adsorbents. If necessary, the tablet may be coated with a material to delay absorption thereof in the gastrointestinal tract. The compositions can also be further formulated into chewable tablets.

Pharmaceutical compositions of this invention for oral use can be obtained by combining a compound of formula (I) with a solid excipient, grinding them and then processing the mixture, if necessary, after adding suitable additional (active) compounds to give tablets or capsules. Suitable solid excipients, in addition to those previously mentioned, include carbohydrates or protein fillers including, but not being limited to, sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; celluloses such as methyl cellulose, hydroxypropylmethyl-cellulose or sodium carboxymethylcellulose; and gums including gum arabic and gum tragacanth; as well as proteins such as gelatin and collagen.

Capsules for oral administration include, but are not limited to, hard gelatin capsules comprising an active ingredient(s) mixed with a solid diluent(s) and soft gelatin capsules comprising an active ingredient(s) mixed with water or an oil (such as peanut oil, mineral oil or olive oil). Suitable sugar coating(s) can be applied on tablet cores. Concentrated sugar solutions, optionally further comprising gum arabic, talc, polyvinylpyrrolidone, carbopolgel, poly(ethylene glycol) and/or titanium dioxide, lacquer solution and suitable organic solvents or solvent mixtures. Pigments or colorants can be introduced to tablets or sugar-coatings cores to distinguish or characterize different (combination) of dosages of an active compound(s).

The pharmaceutical composition can optionally further comprise a suitable solid or gel phase carrier. Examples of such carriers include, but are not limited to, calcium carbonate, calcium phosphate, various types of sugars, starch, cellulose derivatives, gelatin and polymers such as poly(ethylene glycol).

Compounds and pharmaceutical compositions in the present invention include an active ingredient that is administered in a therapeutically effective amount to achieve its intended purpose. The term "therapeutically effective amount" refers to that amount of a compound of formula (I), a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled, alone or in combination with ionizing radiation or an anticancer agent which, upon single or multiple dose administration to the subject, provides the desired effect in the subject under treatment. Toxicity and therapeutic efficacy of such compound can be determined by standard pharmacological procedures with cell cultures or experimental animals, e.g., for determining the IC₅₀ values. As used herein, "IC₅₀" refers to the concentration of an agent which can produce 50% of the maximal inhibitory response by that agent.

The actual amount of a compound or derivatives of formula (I) to be administered will be determined by a physician under relevant circumstances, including the condition to be treated, the size and type of neoplasia or tumor, the possible routes of administration, the specific compound of the invention to be administered, timing of administration of hedgehog pathway modulators relative to other therapies, the subject's type, species, age, weight, gender and medical condition, the subject's renal and liver function, and the severity of the subject's symptoms. Achieving optimal precision in producing drug concentrations within the therapeutic range requires a scheme based on the kinetics of the drug's availability to the target site. This involves the distribution, balance, and elimination of the drug. In some cases, dosage levels below the lowest end of the foregoing ranges may be more than the sufficient amount, while in other cases higher dosages may still be employed.

A "subject" to be treated by the method of the present invention means either a human or non-human animal, such as primate, mammal, and vertebrate.

"In vivo" means within a living subject, as within an animal or human. In this context, agents can be used therapeutically in vivo to retard or eliminate the proliferation of aberrantly replicating cells. The agents also can be used in vivo as a prophylactic to prevent aberrant cell proliferation or the manifestation of symptoms associated therewith.

"In vitro" means outside a living subject. Examples of in vitro cell populations include cell cultures and biological samples, such as fluid or tissue samples from humans or animals. Such samples can be obtained by methods well known in the art. Exemplary biological fluid samples include blood, cerebrospinal fluid, urine and saliva. Exemplary tissue samples include tumors and biopsies thereof. In this context, the present compounds can be employed in numerous applications, both therapeutic and experimental.

"Cancer" refers to a cell proliferative disease state that includes, but is not limited to: cardiac cancers such as sarcomas (e.g., angiosarcoma, fibrosarcoma, rhabdomyosarcoma, and liposarcoma), myxomas, rhabdomyomas, fibromas, lipomas, and teratomas; lung cancers, such as bronchial carcinomas (e.g., squamous cell carcinoma, undifferentiated small cell carcinoma, undifferentiated large cell carcinoma, and adenocarcinoma), alveolar carcinomas (e.g., bronchiolar carcinoma), bronchial adenomas, sarcomas, lymphomas, cartilaginous hamartomas, and mesothelioma; gastrointestinal cancers, such as esophageal cancer (e.g., squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, and lymphoma), gastric cancer (e.g., lymphoma and leiomyosarcoma), pancreatic cancer (e.g., ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid and vasoactive intestinal peptide tumor), small bowel cancer (e.g., adenocarcinoma, lymphoma, carcinoid, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, and fibroma), colorectal cancer (e.g., adenocarcinoma, ductal adenoma, villous adenoma, hamartomas, and leiomyomas); genitourinary tract cancers, such as kidney cancer (e.g., adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, and leukemia), bladder and urethra cancer (e.g., squamous cell carcinoma, transitional cell carcinoma, and adenocarcinoma), prostate cancer (e.g., adenocarcinoma and sarcoma), testicular cancer (e.g., sperm cell carcinoma, teratoma, embryonal tumor, teratoma, choriocarcinoma carcinoma, sarcoma, stromal cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, and lipoma); liver cancer, such as hepatocellular carcinoma (e.g., hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, liver cancer Cellular adenomas and hemangioma; bone cancers such as osteogenic sarcoma (e.g., osteosarcoma), fibrosarcoma, malignant fibrous histiocyoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (e.g., reticular cellular sarcoma), multiple myeloma, malignant giant cell tumor, chordoma, osteochondroma (e.g., osteochondral exostosis), benign enchondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, and Giant cell tumors; cancers of the nervous system, such as skull cancers (e.g., osteomas, hemangiomas, granulomas, xanthomas, and osteitis malformations), meningeal cancers (e.g., meningiomas, meningiosarcomas, and polygliosis), brain cancer (e.g., astrocytoma, medulloblastoma, glioma, ependymoma, blastoma (pineal tumor), glioblastoma multiforme, oligodendroglioma , schwannomas, retinoblastomas, and congenital tumors), spinal neurofibromas, meningiomas, gliomas, and sarcomas; gynecological cancers, such as uterine cancer (e.g., endometrial cancer), cervical cancer (e.g., cervical cancer and preneoplastic cervical dysplasia), ovarian cancer (e.g., serous cystadenocarcinoma, mucinous

cystadenocarcinoma, and carcinoma of unknown category], theca granulosa cell tumors, Steller-Rediger cell tumors (Sertoli-Leydig cell tumor, dysgerminoma, and malignant teratoma), vulvar cancer (e.g., squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, and melanoma), vaginal cancer (e.g., clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma [e.g., embryonal rhabdomyosarcoma], and fallopian tube cancer); blood cancers, such as blood cancers (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferation diseases, multiple myeloma and myelodysplasia), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; skin cancers such as malignant melanoma, basal cell carcinoma, squamous cell carcinoma, cell carcinoma, Kaposi's sarcoma, dysplastic nevus, lipoma, hemangioma, dermatofibroma, keloid, psoriasis; adrenal adenocarcinoma, such as neuroblastoma; or breast cancer.

The present invention also relates to the use of compounds of formula (I) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled for the manufacture of medicaments for modulating the hedgehog pathway.

Furthermore, the present invention relates to a method for treating cancer to a subject in need thereof, comprising administering a compound of formula (I) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled.

The present invention also relates to compounds of formula (I) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled for use in treating cancer.

The compounds or derivatives of formula (I) can be administered as the sole active agent, or in combination with other known cancer therapy.

The term "in combination with" means that the compound or derivative of formula (I) may be administered before, after, concurrently with any one or more other antineoplastic therapies, or before, after, or concurrently with any combination of other antineoplastic therapies. Thus, the compound or derivative of formula (I) and the second anticancer agent may be administered as a single composition or as two separate compositions simultaneously or as two separate compositions sequentially. Likewise, a compound or derivative of formula (I) and chemotherapy or ionizing radiation therapy may be administered simultaneously, separately, or sequentially. One skilled in the art will understand that the amount of a compound of formula (I) administered with an anti-cancer therapy is preferably an amount sufficient to enhance the

effects of the anti-cancer therapy or an amount sufficient to induce apoptosis or cell death in conjunction with anti-cancer therapy to maintain an anti-angiogenic effect.

The term "second anticancer agents" as used herein, unless otherwise indicated, refers to agents capable of inhibiting or preventing the growth of neoplasms or tumors, or inhibiting the maturation and proliferation of malignant (cancer) cells. Second anticancer agents suitable for use in combination with the compounds of formula (I) include, but are not limited to targeted cancer drugs, such as trastuzumab, ramucirumab, vismodegib, sonidegib, bevacizumab, everolimus, tamoxifen, toremifene, fulvestrant, anastrozole, exemestane, lapatinib, letrozole, pertuzumab, ado-trastuzumab emtansine, palbociclib, cetuximab, panitumumab, ziv-aflibercept, regorafenib, Imatinib mesylate, lanreotide acetate, sunitinib, regorafenib, denosumab, alitretinoin, sorafenib, pazopanib, temsirolimus, everolimus, tretinoin, dasatinib, nilotinib, bosutinib, rituximab, alemtuzumab, ofatumumab, obinutuxumab, ibrutinib, idelalisib, blinatumomab, soragenib, crizotinib, erlotinib, gefitinib, afatinib dimaleate, ceritinib, ramucirumab, nivolumab, pembrolizumab, osimertinib, and necitumumab; an alkylating agent, such as busulfan, chlorambucil, cyclophosphamide, iphosphamide, melphalan, nitrogen mustard, streptozocin, thiotepa, uracil nitrogen mustard, triethylenemelamine, temozolomide, and 2-chloroethyl-3-sarcosinamide-1-nitrosourea (SarCNU); an antibiotic or plant alkaloid, such as actinomycin-D, bleomycin, cryptophycins, daunorubicin, doxorubicin, idarubicin, irinotecan, L-asparaginase, mitomycin-C, mitramycin, navelbine, paclitaxel, docetaxel, topotecan, vinblastine, vincristine, teniposide (VM-26), and etoposide (VP-16); a hormone or steroid, such as 5 α -reductase inhibitor, aminoglutethimide, anastrozole, bicalutamide, chlorotrianisene, diethylstilbestrol (DES), dromostanolone, estramustine, ethinyl estradiol, flutamide, fluoxymesterone, goserelin, hydroxyprogesterone, letrozole, leuprolide, medroxyprogesterone acetate, megestrol acetate, methyl prednisolone, methyltestosterone, mitotane, nilutamide, prednisolone, arzoxifene (SERM-3), tamoxifen, testolactone, testosterone, triamcinolone, and zoladex; a synthetic, such as all-trans retinoic acid, carmustine (BCNU), carboplatin (CBDCA), lomustine (CCNU), cis-diaminedichloroplatinum (cisplatin), dacarbazine, gliadel, hexamethylmelamine, hydroxyurea, levamisole, mitoxantrone, o,p'-dichlorodiphenyldichloroethane (o,p'-DDD) (also known as lysodren or mitotane), oxaliplatin, porfimer sodium, procarbazine, and imatinib mesylate (Gleevec®); an antimetabolite, such as chlorodeoxyadenosine, cytosine arabinoside, 2'-deoxycoformycin, fludarabine phosphate, 5-fluorouracil (5-FU), 5-fluoro-2'-deoxyuridine (5-FUDR), gemcitabine, camptothecin, 6-mercaptopurine, methotrexate, and thioguanine; and a biologic, such as alpha interferon, BCG (Bacillus Calmette-Guerin), granulocyte colony stimulating factor (G-CSF), granulocyte-

macrophage colony-stimulating factor (GM-CSF), interleukin-2, and herceptin.

Unless otherwise indicated, the term "treating" as used herein means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. Unless otherwise indicated, the term "treatment" as used herein refers to the behavior or action of "treating" as defined above.

Synthesis of Compound

The invention also relates to a process for the preparation of compounds of formula (I) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled. The compounds of the present invention can be prepared by those skilled in the art using conventional organic synthesis methods and commercially available materials.

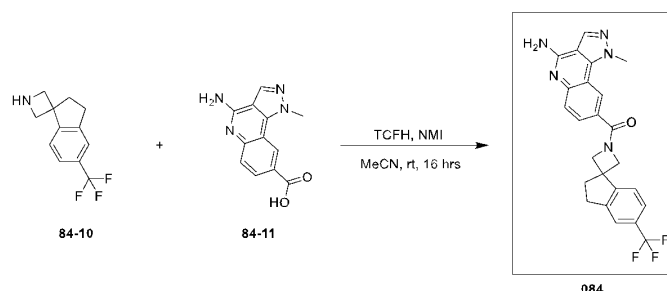
In one embodiment, the invention relates to a method for preparing a compound of formula (I), formula (IC-1), formula (IC-2), formula (IC-3) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing being isotope-labeled. Examples of the methods of preparation comprise, but are not limited to, those procedures illustrated in the examples described herein.

It is to be understood that the examples used herein are for the purpose of explanation but not intended to be limiting. Those skilled person in this field may vary the process or steps of the following examples to obtain the desired products.

EXAMPLES

EXAMPLE 1:

Synthesis of compound 084

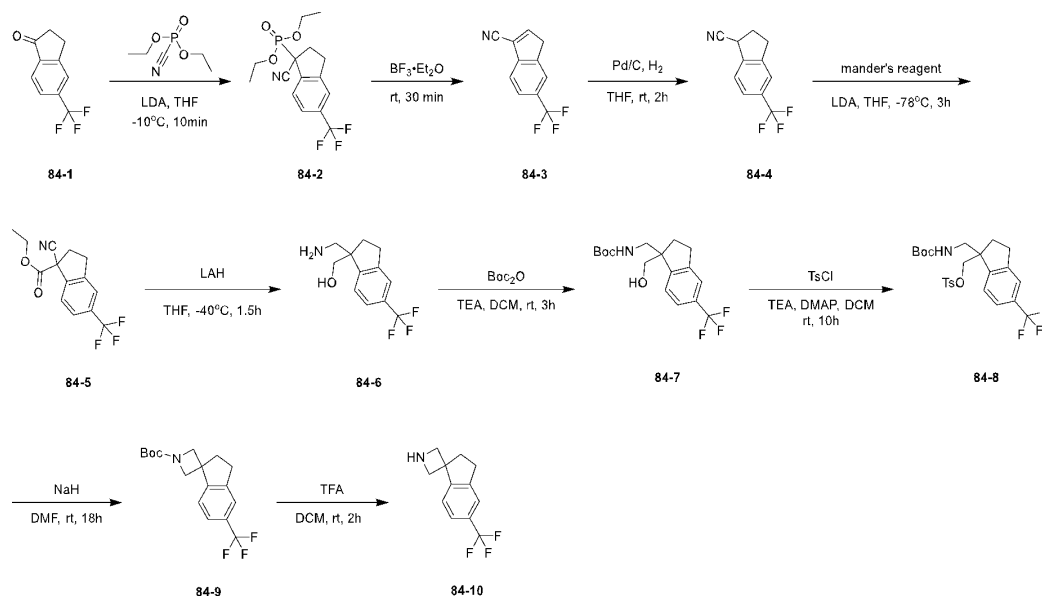


To a solution of **Intermediate 84-10** (134 mg, 0.55 mmol) in acetonitrile (1.5 mL) were added 1-methylimidazole (109 mg, 1.32 mmol) and chloro-N,N,N',N'-

tetramethylformamidine hexafluorophosphate (93 mg, 0.33 mmol); the reaction solution was stirred at room temperature for 2 hours, then **Intermediate 84-11** (50 mg, 0.22 mmol) was added, and stirred at room temperature for 16 hours. The reaction solution was diluted with acetonitrile (5 mL) and filtered. The filter cake was washed with acetonitrile (1 mL) and the filtrate was concentrated. The crude product was purified by prep HPLC (Waters-SunFire-C18-10 μ m-19*250mm, Mobile phase: 0.1% NH₃HCO₃/H₂O B:CH₃CN, 9 min) to obtain **Compound 084** as a white solid (10.19 mg, 0.02 mmol, 10.26 % yield).

MS m/z (ESI): 452.2 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 8.72 (d, J = 1.6 Hz, 1H), 8.10 (s, 1H), 7.89–7.73 (m, 2H), 7.65–7.53 (m, 2H), 7.50 (s, 1H), 5.94 (s, 2H), 4.52 (s, 3H), 4.45 (s, 4H), 3.01 (s, 2H), 2.51 (t, J = 7.2 Hz, 2H)

Synthesis of Intermediate 084-10



Step 1

To a solution of **Compound 84-1** (10.0 g, 49.96 mmol) in THF (100 mL) was added Lithium diisopropylamide (25 mL, 50.0 mmol, 2.0 M) at -10 °C. The reaction solution was stirred for 20 minutes at -10 °C, and then diethoxyphosphorylformonitrile (8.96 g, 54.96 mmol) was added. After stirring for 10 minutes at -10 °C, the reaction was quenched by H₂O (300 mL) and extracted with ethyl acetate (100 mL). Combined organic layers were washed with brine (300 mL) and dried over anhydrous sodium sulfate. After filtration and concentration, the obtained residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to obtain **Intermediate 84-2** as a yellow solid.

Step 2

A solution of **Intermediate 84-2** (16.7 g, 48.09 mmol) in boron trifluoride-diethyl etherate complex (30 mL) was stirred for 30 minutes at room temperature. The reaction solution was quenched by saturated aqueous NH_4Cl (100 mL) and extracted with ethyl acetate (50 mL). Combined organic layers were washed with brine (100 mL) and dried over anhydrous sodium sulfate. After filtration and concentration, the obtained residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to afford **Intermediate 84-3** as a yellow solid (8.32 g, 39.78 mmol, 82.71% yield).

Step 3

A mixture of **Intermediate 84-3** (8.3 g, 39.68 mmol) and 10% Pd/C (800 mg) in THF (50 mL) was stirred for 2 hours at room temperature under nitrogen atmosphere. The reaction mixture was filtrated, and the cake was washed with THF (10 mL). Filtrate was concentrated to afford **Intermediate 84-4** as a red solid (5.2 g, 24.62 mmol, 62.05% yield). The crude product was directly used in the next step.

Step 4

To a solution of **Intermediate 84-4** (1.5 g, 7.10 mmol) in THF (15 mL) was added lithium diisopropylamide (7.81 mL, 15.62 mmol, 2.0 M) dropwise at $-78\text{ }^\circ\text{C}$ under nitrogen atmosphere. The reaction solution was stirred for 30 minutes at $-78\text{ }^\circ\text{C}$, and then methyl cyanofomate (1.21 g, 14.21 mmol) was added. After stirring for 3 hours at $-78\text{ }^\circ\text{C}$, the reaction solution was quenched by saturated aqueous NH_4Cl (30 mL) and extracted with ethyl acetate (30 mL). Combined organic layers were washed with brine (30 mL) and dried over anhydrous sodium sulfate. After filtration and concentration, the obtained residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to obtain **Intermediate 84-5** as a red oil (800 mg, 2.82 mmol, 39.77% yield).

Step 5

To a solution of **Intermediate 84-5** (800 mg, 2.82 mmol) in THF (10 mL) was added LiAlH_4 (214 mg, 5.65 mmol) at $-40\text{ }^\circ\text{C}$. The reaction solution was stirred for 1.5 hours at $-40\text{ }^\circ\text{C}$ and then quenched by sodium sulfate and filtrated. The cake was washed with ethyl acetate (10 mL). Filtrate was concentrated to obtain **Intermediate 84-6** as a colorless oil (190 mg, 0.77 mmol, 27.43% yield). The crude product was directly used for the next step.

Step 6

A solution of **Intermediate 84-6** (190 mg, 0.77 mmol), Boc_2O (338 mg, 1.55 mmol) and TEA (314 mg, 3.10 mmol) in CH_2Cl_2 (1 mL) was stirred for 3 hours at room temperature. The reaction solution was concentrated and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to obtain **Intermediate 84-7** as a white solid (180 mg,

0.52 mmol, 67.28% yield).

Step 7

To a solution of **Intermediate 84-7** (160 mg, 0.46 mmol) in CH₂Cl₂ (2.0 mL) were added TsCl (177 mg, 0.93 mmol), TEA (70 mg, 0.69 mmol) and DMAP (5.7 mg, 0.05 mmol) at room temperature. The reaction solution was stirred for 10 hours at room temperature and then quenched by H₂O (10 mL) and extracted with ethyl acetate (5 mL). Combined organic layers were washed with brine (10 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated to obtain **Intermediate 84-8** as a yellow oil (200 mg, 0.40 mmol, 86.42% yield). The crude product was directly used for the next step.

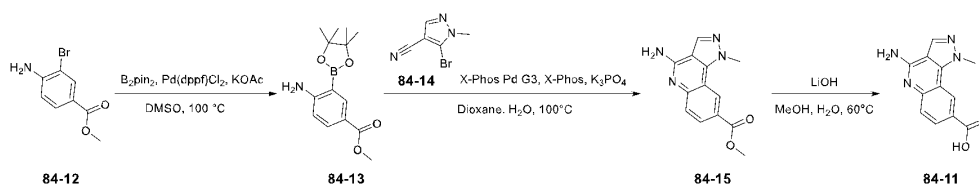
Step 8

A solution of **Intermediate 84-8** (500 mg, 1.00 mmol), and NaH (90 mg, 1.50 mmol) in DMF (5 mL) was stirred for 18 hours at room temperature. The reaction solution was quenched with H₂O (1 mL) at 0 °C and concentrated. The crude product was purified by layer chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to obtain **Intermediate 84-9** as a white solid (300 mg, 0.92 mmol, 91.56% yield).

Step 9

A mixture of **Intermediate 84-9** (40 mg, 0.12 mmol) and trifluoroacetic acid (0.1 mL, 1.34 mmol) in dichloromethane (1 mL) was stirred at room temperature for 2 hours. The reaction solution was concentrated to obtain **Intermediate 84-10** (8 mg, 0.12 mmol, 100% yield) as a brown oil, and the crude product was used directly in the next step.

Synthesis of Intermediate 84-11



Step 1

Under nitrogen atmosphere protection, **Intermediate 84-12** (5 g, 21.73 mmol), bis(pinacolato)diboron (16.56 g, 65.2 mmol), potassium acetate (6.40 g, 65.2 mmol), Pd(dppf)Cl₂ · CH₂Cl₂ (3.18 g, 4.35 mmol) in dimethyl sulfoxide (150 mL) were heated to 100 °C and stirred for 16 hours. After the reaction was completed, the reaction solution was cooled to room temperature and filtered. The filtrate was added with water (500 mL) and extracted with ethyl acetate (300 mL). The organic layers were combined, washed with brine (100 mL),

dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to obtain **Intermediate 84-13** (5.9 g, 21.29 mmol, 97.96 % yield) as a yellow solid.

Step 2

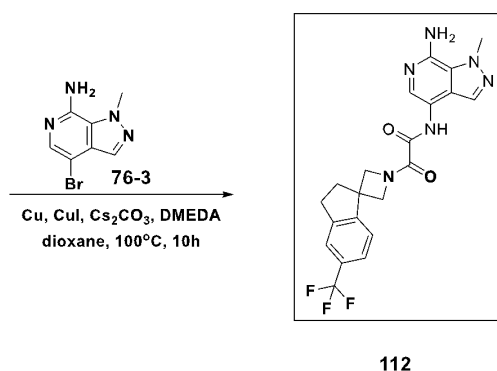
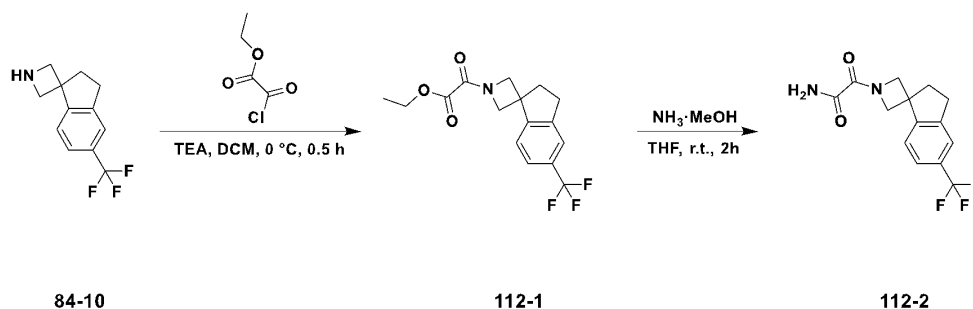
Under nitrogen atmosphere protection, **Intermediate 84-13** (700 mg, 2.53 mmol), **Intermediate 84-14** (563.81 mg, 3.03 mmol), X-Phos Pd G3 (213.8 mg, 0.25 mmol), X-Phos (240.83 mg, 0.51 mmol) and potassium phosphate (1.072 g, 5.05 mmol) in dioxane (5 mL) were heated to 100 °C and stirred for 16 hours. After the reaction was complete, the reaction solution was cooled to room temperature and filtered. The filtrate was added with water (20 mL) and extracted with ethyl acetate (30 mL). Combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to obtain **Intermediate 84-15** as a white solid (630 mg, 2.46 mmol, 97.33% yield).

Step 3

Intermediate 84-15 (90 mg, 0.35 mmol) and lithium hydroxide (133 mg, 3.51 mmol) were dissolved in a mixed solution of methanol (3 mL) and water (0.6 mL), heated to 60 °C and stirred for 16 hours. When the reaction was completed, adjusting the reaction solution to pH = 3 with 1.0 N hydrochloric acid aqueous solution to render solid precipitates. After filtration, the filter cake was washed with water (3 mL). The solid was dried under reduced pressure to obtain **Intermediate 84-11** as a white solid. (54 mg, 0.22 mmol, 63.47% yield).

EXAMPLE 2

Synthesis of Compound 112



Step 1

To a solution of **Intermediate 84-10** (250 mg, 1.10 mmol) and TEA (0.46 mL, 3.30 mmol) in dichloromethane (3 mL) was added mono-ethyl oxalyl chloride (180 mg, 1.32 mmol) in an ice bath. The reaction solution was stirred at room temperature for 0.5 hours, quenched with water (10 mL), and then extracted with ethyl acetate (3 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The crude **Intermediate 112-1** (250 mg, 0.76 mmol, 69.43% yield) was obtained as a yellow oil. The crude product was used directly in the next step.

Step 2

A solution of **Intermediate 112-1** (200 mg, 0.61 mmol) in THF (1 mL) and ammonia-methanol (1 mL, 7M) was stirred at room temperature for 2 h. The reaction solution was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (dichloromethane/methanol = 10/1) to obtain **Intermediate 112-2** as a yellow solid (160 mg, 0.54 mmol, 87.79% yield).

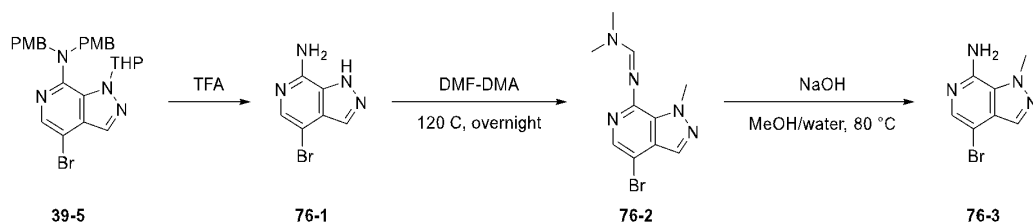
Step 3

A mixture of **Intermediate 112-2** (131 mg, 0.44 mmol), **Intermediate 76-3** (100 mg,

0.44 mmol), copper powder (5.6 mg, 0.09 mmol), cuprous iodide (126 mg, 0.66 mmol), cesium carbonate (430 mg, 1.32 mmol) and N,N'-dimethylethylenediamine (116 mg, 1.32 mmol) in 1,4-dioxane (2 mL) was stirred under nitrogen atmosphere protection at 100 °C for 10 hours. The reaction solution was cooled to room temperature and filtered. The filtrate was diluted with water (5 mL) and extracted with ethyl acetate (2 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The crude product was purified by prep-HPLC (Column: Waters-Xbridge-C18-10 μ m-19*250mm, Mobile phase: A: 10mM NH₄HCO₃/ H₂O B: CAN, 40%A-50%B; Ret 9.0 min) to obtain **Compound 112** as a white solid. (19.28 mg, 0.04 mmol, 9.85% yield)

MS m/z (ESI): 445.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.46 (s, 1H), 7.88 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.60 (s, 1H), 6.21 (s, 2H), 4.74–4.64 (m, 2H), 4.26 (s, 3H), 4.25–4.15 (m, 2H), 2.96 (t, *J* = 7.2 Hz, 2H), 2.46 (t, *J* = 7.2 Hz, 2H).

Synthesis of Intermediate 76-3



Step 1

Compound 39-5 (4.0 g, 7.44 mmol) was added to TFA (30 mL) solution and stirred at 90 °C overnight. After the reaction was completed, the reaction solution was cooled to room temperature and then concentrated. The crude product was purified by prep-HPLC (Waters-SunFire-C18-10 μ m-19*250mm, Mobile phase: 0.1% FA/H₂O B:CH₃CN) to obtain **Intermediate 76-1** (1.4 g, 6.57 mmol, 88.3%yield) as a white solid.

Step 2

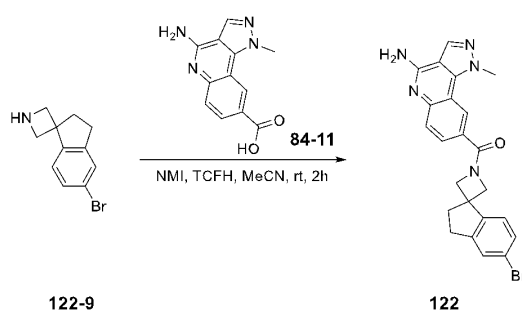
Intermediate 76-1 (1.0 g, 4.69 mmol) was added to (dimethylamino)dimethoxymethane (30 mL) solution under nitrogen atmosphere and stirred at 120 °C overnight. After the reaction was completed, the reaction solution was cooled to room temperature and then concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 2/1) to obtain **Intermediate 76-2** (750 mg, 2.38 mmol, 50.71%) as a white solid.

Step 3

To a methanol/water (20 mL 1:1) solution of **Intermediate 76-2** (1.0 g, 3.54 mmol) was added sodium hydroxide (0.57 g, 14.18 mmol) and stirred at 120 °C overnight. After the reaction was completed, the reaction solution was cooled to room temperature and then concentrated. The crude product was purified by column chromatography on silica gel (dichloromethane/methanol = 10/1) to obtain **Intermediate 76-3** as a white solid (500 mg, 1.86 mmol, 52.56% yield).

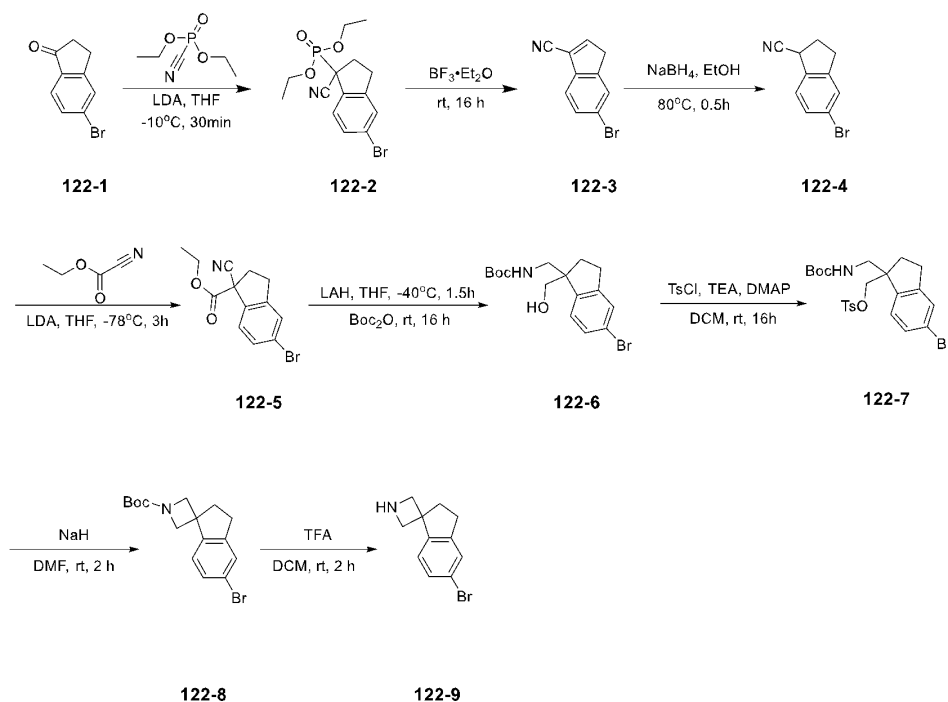
EXAMPLE 3:

Synthesis of Compound 122



At room temperature, **Intermediate 122-9** (30 mg, 0.13 mmol) was added to acetonitrile (2 mL), followed by addition of **Intermediate 84-11** (61 mg, 0.26 mmol) and N-methylimidazole (31 mg, 0.39 mmol) and chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (53 mg, 0.59 mmol) in sequence. The resulting mixture was stirred for 2 hours and then filtered. The filter cake was washed with water (5 mL) and dried, and further purified by prep-HPLC (Waters-Xbridge-C18-10 μ m-19*250 mm, mobile phase: A: 10 mM NH_4HCO_3 ; B: ACN, gradient: 40-50%, retention time: 8.5 min) to obtain **Compound 122** (6.30 mg, 0.01 mmol, 10.80% yield) as a white solid.

Synthesis of Compound 122-9



Step 1

To a solution of **Intermediate 122-1** (100 g, 476 mmol) in THF (1000 mL) was added lithium diisopropylamide (25 mL, 50.0 mmol, 2.0 M) at -10 °C. The reaction solution was stirred for 20 minutes at -10 °C under nitrogen atmosphere, then diethoxyphosphorylformonitrile (85 g, 524 mmol) was added. After stirring for 30 minutes at -10 °C, the reaction was quenched by ice water (1000 mL) and extracted with ethyl acetate (800 mL). Combined organic layers were washed with brine (1000 mL) and dried over anhydrous sodium sulfate. After filtration and concentration, the obtained residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4/1) to obtain **Intermediate 122-2** as a brown oil (130.0 g, 364.15 mmol, yield 76.47 %).

Step 2

Intermediate 122-2 (130 g, 364 mmol) was added to boron trifluoride-diethyl etherate solution (900 mL) at 0 °C, and then the solution was stirred at room temperature for 16 hours. After the reaction was completed, it was quenched with saturated ammonium chloride solution (800 mL) and extracted with ethyl acetate (800 mL). Combined organic layers were washed with saturated sodium bicarbonate solution (800 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The obtained residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 122-3** (63.5 g, 289.99 mmol, yield 80.38%) as a light yellow solid.

Step 3

Intermediate 122-3 (63.5 g, 289.99 mmol) was added to ethanol (700 mL) at 0 °C, followed by sodium borohydride (65.77 g, 1.74 mol), and then stirred at 80 °C for half an hour. After the reaction was completed, the reaction solution was quenched with ice water (700 mL) and extracted with ethyl acetate (600 mL). Combined organic layers were washed with brine (800 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to obtain **Intermediate 122-4** (54.0 g, 244 mmol, yield 84.4%) as a brown oil.

Step 4

To a solution of **Intermediate 122-4** (54 g, 244 mmol) in THF (600 mL) was added lithium diisopropylamide (269 mL, 2.0 M, 538 mmol) at -78 °C and the solution was stirred for 30 minutes under nitrogen atmosphere. Ethyl cyanoformate (48.4 g, 489 mmol) was then added and the mixture was stirred for 3 hours. The reaction was quenched with saturated ammonium chloride solution (600 mL) and extracted with ethyl acetate (500 mL). Combined organic layers were washed with brine (800 mL), dried over anhydrous sodium sulfate. After filtration and concentration, the obtained residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 122-5** (42.0 g, 143.34 mmol, yield 56.66%) as a brown oil.

Step 5

To a solution of **Intermediate 122-5** (42.0 g, 143 mmol) in THF (450 mL) was added lithium aluminum hydride (115 mL, 2.5 M, 287 mmol) at -40 °C and the solution was stirred for 1.5 hours. The reaction was quenched with water (300 mL) and the resulting mixture was stirred at 0°C for 30 minutes. Di-tert-butyl dicarbonate (62.5 g, 287 mmol) was then added to the reaction solution at room temperature and stirred for 16 hours, followed by filtration. The filtrate was extracted with ethyl acetate (500 mL). Combined organic layers were washed with brine (800 mL), dried over anhydrous sodium sulfate. After filtration and concentration, the obtained residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to obtain **Intermediate 122-6** (15.0 g, 51.19 mmol, yield 29.53%) as a light yellow solid.

Step 6

Intermediate 122-6 (15.0 g, 51.19 mmol) was added to THF (150 mL) and then TEA (8.5 g, 102 mmol), DMAP (6.2 g, 61.4 mmol) and TsCl (12.8 g, 81.9 mmol) were added thereto in sequence at room temperature. The solution was stirred for 16 hours and then quenched with water (150 mL), followed by extraction with dichloromethane (150 mL). Combined organic layers were washed with brine (300 mL), dried over anhydrous sodium sulfate. After filtration

and concentration, the obtained residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 122-7** (14.0 g, 27.50 mmol, yield 65.12%) as a white solid.

Step 7

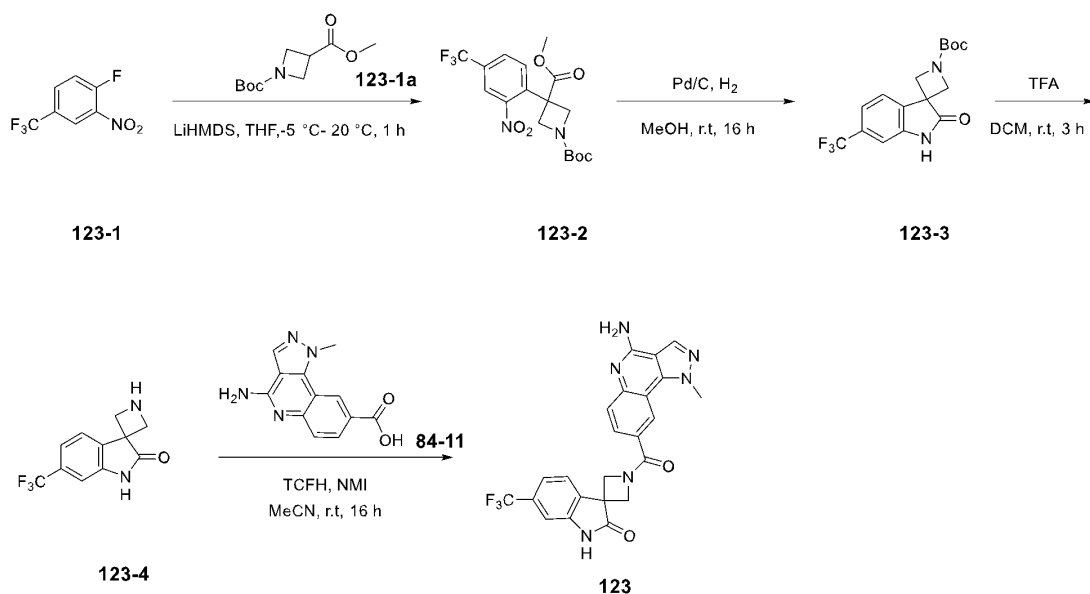
To a solution of **Intermediate 122-7** (14.0 g, 27.50 mmol) in *N,N*-dimethylformamide (150 mL) was added sodium hydride (2.20 g, 55.00 mmol) at 0 °C and the solution was stirred for 2 hours. The reaction solution was quenched with ice water (250 mL) and extracted with ethyl acetate (150 mL). The organic layer was washed with brine (400 mL), dried over anhydrous sodium sulfate. After filtration and concentration, the obtained residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 122-8** (1.4 g, 4.15 mmol, yield 15.1%) as a white solid.

Step 8

Intermediate 122-8 (50 mg, 0.15 mmol) was added to dichloromethane (2 mL), followed by trifluoroacetic acid (0.2 mL). After stirring at room temperature for 2 hours, the reaction solution was concentrated under reduced pressure, and then diluted with water and adjusted pH = 8 with saturated sodium bicarbonate solution, followed by extraction with ethyl acetate (2 mL). Combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to obtain **Intermediate 122-9** (30 mg, 0.13 mmol, yield 85.71%) as a yellow solid.

EXAMPLE 4:

Synthesis of Compound 123



Step 1

To a solution of **Intermediate 123-1a** (500 mg, 2.32 mmol) and **Intermediate 123-1** (486 mg, 2.32 mmol) in tetrahydrofuran (8 mL) was added lithium bis(trimethylsilyl)amide (1.0 N in THF, 2.56 mL, 2.56 mmol) under nitrogen atmosphere and cooled to -5 °C. The reaction solution was stirred for 1 hour, then heated to room temperature and stirred for 1 hour. The reaction was quenched with water (10 mL) and extracted with ethyl acetate (10 mL). Combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to obtain a yellow oil. **Intermediate 123-2** (300 mg, 0.74 mmol, yield 31.94%).

Step 2

To a solution of **Intermediate 123-2** (300 mg, 0.74 mmol) in methanol (5 mL) was added 10% wet Pd/C (50 mg, 0.05 mmol) under nitrogen atmosphere. The atmosphere was then replaced with hydrogen atmosphere and stirred for 16 hours. After filtration, the filter cake was washed with methanol (2 mL). The filtrate was concentrated under reduced pressure, and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to obtain **Intermediate 123-3** (120 mg) as a yellow solid, 0.35 mmol, yield 47.25%).

Step 3

To a solution of **Intermediate 123-3** (110 mg, 0.32 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (0.5 mL) at room temperature and the solution was stirred for 3 hours. The reaction solution was then concentrated under reduced pressure. The obtained

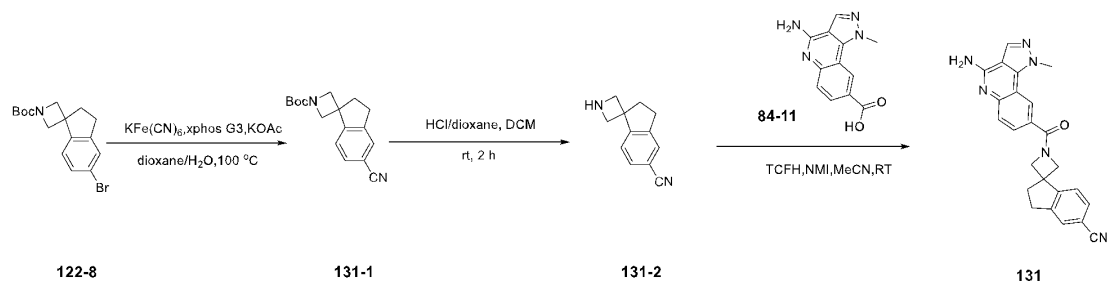
residue was added to saturated aqueous sodium bicarbonate solution (5 mL), then stirred and followed by extraction with dichloromethane (5 mL). Combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain a yellow solid **Intermediate 123-4** (50 mg, 0.21 mmol, yield 64.24%).

Step 4

To a solution of **Intermediate 84-11** (90 mg, 0.37 mmol) in acetonitrile (1.5 mL) were added Chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (78 mg, 0.28 mmol) and *N*-methyl imidazole (92 mg, 1.11 mmol) at room temperature under nitrogen atmosphere and the solution was stirred for 30 minutes, followed by adding **Intermediate 123-4** (45 mg, 0.19 mmol), and the reaction solution was stirred for 16 hours. The mixture was diluted with acetonitrile (5 mL) and then filtered. After filtration, the filter cake was washed with acetonitrile (2 mL) and concentrated under reduced pressure. The obtained residue was purified by HPLC (waters-xbridge-C18-10um-19*250mm, mobile phase: 0.1% $\text{NH}_4\text{HCO}_3/\text{H}_2\text{O}$ B: CH_3CN , gradient: 55 % B - 85% B, retention time 8.5 min) obtain **Compound 123** as a white solid (1.43 mg, 0.003 mmol, 1.65% yield). MS m/z (ESI): 467.1 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.82 (s, 1H), 8.53 (d, $J = 2.0$ Hz, 1H), 8.26 (s, 1H), 7.97 (d, $J = 8.0$ Hz, 1H), 7.89 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.61 (d, $J = 8.8$ Hz, 1H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.28 (s, 2H), 7.07 (s, 1H), 4.87–4.57 (m, 2H), 4.42 (s, 3H), 4.41–4.22 (m, 2H).

EXAMPLE 5:

Synthesis of Compound 131



Step 1

To a solution of **Intermediate 122-8** (150 mg, 0.44 mmol) in dioxane/water = 1:1 (10 mL) solution were added potassium ferrocyanide (749 mg, 1.77 mmol), Xphos G3 (75 mg, 0.09 mmol), and potassium acetate (87 mg, 0.89 mmol) under nitrogen atmosphere at 100 °C and the solution was stirred for 16 hours. The reaction solution was filtered, quenched with ice water (10 mL), and extracted three times with ethyl acetate (10 mL). Combined organic layers

were washed with brine (20 mL) and dried over anhydrous sodium sulfate. After filtration and concentration, the obtained residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to obtain **Intermediate 131-1** as a colorless oil (100 mg, 0.35 mmol, yield 79.30%).

Step 2

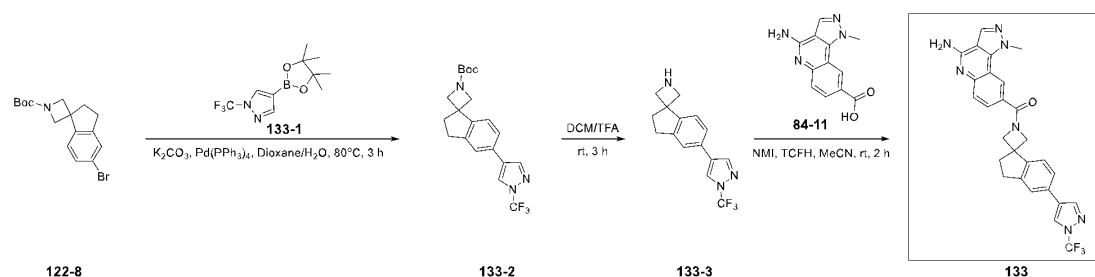
To a solution of **Intermediate 131-1** (100 mg, 0.35 mmol) in dichloromethane (5 mL) was added dioxane hydrochloride (3 mL) at room temperature and the solution was stirred for 2 hours. The reaction solution was then concentrated under reduced pressure to obtain a white solid **Intermediate 131-2** (60 mg, 0.33 mmol, yield 98.61%).

Step 3

To a solution of **Intermediate 131-2** (30 mg, 0.16 mmol) in acetonitrile (1 mL) were added **Intermediate 84-11** (98 mg, 0.41 mmol), *N*-methylimidazole (33 mg, 0.41 mmol) and chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (68 mg, 0.24 mmol) at room temperature and the solution was stirred for 16 hours. The reaction solution was quenched with water (2 mL) and extracted with ethyl acetate (2 mL). Combined organic layers were washed with brine (5 mL) and dried over anhydrous sodium sulfate. After filtration and concentration, the obtained residue was purified by prep-TLC (dichloromethane/methanol = 20/1) and then by HPLC (column: Welch ultimate XB-NH2 250*50*10um, mobile phase: [Heptane-EtOH (0.1%NH₃H:O)] ; B% 10%-10%, 10 min) to obtain **Compound 131** as a white solid (4.71 mg, 10 umol, yield 7.08%). MS *m/z* (ESI): 409.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.52 (d, *J* = 2.0 Hz, 1H), 8.28 (s, 1H), 7.84 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.76–7.68 (m, 2H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.24 (s, 2H), 4.64 (s, 2H), 4.44 (s, 3H), 4.24 (d, *J* = 28.0 Hz, 2H), 3.00–2.90 (m, 2H), 2.44 (t, *J* = 7.2 Hz, 2H).

EXAMPLE 6:

Synthesis of Compound 133



Step 1

Intermediate 122-8 (100 mg, 0.30 mmol), **Intermediate 133-1** (77.74 mg, 0.30 mmol), potassium carbonate (122.85 mg, 0.90 mmol), and Pd(PPh₃)₄ (34.29 mg, 0.03 mmol) were mixed in 1,4-dioxane (4 mL)/water (1 mL) solution at 80°C and stirred for 3 hours under nitrogen atmosphere. The reaction solution was concentrated under reduced pressure, diluted with water (3 mL) and extracted with ethyl acetate (3 mL). Combined organic layers were washed with brine (6 mL) and dried over anhydrous sodium sulfate. After filtration and concentration, the obtained residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 133-2** (80 mg, 0.20 mmol, yield 68.60%) as a white solid.

Step 2

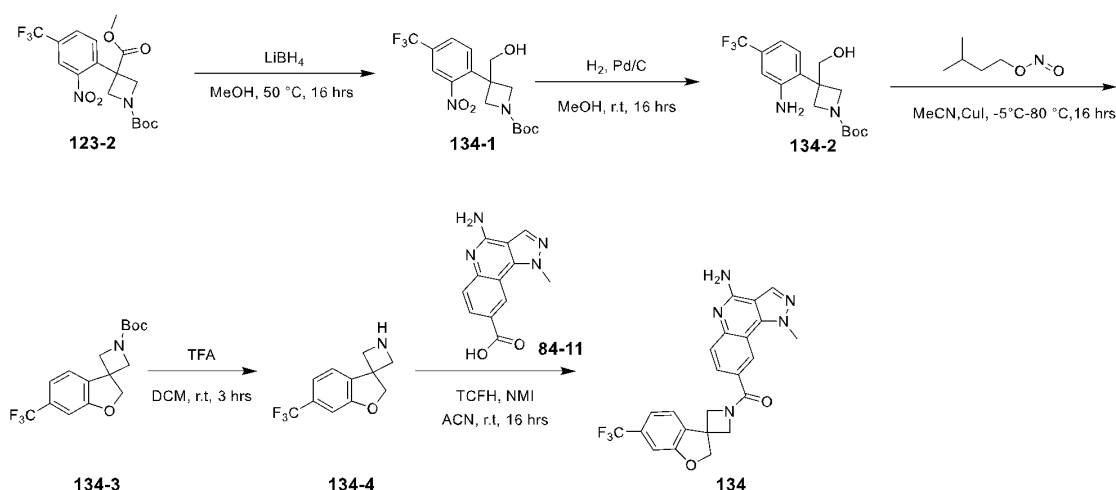
To a solution of **Intermediate 133-2** (80 mg, 0.20 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.2 mL) at room temperature and the solution was stirred for 3 hours. The reaction solution was concentrated under reduced pressure then diluted with water and adjusted to pH=8 with saturated sodium bicarbonate solution. After extraction with ethyl acetate (2 mL), combined organic layers were washed with brine (6 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to obtain **Intermediate 133-3** (50 mg, 0.17 mmol, yield 84.75%) as a yellow solid.

Step 3

To a solution of **Intermediate 133-3** (50 mg, 0.17 mmol) in acetonitrile (2 mL) were added **Intermediate 84-11** (82.59 mg, 0.34 mmol), *N*-methylimidazole (41.98 mg, 0.51 mmol), and chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (71.67 mg, 0.26 mmol) at room temperature and the solution was stirred for 2 hours. The reaction solution was filtered, and the filter cake was washed with water (2 mL), dried, and passed through prep-HPLC (Waters-Xbridge-C18-10μm-19*250mm, mobile phase: A: 10 mM NH₄HCO₃; B: ACN, gradient: 40-50 %, retention time: 8.5 min) to obtain **Compound 133** (21.03 mg, 0.04 mmol, yield 23.86%) as a white solid. MS *m/z* (ESI): 518.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.97 (s, 1H), 8.55 (d, *J* = 2.0 Hz, 1H), 8.47 (s, 1H), 8.27 (s, 1H), 7.97–7.80 (m, 1H), 7.71–7.55 (m, 4H), 7.29 (s, 2H), 4.71 (s, 2H), 4.43 (s, 3H), 4.34–4.14 (m, 2H), 2.97–2.86 (m, 2H), 2.44 (t, *J* = 7.2 Hz, 2H).

EXAMPLE 7:

Synthesis of Compound 134



Step 1

Under nitrogen atmosphere, **Intermediate 123-2** (3.3 g, 8.16 mmol) was added to methanol (50 mL) and cooled to 0 °C. Lithium borohydride (267 mg, 12.24 mmol) was added batchwise. After the mixture was slowly heated to room temperature, the reaction solution was stirred for 20 minutes, then heated to 50°C in an oil bath, and stirred for 16 hours. The reaction solution was then concentrated under reduced pressure and the obtained residue was washed with saturated ammonium chloride solution (50 mL) and extracted with ethyl acetate (50 mL). Combined organic layers were washed with brine (50 mL) and dried over anhydrous sodium sulfate. After filtration and concentration, the obtained residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to obtain **Intermediate 134-1** (2 g, 5.31 mmol, 65.12% yield) as a yellow solid.

Step 2

To a solution of **Intermediate 134-1** (1.9, 5.05 mmol) in methanol (25 mL) was added Pd/C (10% activated carbon mixture, 100 mg, 0.09 mmol) under nitrogen atmosphere, and then the atmosphere was replaced with hydrogen for three times. The mixture was stirred under hydrogen atmosphere at room temperature for 16 hours. After the reaction was completed, the reaction solution was filtered, the solid was washed with methanol (2 mL) and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (dichloromethane/methanol = 50/1) to obtain **Intermediate 134-2** as a white solid (1.3 g, 3.75 mmol, yield 74.34%).

Step 3

Under nitrogen atmosphere at -5 °C, **Intermediate 134-2** (500 mg, 1.44 mmol) and cuprous iodide (550 mg, 2.89 mmol) were added to acetonitrile (8 mL), and then isoamyl nitrite

(203 mg, 1.73 mmol) was added to the solution and the solution was stirred for 20 minutes. The temperature was raised to 80 °C and the solution was stirred for another 16 hours. When the reaction was completed, the reaction solution was cooled to room temperature and filtered. The filter cake was washed with dichloromethane (2 mL), and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) and then HPLC (mobile phase: A: 10 mM NH₄HCO₃; B: ACN, gradient: 40-50%, retention time: 8 min) to obtain **Intermediate 134-3** (100 mg, 0.30 mmol, 21.03% yield) as a white solid.

Step 4

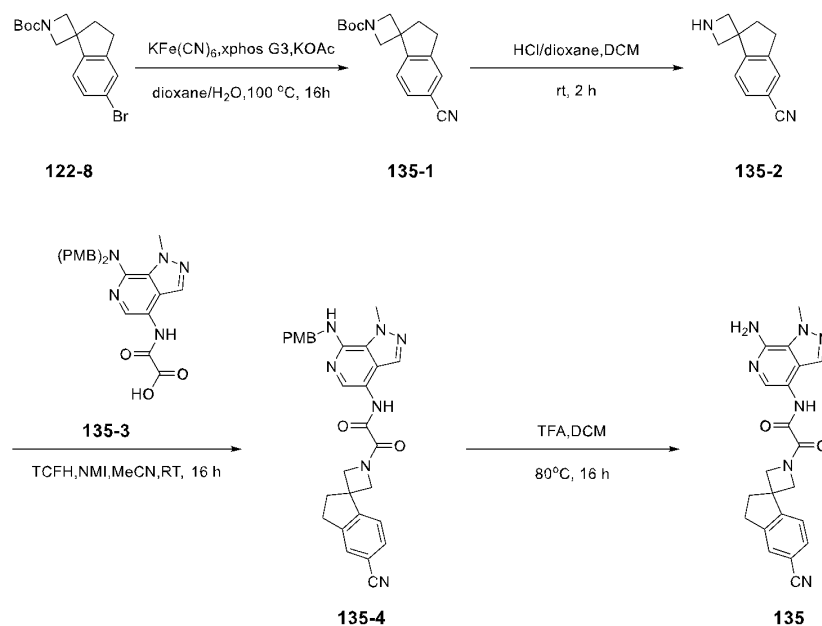
To a solution of **Intermediate 134-3** (100 mg, 0.30 mmol) in dichloromethane (0.5 mL) was added trifluoroacetic acid (0.5 mL, 6.71 mmol) at room temperature and the solution stirred for 3 hours. The reaction solution was diluted with dichloromethane (10 mL) and then concentrated under reduced pressure at 40°C to obtain **Intermediate 134-4** (70 mg, 0.31 mmol, 100% yield). The crude product was directly used in the next step.

Step 5

To a solution of **Intermediate 84-11** (148 mg, 0.61 mmol) in acetonitrile (2.5 mL) were added chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (128 mg, 0.46 mmol) and *N*-methylimidazole (151 mg, 1.83 mmol) at room temperature and the solution was stirred for 30 minutes. **Intermediate 134-4** (70 mg, 0.31 mmol) was then added and the reaction solution was stirred at room temperature for 16 hours. After the reaction was completed, the reaction solution was diluted with dimethyl sulfoxide (3 mL) and filtered. The filter cake was washed with dimethyl sulfoxide (1 mL) twice. The filtrate was purified by prep-HPLC (mobile phase: A: 10 mM NH₄HCO₃; B: ACN, gradient: 40-50%, retention time: 8.5 min) to obtain **Compound 134** as a white solid (50.37 mg, 0.11 mmol, 36.37 % yield). MS *m/z* (ESI): 454.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.52 (d, *J* = 2.0 Hz, 1H), 8.27 (d, *J* = 1.2 Hz, 1H), 7.87 (dd, *J* = 4.0, 8.4 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 2H), 7.17 (d, *J* = 1.6 Hz, 1H), 4.90 (s, 2H), 4.74 (s, 2H), 4.43 (s, 1H), 4.42 (s, 3H), 4.32 (s, 1H).

EXAMPLE 8:

Synthesis of Compound 135



Step 1

To a solution of **Intermediate 122-8** (150 mg, 0.44 mmol) in dioxane/water = 1:1 (10 mL) solution were added potassium ferrocyanide (749 mg, 1.77 mmol), Xphos G3 (75 mg, 0.09 mmol) and potassium acetate (87 mg, 0.89 mmol) under nitrogen atmosphere at 100 °C and the solution was stirred for 16 hours. The reaction solution was filtered, quenched with ice water (10 mL), and extracted with ethyl acetate (10 mL) three times. Combined organic layers were washed with brine (20 mL) and dried over anhydrous sodium sulfate. After filtration and concentration, the obtained residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to obtain **Intermediate 135-1** (100 mg, 0.35 mmol, yield 79.30%) as a colorless oil.

Step 2

To a solution of **Intermediate 135-1** (100 mg, 0.35 mmol) in dichloromethane (5 mL) was added dioxane hydrochloride (3 mL) at room temperature and the solution was stirred for 2 hours. The reaction solution was then concentrated under reduced pressure to obtain a white solid **Intermediate 135-2** (60 mg, 0.33 mmol, yield 98.61%).

Step 3

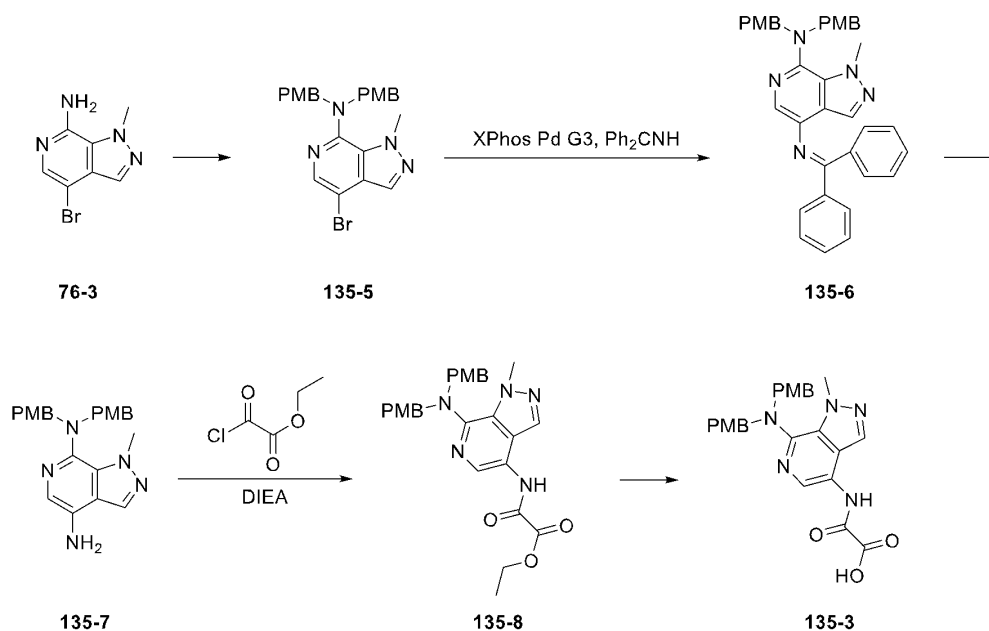
To a solution of **Intermediate 135-2** (25 mg, 0.14 mmol) in acetonitrile (1 mL) were added **Intermediate 135-3** (125.55 mg, 0.34 mmol), *N*-methylimidazole (27.85 mg, 0.34

mmol), and chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (57.11 mg, 0.20 mmol) at room temperature and the solution was stirred for 16 hours. The reaction solution was quenched with water (2 mL) and extracted with ethyl acetate (2 mL). Combined organic layers were washed with brine (4 mL) and dried over anhydrous sodium sulfate. After filtration and concentration, the obtained residue was purified by prep-TLC (dichloromethane/methanol = 20/1) to obtain **Intermediate 135-4** as a white solid (16 mg, 0.02 mmol, yield 18.09%).

Step 4

To a solution of **Intermediate 135-4** (16 mg, 0.03 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) at 80 °C and the solution was stirred for 16 hours. The reaction solution was cooled to room temperature and concentrated. The crude product was purified by prep-HPLC (waters-xbridge-C18-10um-19*250mm, mobile phase: 0.1% $\text{NH}_4\text{HCO}_3/\text{H}_2\text{O}$ B: CH_3CN , gradient: 55% B - 85% B, retention time 6.8 min) to obtain a white solid **Compound 135** (1.0 mg, 2.49 μmol , 8.12% yield) MS m/z (ESI): 402.2 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ 7.96 (s, 1H), 7.80 (s, 1H), 7.72 (s, 1H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.60 (s, 1H), 4.83–4.76 (m, 2H), 4.36 (s, 3H), 4.28 (t, $J = 10.4$ Hz, 2H), 3.00 (t, $J = 7.2$ Hz, 2H), 2.52 (t, $J = 7.2$ Hz, 2H).

Synthesis of Intermediate 135-3



Step 1:

At 0 °C, to a solution of **Compound 76-3** (1.0 g, 4.40 mmol) in DMF (15 mL) was added NaH (0.53 g, 13.21 mmol, purity 60%) batchwise. After being stirred for 30 minutes at 0 °C, the reaction solution was added with 4-(chloromethyl)-1-methoxybenzene (2.07 g, 13.21 mmol) and stirred at room temperature overnight. The reaction solution was quenched with water (50 mL) and then extracted with EtOAc (30 mL). The combined organic phases were washed with water (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, eluted with DCM:MeOH = 10:1) to obtain **Compound 135-5** (1.2 g, 2.57 mmol, 58.30% yield) as a white solid.

Step 2:

A mixture of **Compound 135-5** (1.0 g, 2.14 mmol), diphenylamine (1.16 g, 6.42 mmol), X-PHOS (0.41 g, 0.86 mmol), XPhos Pd G3 (0.36 g, 0.43 mmol) and Cs₂CO₃ (1.39 g, 4.28 mmol) was dissolved in 1,4-dioxane (20 mL), degassed and purged with nitrogen three times, stirred at 110 °C for 2 hours, concentrated under reduced pressure, and purified by flash column chromatography (SiO₂, PE: EtOAc = 3:1 elution) to obtain **Compound 135-6** (700 mg, 1.03 mmol, 48.35% yield) as a white solid.

Step 3:

To a solution of **Compound 135-6** (1.0 g, 1.76 mmol) in MeOH (10 mL) were add NaOAc (0.36 g, 4.40 mmol) and NH₂OH.HCl (0.24 g, 3.52 mmol). The mixture was stirred at room temperature overnight, diluted with water (50 mL) and extracted with EtOAc (50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain crude **Compound 135-7** (1.0 g) as a white solid, which can be directly used in the next step.

Step 4:

To a solution of **Compound 135-7** (120 mg, 0.30 mmol) in DMF (5 mL) were added ethyl 2-chloro-2-oxoacetate (41 mg, 0.30 mmol) and DIEA (77 mg, 0.59 mmol), and the solution was stirred at room temperature for 2 hours. The reaction solution was quenched with water (20 mL) and extracted with EtOAc (10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, eluted with PE: EtOAc = 3:1) to obtain **Compound 135-8** (100 mg, 0.16 mmol, 53.10% yield) as a yellow

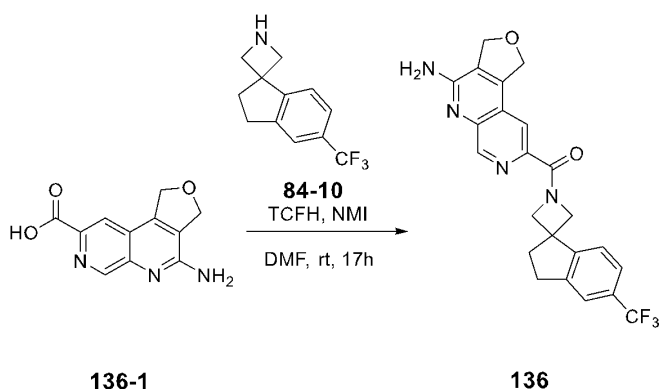
solid.

Step 5:

To a solution of **Compound 135-8** (100 mg, 0.20 mmol) in MeOH (8 mL) and H₂O (1 mL) was added NaOH (31.7 mg, 0.79 mmol). The mixture was stirred at room temperature overnight. The reaction solution was concentrated and lyophilized to obtain crude **Compound 135-3** (100 mg) as a white solid, which was directly used in the subsequent step without further purification.

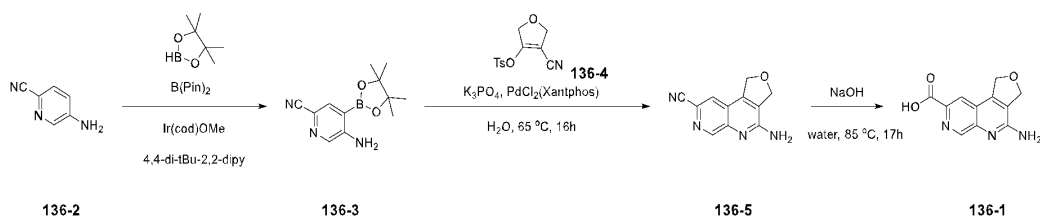
EXAMPLE 9:

Synthesis of Compound 136



To a solution of **Intermediate 136-1** (30 mg, 0.13 mmol) in *N,N*-dimethylformamide (2 mL) were added **Intermediate 84-10** (29.4 mg, 0.13 mmol), chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (43.6 mg, 0.16 mmol) and *N*-methylimidazole (27.7 mg, 0.34 mmol), and the mixture was stirred at room temperature for 17 hours. The mixture was extracted with ethyl acetate (30 mL) and washed 3 times with water (10 mL). Combined organic layers were dried over saturated sodium sulfate, filtered and concentrated under reduced pressure. The obtained residue was purified by prep-HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10 mM NH₄HCO₃; B: ACN, gradient: 40-60%, retention time: 9.0 min) to obtain white **Compound 136** as a white solid (7.98 mg, 0.02 mmol, 13.96% yield). MS *m/z* (ESI): 441.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.84 (s, 1H), 8.10 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 5.2 Hz, 2H), 7.13 (s, 2H), 5.41 (t, *J* = 3.6 Hz, 2H), 5.04 (d, *J* = 3.6 Hz, 2H), 4.88–4.73 (m, 2H), 4.31–4.17 (m, 2H), 2.97 (t, *J* = 7.2 Hz, 2H), 2.46 (t, *J* = 7.2 Hz, 2H).

Synthesis of Intermediate 136-1



Step 1

To a solution of **Intermediate 136-2** (3 g, 25.18 mmol) in tetrahydrofuran (24 mL) was slowly added 4,4,5,5-tetramethyl-1,3,2-dioxaborane (4.83 g, 37.77 mmol) under nitrogen atmosphere and the internal temperature was maintained below about $50\text{ }^\circ\text{C}$. The reaction mixture was stirred at $50\text{ }^\circ\text{C}$ for 1 hour and then cooled to $25\text{ }^\circ\text{C}$. To the cooled reaction solution was added THF solution (12 mL) of bis(pinacolato)diboron (6.39 g, 25.18 mmol), 4,4'-di-*tert*-butyl-2,2'-dipyridine (0.41 g, 1.51 mmol), (1,5-Cyclooctadiene)(methoxy)iridium(I) dimer (0.49 g, 0.76 mmol). The resulting solution was heated to $65\text{ }^\circ\text{C}$ and reacted for 3 hours, then cooled to $40\text{ }^\circ\text{C}$ and quenched with isopropanol (3 mL), and stirred at the same temperature for 20 min. The mixture was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3/2) to obtain **Intermediate 136-3** (4.5 g, 18.36 mmol, 72.91 % yield) as a white solid.

Step 2

To a solution of **Intermediate 136-3** (2 g, 8.16 mmol) in tetrahydrofuran (24 mL) were added dichloro[9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene] palladium(II) (0.31 g, 0.41 mmol) and **Intermediate 136-4** (2.16 g, 8.16 mmol) for reaction at $65\text{ }^\circ\text{C}$ for 2 hours under nitrogen atmosphere protection. The reaction mixture was filtered, and the filter cake was washed with tetrahydrofuran and methanol, then dried under vacuum to obtain a pale yellow crude product **Intermediate 136-5** (650 mg, 2.72 mmol, 33.28 % yield).

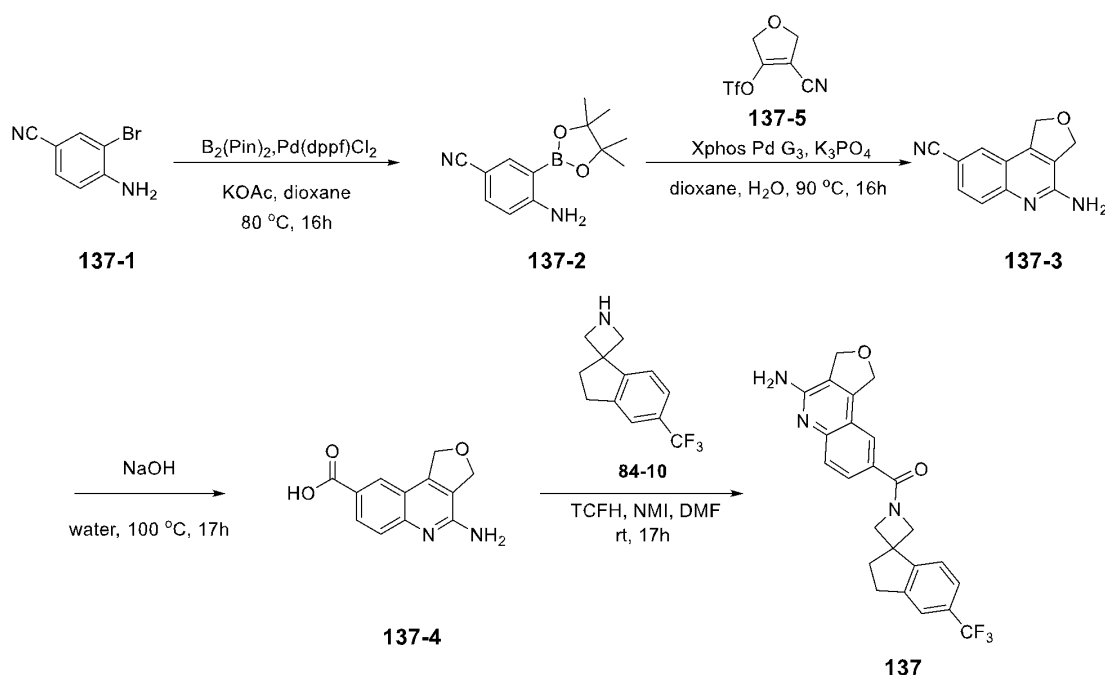
Step 3

To a solution of **Intermediate 136-5** (600 mg, 2.83 mol) in water (12 mL) was added sodium hydroxide (1.2 mL, 12.0 mmol, 10 mol/L). The resulting solution was stirred at $80\text{ }^\circ\text{C}$ for 16 hours. The mixture was washed with water and the reaction solution was heated to $55\text{ }^\circ\text{C}$ and HCl (37 wt%, 1.2 mL) was added and the temperature was maintained below approximately $60\text{ }^\circ\text{C}$. The resulting slurry was allowed to stand at $55\text{ }^\circ\text{C}$ for approximately 0.5 hours, cooled

to 20°C, and then allowed to stand for an additional 1.0 hour. The resulting slurry was filtered and the filter cake was washed with water (15 mL) twice and isopropyl alcohol (15 mL) twice. The product cake was then concentrated under reduced pressure to obtain white solid product **Intermediate 136-1** (350 mg, 1.51 mmol, 53.54% yield).

EXAMPLE 10:

Synthesis of Compound 137



Step 1

To a solution of **Intermediate 137-1** (1.0 g, 5.08 mmol) in dioxane (10 mL) were added bis(pinacolato)diboron (2.58 g, 10.15 mmol), potassium acetate (1.49 g, 15.23 mmol) and Pd(dppf)Cl₂ (0.37 g, 0.51 mmol). The reaction solution was stirred at 80°C under nitrogen atmosphere for 16 hours. After the reaction was completed, the mixture was concentrated under reduced pressure. The obtained residue was purified by column chromatography (methanol/dichloromethane = 0-30%) to obtain off-white solid **Intermediate 137-2** (1.10 g, 4.51 mmol, 88.79% yield).

Step 2

To a solution of **Intermediate 137-5** (300 mg, 1.13 mmol) in dioxane (10 mL) and water

(2 mL) were added **Intermediate 137-2** (414.07 mg, 1.70 mmol), potassium phosphate (720 mg, 3.39 mmol) and XPhos Pd G3 (191.45 mg, 0.23 mmol) at room temperature. The solution was then stirred at 90°C under nitrogen for 16 hours. After the reaction was completed, the mixture was concentrated under reduced pressure to obtain crude **Intermediate 137-3**, which was directly used in subsequent steps without further purification.

Step 3

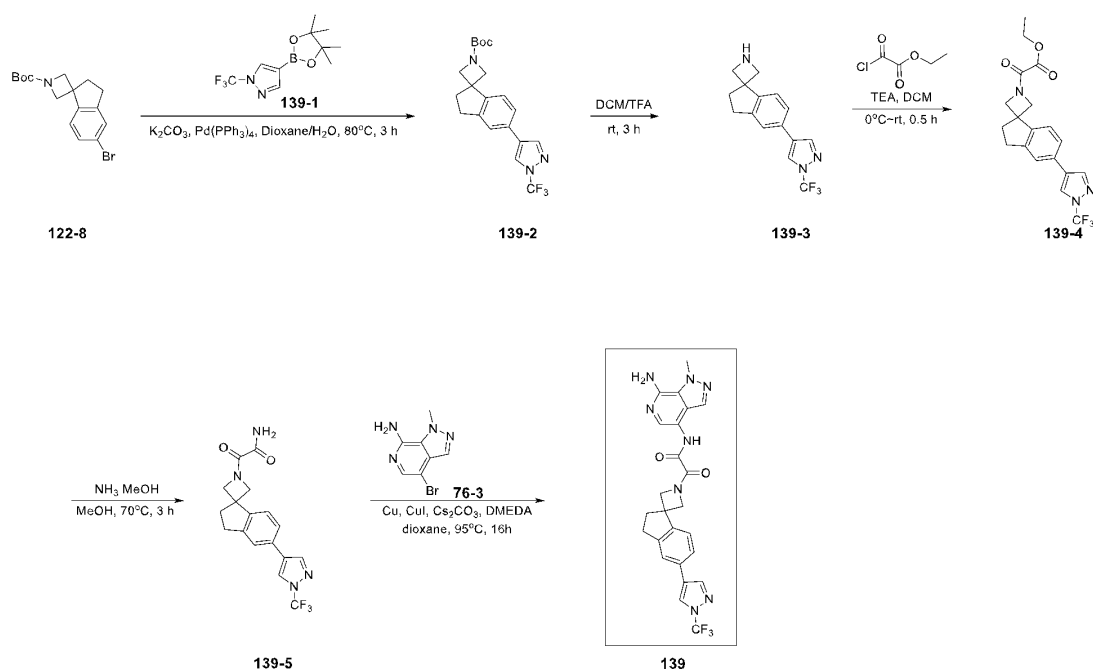
To a solution of **Intermediate 137-3** (230 mg, 1.09 mmol) in H₂O (10 mL) was added NaOH (435 mg, 10.9 mmol) at room temperature. The mixture was stirred at 100 °C under nitrogen atmosphere protection for 16 hours. After the reaction is completed, formic acid solution was used to adjust to pH = 6.0. Acidification of the aqueous solution gave a brown precipitate, which was collected by filtration; the collected precipitate was washed with water (10 mL) then ethyl acetate (10 mL), dried under vacuum, and the mixture was concentrated under reduced pressure to obtain crude **Intermediate 137-4**, which was directly used in the subsequent step without further purification.

Step 4

To a solution of **Intermediate 137-4** (101 mg, 0.44 mmol) in DMF (3 mL) were added N-methylimidazole (0.05 mL, 0.66 mmol), chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (123 mg, 0.44 mmol) and **Intermediate 84-10** (50 mg, 0.22 mmol). The mixture was stirred at room temperature under nitrogen atmosphere for 16 hours. The reaction mixture was concentrated under reduced pressure and purified by prep-HPLC (Waters-Xbridge-C18-10µm-19*250mm, mobile phase: A: 10 mM NH₄HCO₃; B: ACN, gradient: 10%-10%, retention time: 10 min) to obtain an off-white solid **Compound 137**. MS m/z (ESI): 440.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.85–7.80 (m, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.60 (s, 1H), 7.59–7.54 (m, 1H), 6.79 (s, 2H), 5.37 (t, *J* = 3.6 Hz, 2H), 5.01 (t, *J* = 3.6 Hz, 2H), 4.55 (s, 2H), 4.31–4.16 (m, 2H), 2.95 (s, 2H), 2.43 (t, *J* = 7.2 Hz, 2H).

EXAMPLE 11:

Synthesis of Compound 139



Step 1:

To a solution of **Intermediate 122-8** (250 mg, 0.75 mmol) in 4-dioxane (10 mL) and water (2.5 mL) were added **Intermediate 139-1** (194.35 mg, 0.75 mmol), potassium carbonate (307.13 mg, 2.25 mmol) and $Pd(PPh_3)_4$ (85.73 mg, 0.08 mmol). The mixture was stirred at $80^\circ C$ in a nitrogen atmosphere for 3 hours. The reaction solution was concentrated under reduced pressure, diluted with water (10 mL), and extracted with ethyl acetate (10 mL) three times. The combined organic phases were washed with saturated brine (20 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 139-2** (200 mg, 0.51 mmol, 68.72% yield) as a white solid.

Step 2

To a solution of **Intermediate 139-2** (200 mg, 0.51 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.5 mL). The reaction solution was stirred at room temperature for 3 hours. The reaction solution was concentrated under reduced pressure, diluted with water and adjusted to pH=8 with saturated sodium bicarbonate solution, and then extracted with ethyl acetate (5 mL) three times. The combined organic phases were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to obtain **Intermediate 139-3** (130 mg, 0.44 mmol, 87.25% yield) as a yellow solid. The crude product

was directly used in the subsequent step.

Step 3

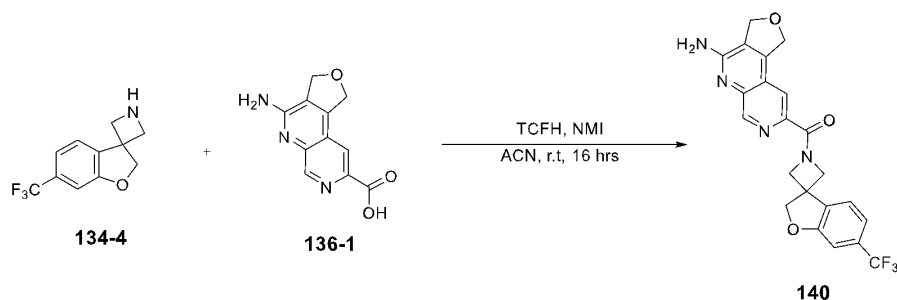
To a solution of **Intermediate 139-3** (130 mg, 0.44 mmol) and triethylamine (89.62 mg, 0.88 mmol) in dichloromethane (4 mL) under ice bath was added monoethyl oxalyl chloride (90.51 mg, 0.66 mmol). The reaction solution was stirred at room temperature for 0.5 hours, followed by quenched with water (5 mL) and extracted with ethyl acetate (5 mL) three times. The combined organic phases were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 139-4** as a yellow solid (130 mg, 0.33 mmol, 74.71% yield)

Step 4

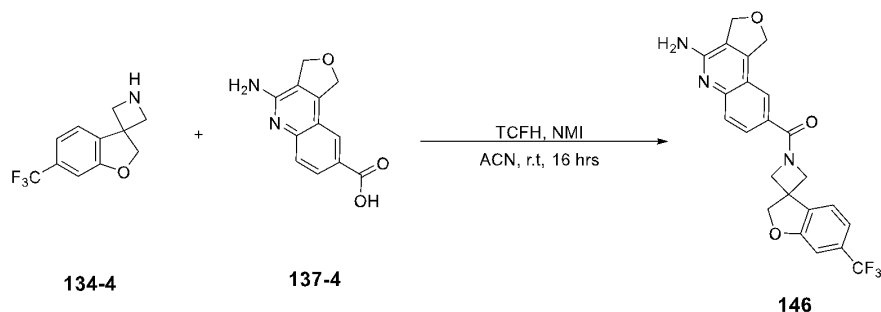
A solution of **Intermediate 139-4** (130 mg, 0.33 mmol) in ammonia-methanol (1 mL, 7M) was stirred at 70 °C for 3 h. The reaction solution was concentrated under reduced pressure. The crude **Intermediate 139-5** (120 mg, 0.36 mmol, 99.40% yield) was obtained as a yellow solid, and was directly used in the subsequent step.

Step 5

A mixture of **Intermediate 139-5** (120 mg, 0.36 mmol), **Intermediate 76-3** (89.74 mg, 0.43 mmol), copper powder (25.12 mg, 0.43 mmol), cuprous iodide (125.46 mg, 0.72 mmol), cesium carbonate (321.95 mg, 1.08 mmol) and N,N'-dimethylethylenediamine (58.07 mg, 0.72 mmol) in 1,4-dioxane (2 mL) was stirred under nitrogen atmosphere at 95 °C for 16 hours. The reaction solution was concentrated under reduced pressure, diluted with water (6 mL), and extracted with ethyl acetate three times (5 mL). The combined organic phases were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated. The obtained residue was purified by column chromatography (dichloromethane/methanol = 10/1) and then by prep-HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, with mobile phase: A: 10 mM NH₄HCO₃; B: ACN (Gradient: 40-50%, retention time: 8.5 min), to obtain **Compound 139** as a white solid (34.58 mg, 0.07 mmol, 20.58% yield). MS m/z (ESI): 511.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.51 (s, 1H), 8.98 (s, 1H), 8.47 (s, 1H), 7.89 (s, 1H), 7.81–7.55 (m, 4H), 6.25 (s, 2H), 4.68 (q, *J* = 10.4 Hz, 2H), 4.27 (s, 3H), 4.25–4.13 (m, 2H), 2.92 (t, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 6.8 Hz, 2H).

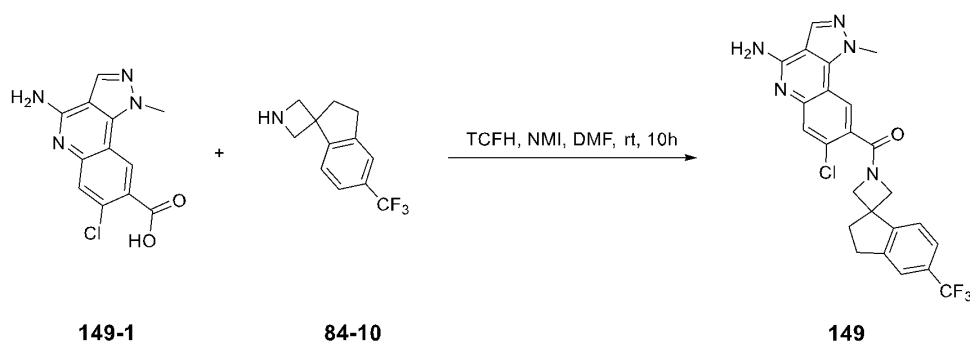
EXAMPLE 12:**Synthesis of Compound 140****Step 1**

To a solution of **Intermediate 134-4** (101 mg, 0.44 mmol) in acetonitrile (2.5 mL) were added chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (184 mg, 0.65 mmol) and N-methylimidazole (83 mg, 2.62 mmol) and the solution was stirred at room temperature for 30 minutes, followed by adding **Intermediate 136-1** (100 mg, 0.31 mmol). The reaction solution was stirred at room temperature for 16 hours. After the reaction is completed, the reaction solution was diluted with dimethyl sulfoxide (3 mL) and filtered. The solid was washed with dimethyl sulfoxide (1 mL) twice. The filtrate was purified by prep-HPLC (mobile phase: A: 10 mM NH_4HCO_3 ; B: ACN, gradient: 40-50%, retention time: 8.5 min) to obtain **Compound 140** (64.5 mg, 0.15 mmol, 33.42% yield) as a white solid. MS m/z (ESI): 443.2 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.84 (d, $J = 0.8$ Hz, 1H), 8.10 (d, $J = 0.8$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.30 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.23–7.09 (m, 3H), 5.41 (t, $J = 3.6$ Hz, 2H), 5.05 (t, $J = 3.6$ Hz, 2H), 4.97 (d, $J = 10.4$ Hz, 1H), 4.89 (d, $J = 10.4$ Hz, 3H), 4.40 (d, $J = 10.4$ Hz, 1H), 4.29 (d, $J = 10.4$ Hz, 1H).

Example 13**Synthesis of Compound 146**

Step 1

To a solution of **Intermediate 137-4** (148 mg, 0.61 mmol) in acetonitrile (2.5 mL) were added chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (184 mg, 0.65 mmol) and *N*-methylimidazole (83 mg, 2.62 mmol), and the solution was stirred at room temperature for 30 minutes, followed by adding **Intermediate 134-4** (100 mg, 0.31 mmol). The reaction solution was stirred at room temperature for 16 hours. After the reaction was completed, the reaction solution was diluted with dimethyl sulfoxide (3 mL) and filtered. The solid was washed with dimethyl sulfoxide (1 mL) twice. The filtrate was purified by prep-HPLC (mobile phase: A: 10 mM NH_4HCO_3 ; B: ACN, gradient: 40-50%, retention time: 8.5 min) to obtain **compound 146** as a white solid (32.23 mg, 0.07 mmol, 16.74 % yield). MS m/z (ESI): 442.1 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.91–7.77 (m, 3H), 7.57 (d, $J = 9.6$ Hz, 1H), 7.34 (d, $J = 8.0$ Hz, 1H), 7.16 (s, 1H), 6.80 (s, 2H), 5.37 (s, 2H), 5.01 (s, 2H), 4.87 (s, 2H), 4.66 (s, 2H), 4.43–4.22 (m, 2H).

EXAMPLE 14:**Synthesis of Compound 149**

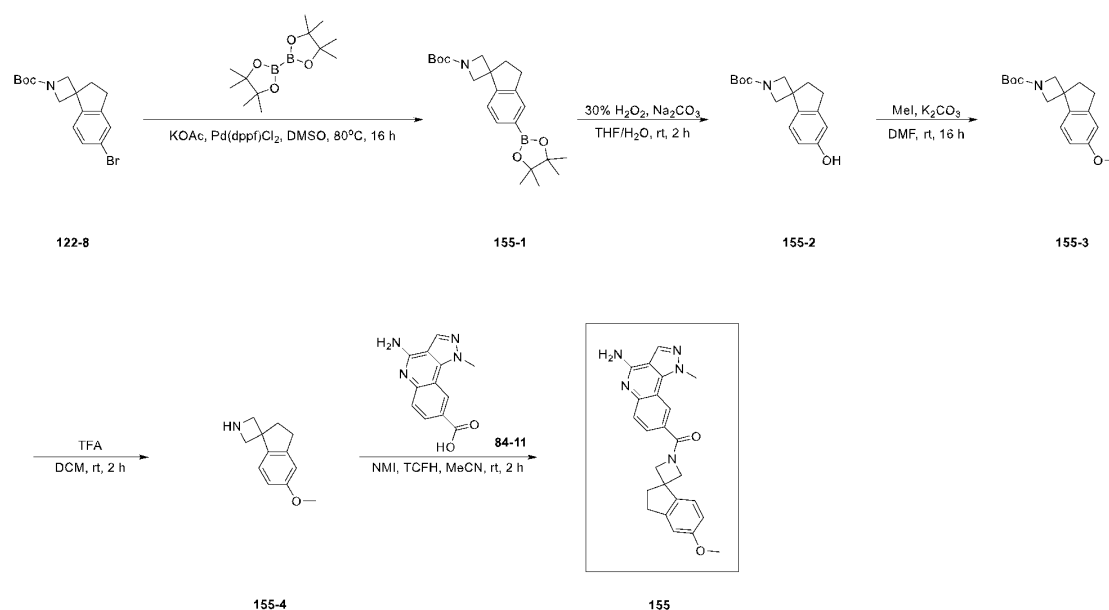
Step 1

To a solution of **Intermediate 149-1** (50 mg, 0.22 mmol) in acetonitrile (2 mL) were added **Intermediate 84-10** (243 mg, 0.88 mmol), *N*-methylimidazole (126 mg, 1.54 mmol), and chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (92 mg, 0.33 mmol) at room temperature and the solution was stirred for 10 hours. After the reaction was completed, the reaction solution was diluted with water (10 mL) and extracted with ethyl acetate (5 mL) three times. The organic layers were combined, washed with saturated brine (10 mL), and dried over anhydrous sodium sulfate. After concentrated under reduced pressure, the obtained

residue was purified by prep-HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10 mM NH₄HCO₃; B: ACN, gradient: 5-61%, retention time: 9.5 min) to obtain **Compound 149** (26.72 mg, 0.05 mmol, 24.99% yield). MS m/z (ESI): 486.0, 488.0 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 8.27 (s, 2H), 7.79 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.59 (s, 1H), 7.32 (s, 2H), 4.42 (s, 3H), 4.30 (d, J = 10.0 Hz, 1H), 4.21 (d, J = 10.0 Hz, 1H), 4.15 (d, J = 8.8 Hz, 1H), 4.07 (d, J = 8.8 Hz, 1H), 3.01–2.87 (m, 2H), 2.49–2.35 (m, 2H).

Example 15

Synthesis of Compound 155



Step 1

The solution of **Intermediate 122-8** (200 mg, 0.59 mmol), bis(pinacolato)diboron (180 mg, 0.71 mmol), potassium acetate (116 mg, 1.18 mmol) and Pd(dppf)Cl₂ (43 mg, 0.06 mmol) in dimethyl sulfoxide (3 mL) was stirred at 80 °C under nitrogen atmosphere for 16 hours. The reaction solution was diluted with water (5 mL) and extracted with ethyl acetate (5 mL) three times. The combined organic phases were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The obtained residue was purified by column chromatography (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 155-1** as a yellow oil (200 mg, 0.52 mmol, 51.95% yield).

Step 2

To a solution of **Intermediate 155-1** (200 mg, 0.52 mmol) in tetrahydrofuran (4 mL) and water (1 mL) were added sodium carbonate (275 mg, 2.60 mmol) and 30% hydrogen peroxide solution (1 mL). The reaction solution was stirred at room temperature for 2 hours. The reaction solution was quenched with saturated sodium thiosulfate solution (5 mL) and extracted with ethyl acetate (5 mL) three times. The combined organic phases were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated. The obtained residue was purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to obtain **Intermediate 155-2** (100 mg, 0.36 mmol, 70.42% yield) as a white solid.

Step 3

To a solution of **Intermediate 155-2** (100 mg, 0.36 mmol) in N,N-dimethylformamide (3 mL) were added potassium carbonate (150 mg, 1.08 mmol) and methyl iodide (103 mg, 0.72 mmol). The reaction solution was stirred at room temperature for 16 hours. The reaction solution was quenched with water (5 mL) and extracted with ethyl acetate (5 mL) three times. The combined organic phases were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated. The obtained residue was purified by column chromatography (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 155-3** (60 mg, 0.21 mmol, 57.14% yield) as a yellow solid.

Step 4

To a solution of **Intermediate 155-3** (60 mg, 0.21 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.2 mL). The reaction solution was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, diluted with water and adjusted to pH=8 with saturated sodium bicarbonate solution, and then extracted with ethyl acetate (2 mL) three times. The combined organic phases were washed with saturated brine (5 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to obtain crude **Intermediate 155-4** (35 mg, 0.19 mmol, 89.74% yield) as a yellow solid. The crude product was directly used in the subsequent step.

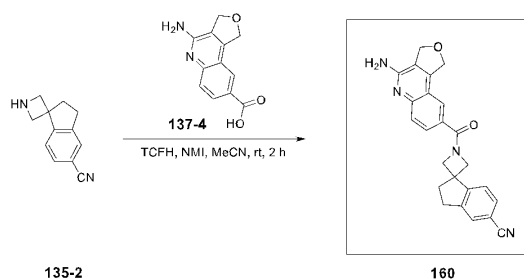
Step 5

To a solution of **Intermediate 155-4** (30 mg, 0.19 mmol) in acetonitrile (2 mL) were added **Intermediate 88-11** (77 mg, 0.38 mmol), N-methylimidazole (39 mg, 0.57 mmol) and chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (67 mg, 0.29 mmol) in

sequence at room temperature. The reaction solution was stirred at room temperature for 2 hours. The mixture was filtered, and the solid was washed with water (5 mL) twice and dried, and then passed through prep-HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10 mM NH₄HCO₃; B: ACN, gradient: 5- 61%, retention time: 9.5 min) to obtain **Compound 155** as a white solid (4.13 mg, 0.01 mmol, 6.30% yield). MS m/z (ESI): 414.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.52 (d, *J* = 2.0 Hz, 1H), 8.26 (s, 1H), 7.86 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.23 (s, 2H), 6.88–6.77 (m, 2H), 4.57 (d, *J* = 14.0 Hz, 2H), 4.42 (s, 3H), 4.20 (d, *J* = 29.2 Hz, 2H), 3.73 (s, 3H), 2.85 (t, *J* = 7.2 Hz, 2H), 2.39 (t, *J* = 7.2 Hz, 2H).

Example 16

Synthesis of Compound 160

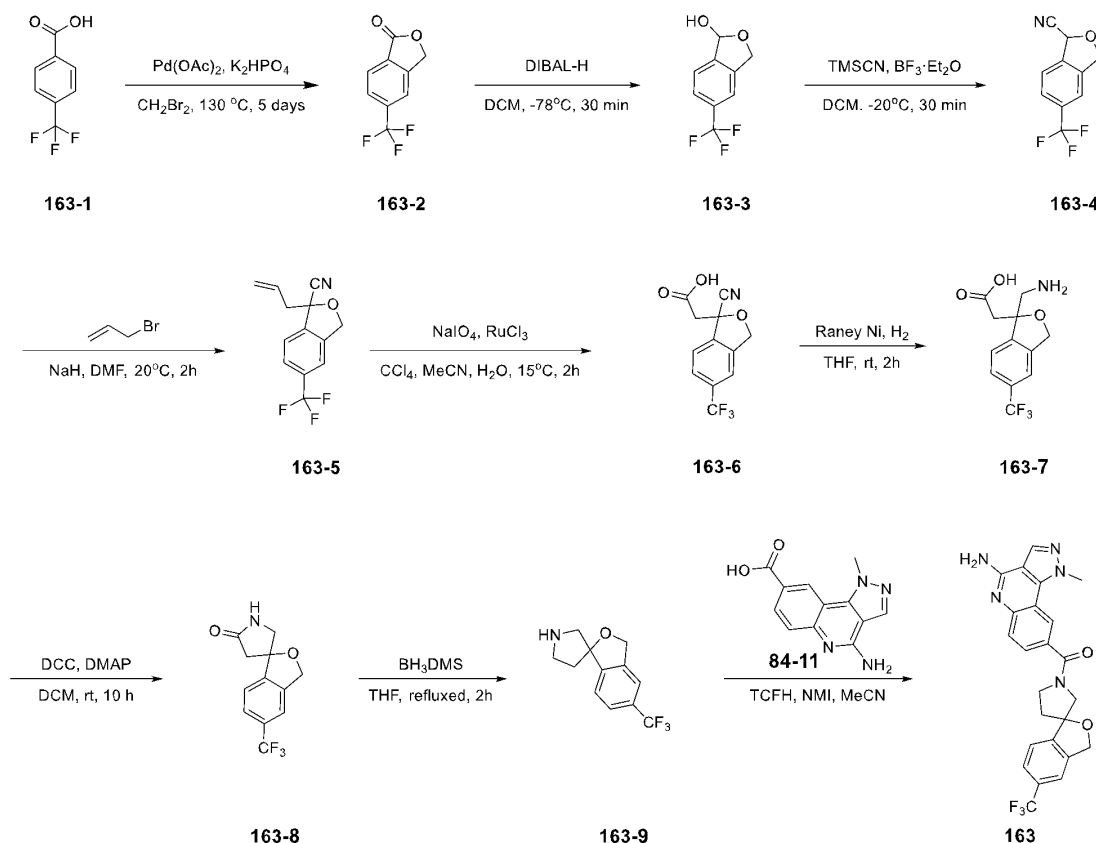


Step 1

To a solution of **Intermediate 135-2** (40 mg, 0.22 mmol) in acetonitrile (2 mL) were added **Intermediate 137-4** (100 mg, 0.44 mmol), N-methylimidazole (53 mg, 0.66 mmol) and chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (91 mg, 0.33 mmol) and the reaction solution was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, diluted with water (4 mL), and extracted with ethyl acetate (5 mL) three times. The combined organic phases were washed with saturated brine (5 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated. The crude product was purified by prep-HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10 mM NH₄HCO₃; B: ACN, gradient: 5-61%, retention time: 9.5 min) to obtain **Compound 160** (2.37 mg, 6.00 μ mol, 2.80% yield) as a white solid. MS *m/z* (ESI): 397.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.83–7.68 (m, 5H), 7.56 (m, 1H), 6.77 (s, 2H), 5.37 (t, *J* = 3.6 Hz, 2H), 5.01 (t, *J* = 3.6 Hz, 2H), 4.54 (s, 2H), 4.32–4.05 (m, 2H), 3.00–2.87 (m, 2H), 2.42 (t, *J* = 7.2 Hz, 2H).

Example 17

Synthesis of Compound 163



Step 1

To a solution of **Intermediate 163-1** (20 g, 105.26 mmol) in dibromomethane (150 mL) were added potassium hydrogen phosphate (55 g, 315.8 mmol) and palladium acetate (2.4 g, 10.52 mmol) under nitrogen atmosphere at room temperature. The reaction solution was stirred at 130°C for 5 days. The reaction solution was filtered and the filtrate was concentrated. The crude product was purified by prep TLC (petroleum ether/ethyl acetate = 10/1) to obtain **Intermediate 163-2** (6.5 g, 32.13 mmol, 24.46% yield).

Step 2

To a solution of **Intermediate 163-2** (13 g, 64.32 mmol) in dichloromethane (130 mL) was added diisobutylaluminum hydride (70 mL, 1N, 70 mmol) under nitrogen atmosphere at -78°C and stirred at -78°C for 2 hours. Water (250 mL) was added to the reaction solution, and

the mixture was extracted with ethyl acetate (150 mL) three times. The organic layers were combined, washed with saturated brine (500 mL), and dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by prep TLC (petroleum ether/ethyl acetate = 3/1) to obtain **Intermediate 163-3** (8 g, 39.19 mmol, 60.93% yield).

Step 3

To a solution of **Intermediate 163-3** (6 g, 29.39 mmol) in dichloromethane (60 mL) were added boron trifluoride ether (6.26 g, 44.09 mmol) and trimethylsilyl cyanide (8.75 g, 88.17 at -20°C and the solution was stirred at -20°C for 30 minutes. Water (100 mL) was added to the reaction solution, and the mixture was extracted with ethyl acetate (50 mL) three times. The organic layers were combined, washed with saturated brine (100 mL), and dried over anhydrous sodium sulfate. It was concentrated under reduced pressure, and the crude product was purified by prep TLC (petroleum ether/ethyl acetate = 10/1) to obtain **Intermediate 163-4** (5.5 g, 25.80 mmol, 87.79% yield).

Step 4

To a solution of **Intermediate 163-4** (5.5 g, 25.80 mmol) and 3-bromopropene (9.36 g, 77.41 mmol) in N,N-dimethylformamide (50 mL) was added sodium hydride (2.06 g, 51.60 mmol) at room temperature and the solution was stirred for 2 hours. Saturated aqueous ammonium chloride solution (200 mL) was added to the reaction solution, and the mixture was extracted with ethyl acetate (50 mL) three times. The organic layers were combined, washed with saturated brine (100 mL), and dried over anhydrous sodium sulfate. It was concentrated under reduced pressure, and the crude product was purified by prep TLC (petroleum ether/ethyl acetate = 10/1) to obtain **Intermediate 163-5** (5.3 g, 20.93 mmol, 81.12% yield).

Step 5

To a mixture of **Intermediate 163-5** (50 mg, 0.22 mmol), ruthenium trichloride (0.21 g, 0.79 mmol), acetonitrile (10 mL), tetrahydrofuran (10 mL), and water (10 mL) was added sodium periodate (8.45 g, 39.49 mmol) batchwise at room temperature. The reaction solution was stirred at room temperature for 2 hours then dried over anhydrous sodium sulfate. It was concentrated under reduced pressure, and the crude product was purified by prep TLC (dichloromethane/acetonitrile = 10/1) to obtain **Intermediate 163-6** (1.1 g, 4.06 mmol, 51.35% yield).

Step 6

To a solution of **Intermediate 163-6** (1 g, 3.69 mmol) in methanol (10 mL) was added Raney Nickel (100 mg) under nitrogen atmosphere at room temperature. The reaction solution was stirred at room temperature for 2 hours and filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by C18 column chromatography (acetonitrile/water (0.1% FA) = 20/1) to obtain **Intermediate 163-7** (300 mg, 1.09 mmol, 29.56% yield).

Step 7

The solution of **Intermediate 163-7** (300 mg, 1.09 mmol), N,N'-dicyclohexylcarbodiimide (292 mg, 0.79 mmol), 4-dimethylaminopyridine (173 mg, 1.42 mmol) in dichloromethane (10 mL) was stirred at room temperature for 10 hours. The reaction solution was concentrated under reduced pressure, and the crude product was purified by prep TLC (petroleum ether/ethyl acetate = 1/10) to obtain **Intermediate 163-8** (100 mg, 0.39 mmol, 35.67% yield).

Step 8

To a solution of **Intermediate 163-8** (40 mg, 0.16 mmol) in tetrahydrofuran (3 mL) was added borane dimethyl sulfide (.03 mL, 10.0 M, 0.3 mmol) at room temperature. The reaction solution was refluxed for 2 hours and then cooled to room temperature. Adding methanol to the reaction solution until no bubbles were generated. The resulting solution was concentrated under reduced pressure, and the crude product was purified by C18 column chromatography (acetonitrile/water (0.1% NH₄HCO₃) = 20/1) to obtain **Intermediate 163-9** (12 mg, 0.05 mmol, 31.72% yield).

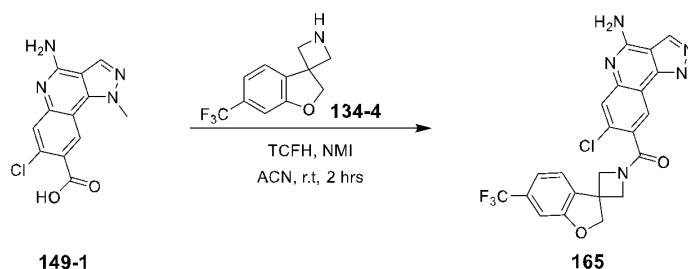
Step 9

To a solution of **Intermediate 163-9** (12 mg, 0.05 mmol) and **Intermediate 84-11** (12 mg, 0.05 mmol) in N,N-dimethylformamide (2 mL) were added N-methylimidazole (32 mg, 0.40 mmol) and chloro-N,N,N',N'-tetramethylformamidium hexafluorophosphate (21 mg, 0.07 mmol) at room temperature and stirred for 2 hours. The reaction solution was concentrated under reduced pressure, and the crude product was purified by Prep-HPLC (Waters-Xbridge-C18-10µm-19*250mm, mobile phase: A: 10 mM NH₄HCO₃; B: ACN, gradient: 5-55%, retention time: 9.1 min) to obtain **Compound 163** (4.24 mg, 0.01 mmol, 18.11% yield). MS

m/z (ESI): 468.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 8.61 (d, J = 14.0 Hz, 1H), 8.53–8.39 (m, 1H), 8.03–7.89 (m, 1H), 7.85–7.65 (m, 4H), 5.19–4.96 (m, 2H), 4.49 (d, J = 19.2 Hz, 3H), 4.06–3.67 (m, 4H), 2.42 (d, J = 10.4 Hz, 1H), 2.28–2.16 (m, 1H).

Example 18

Synthesis of Compound 165

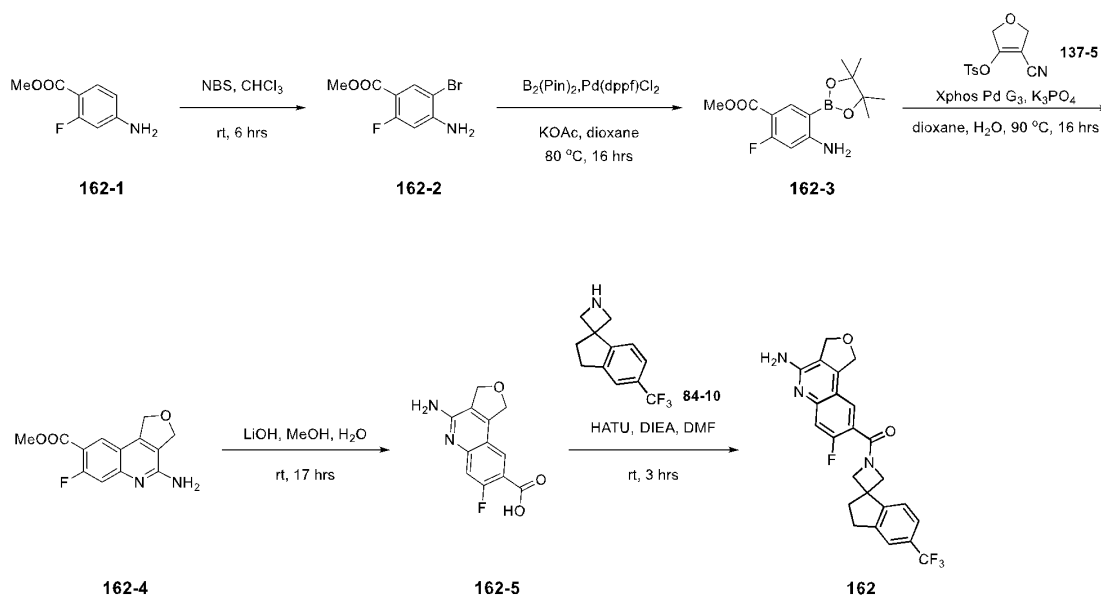


Step 1

To a solution of **Intermediate 149-1** (181 mg, 0.65 mmol) and **Intermediate 134-4** (50 mg, 0.22 mmol) in N,N-dimethylformamide (2 mL) were added N-methylimidazole (71 mg, 0.87 mmol), and chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (91 mg, 0.33 mmol) was further added at room temperature and the solution was stirred for 2 hours. The reaction solution was concentrated under reduced pressure, and the crude product was purified by Prep-HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10 mM NH_4HCO_3 ; B: ACN, gradient: 5-60%, retention time: 8.5 min) to obtain **Compound 165** (30.66 mg, 0.06 mmol, 28.81% yield) MS m/z (ESI): 488.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 8.29 (s, 1H), 8.27 (s, 1H), 7.82 (d, J = 76 Hz, 1H), 7.61 (s, 1H), 7.37 (d, 1H), 7.32 (s, 2H), 7.15 (d, J = 1.6 Hz, 1H), 4.92 (d, J = 10.0 Hz, 1H), 4.82 (d, J = 10.0 Hz, 1H), 4.46–4.39 (m, 4H), 4.33–4.25 (m, 2H), 4.18 (d, J = 9.2 Hz, 1H).

Example 19

Synthesis of Compound 162



Step 1

To a solution of **Intermediate 162-1** (6.0 g, 35.47 mmol) in chloroform (60 mL) was added N-bromosuccinimide (6.31 g, 35.47 mmol) under nitrogen atmosphere at 0°C and the solution was stirred at room temperature for 6 hours. The reaction mixture was quenched with saturated sodium bicarbonate (60 mL), and then extracted three times with dichloromethane (100 mL). The combined organic phases were washed with saturated brine (300 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the crude product was purified by column chromatography (petroleum ether/ethyl acetate = 9/1) to obtain off-white **Intermediate 162-2** (7.8 g, 31.45 mmol, yield 88.65%).

Step 2

To a solution of **Intermediate 162-2** (2.0 g, 8.06 mmol) in 1,4-dioxane (20 mL) were added bis(pinacolato)diboron (4.09 g, 16.13 mmol), potassium acetate (2.37 g, 24.19 mmol) and bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.18 g, 1.61 mmol) at room temperature. The reaction solution was stirred at 80°C for 16 hours and then concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to obtain white solid **Intermediate 162-3** (2.2 g, 7.45 mmol, yield 92.46%).

Step 3

To a solution of **Intermediate 137-5** (500.0 mg, 1.88 mmol) in 1,4-dioxane (10 mL) and water (2 mL) were added **Intermediate 162-3** (832 mg, 2.82 mmol), tripotassium phosphate (1.2 g, 5.64 mmol) and methanesulfonato(2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl)(2'-methylamino-1,1'-biphenyl-2-yl)palladium(II) (318 mg, 0.376 mmol) at room temperature. The reaction solution was stirred at 90°C for 16 hours and then concentrated under reduced pressure. The crude product was purified by a C18 reverse-phase column (water (0.1% NH₃·H₂O)/MeCN = 3/2) to obtain **Intermediate 162-4** (150 mg, 0.57 mmol, yield 30.40%) as a yellow solid.

Step 4

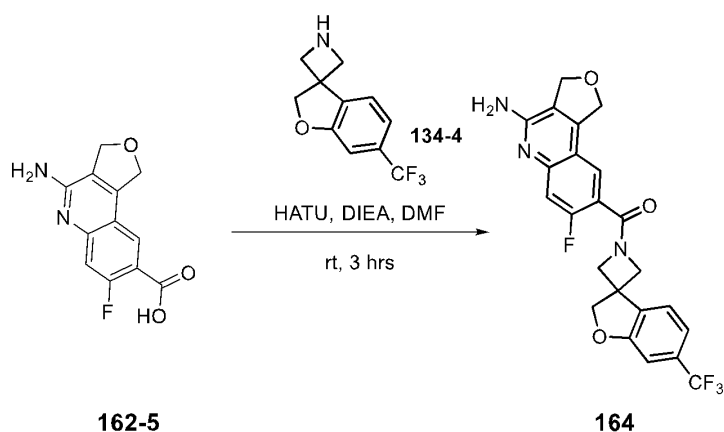
To a solution of **Intermediate 162-4** (100 mg, 0.38 mmol) in methanol (5 mL) and water (5 mL) was added lithium hydroxide (80.0 mg, 1.91 mmol) at room temperature and the solution was stirred for 17 hours. The reaction mixture was concentrated under reduced pressure to obtain **Intermediate 162-5** as a yellow solid (90 mg, 0.36 mmol, yield 95.09%). The crude product was used directly in the next step.

Step 5

To a solution of **Intermediate 162-5** (54 mg, 0.22 mmol) and **Intermediate 84-10** (50 mg, 0.22 mmol) in N,N-dimethylformamide (5 mL) were added hexafluorophosphate azabenzotriazole tetramethyl uronium (124 mg, 0.33 mmol) and N,N-diisopropylethylamine (0.11 mL, 0.65 mmol) at room temperature. The reaction solution was stirred at room temperature for 3 hours and then concentrated under reduced pressure. The crude product was purified by Prep-HPLC column (Waters-CORTECS-C18-2.7μm-4.6*30mm, mobile phase: 0.1% (NH₄HCO₃, B:CH₃CN, gradient: 36%-76%, retention time: 8 min) to obtain **Compound 162** (4.73 mg, 0.01 mmol, yield 4.68%) as a white solid. MS *m/z* (ESI): 458.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.79–7.70 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.59 (s, 1H), 7.29 (d, *J* = 12.4 Hz, 1H), 6.88 (s, 2H), 5.40–5.31 (m, 2H), 5.04–4.96 (m, 2H), 4.28–4.21 (m, 2H), 4.21–4.13 (m, 2H), 2.98–2.91 (m, 2H), 2.45–2.39 (m, 2H).

Example 20

Synthesis of Compound 164

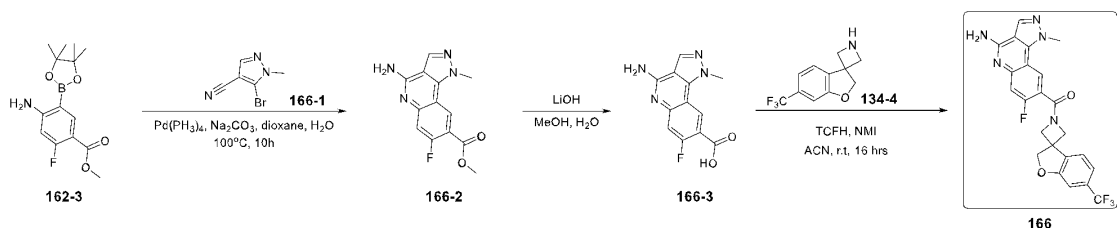


Step 1

To a solution of **Intermediate 162-5** (54 mg, 0.22 mmol) and **Intermediate 134-4** (50 mg, 0.22 mmol) in N,N-dimethylformamide (5 mL) were added hexafluorophosphate azabenzotriazole tetramethyl uronium (125 mg, 0.33 mmol) and N,N-diisopropylethylamine (0.11 mL, 0.65 mmol) at room temperature. The reaction solution was stirred at room temperature for 3 hours and then concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Waters-SunFire-C18-10 μ m-19*250mm, mobile phase: A: 0.1% FA/H₂O, B:ACN, gradient: 21%-51%, retention time: 8 min) to obtain **Compound 164** as a white solid (4.82 mg, 0.01 mmol, yield 4.81%). MS m/z (ESI): 460.0 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.83–7.75 (m, 2H), 7.39–7.31 (m, 2H), 7.15 (s, 1H), 5.36 (s, 2H), 5.01 (s, 2H), 4.93–4.79 (m, 2H), 4.42–4.34 (m, 2H), 4.33–4.22 (m, 2H).

Example 21

Synthesis of Compound 166



Step 1

To a solution of **Intermediate 162-3** (1.0 g, 3.39 mmol) in dioxane (10 mL) and water (1 mL) were added **Intermediate 166-1** (0.63 g, 3.39 mmol), tetrakis(triphenylphosphine) palladium (0.39 g, 0.34 mmol) and sodium carbonate (0.72 g, 6.78 mmol) at room temperature.

The reaction solution was stirred at 100°C for 10 hours under nitrogen atmosphere then cooled to room temperature. The resulting precipitated solid was filtered, and the filter cake was washed with water (30 mL). After drying **Intermediate 166-2** (300 mg, 1.09 mmol, 32.28% yield) was obtained.

Step 2

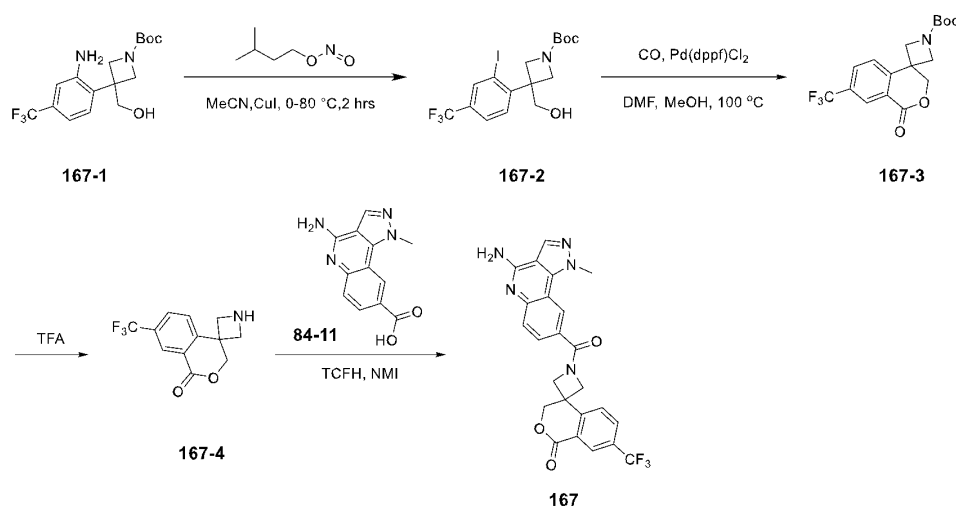
The solution of **Intermediate 166-2** (300 mg, 1.09 mmol) and lithium hydroxide (137 mg, 3.28 mmol) in methanol (5 mL) and water (1 mL) was stirred at 50°C for 2 hours. The reaction solution was cooled to room temperature and concentrated under reduced pressure. 1M dilute hydrochloric acid was added to adjust the pH to 3. The mixture was filtered, and the filter cake was dried to obtain **Intermediate 166-3** (200 mg, 0.77 mmol, 70.26% yield).

Step 3

To a solution of **Intermediate 166-3** (136 mg, 0.52 mmol), **Intermediate 134-4** (40 mg, 0.17 mmol) in N,N-dimethylformamide (2 mL) were added N-methylimidazole (57 mg, 0.70 mmol) and chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (73 mg, 0.26 mmol) at room temperature and the solution was stirred for 2 hours. The reaction solution was concentrated under reduced pressure, and the crude product was purified by Prep-HPLC (Waters-Xbridge-C18-10μm-19*250mm, mobile phase: A: 10 mM NH₄HCO₃; B: ACN, gradient: 5-70%, retention time: 8.1 min) to obtain **Compound 166** (26.56 mg, 0.06 mmol, 32.28% yield). MS m/z (ESI): 472.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.39 (d, *J* = 7.6 Hz, 1H), 8.26 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.41–7.25 (m, 4H), 7.15 (s, 1H), 4.95–4.80 (m, 2H), 4.47–4.38 (m, 5H), 4.37–4.27 (m, 2H).

Example 22

Synthesis of Compound 167



Step 1

To a solution of **Intermediate 167-1** (2.5 g, 7.22 mmol) and copper iodide (2.75 g, 14.44 mmol) in acetonitrile (30 mL) was added isoamyl nitrite (14.4 g, 12.27 mmol) dropwise at 0 °C. After the addition was completed, the reaction solution was heated to 80 °C and stirred for 2 hours. After the reaction was completed, the reaction solution was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the crude product is purified by column chromatography (ethyl acetate/petroleum ether = 1/3) to obtain **Intermediate 167-2** as a light yellow solid (0.9 g, 1.97 mmol, 27.27% yield).

Step 2

The mixture of **Intermediate 167-2** (900 mg, 1.97 mmol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (144 mg, 0.2 mmol), N,N-dimethylformamide (5 mL) and methanol (2 mL) was heated to 100 °C under carbon monoxide atmosphere and stirred for 16 hours. When the reaction was completed, the reaction solution was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 1/3) to obtain **Intermediate 167-3** (350 mg, 0.98 mmol, 49.7% yield) as a light-yellow solid.

Step 3

To a solution of **Intermediate 167-3** (150 mg, 0.42 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (1 mL) and the solution was stirred at room temperature for 3

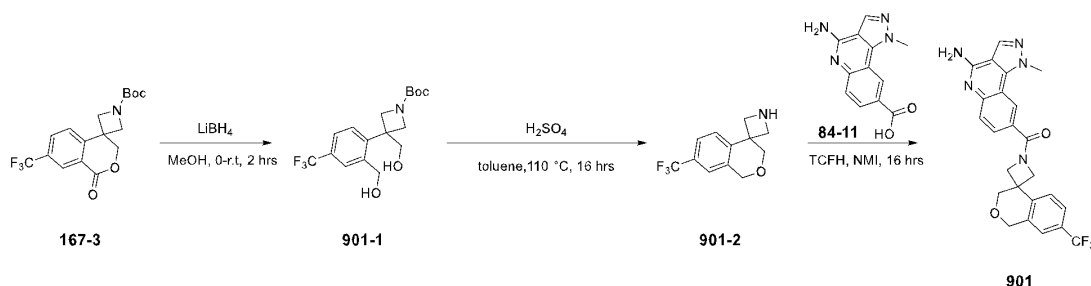
hours. After the reaction was completed, the reaction solution was concentrated under reduced pressure to obtain crude **Intermediate 167-4** (110 mg, 0.42 mmol, 100% yield) as a yellow solid. The crude product was directly used in the subsequent step.

Step 4

A solution of **Intermediate 84-11** (66 mg, 0.27mmol), chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (115 mg, 0.41 mmol), *N*-methylimidazole in acetonitrile (3 mL) was stirred at room temperature under nitrogen atmosphere for 30 minutes, followed by addition of **Intermediate 167-4** (70 mg, 0.27 mmol). The reaction solution was then stirred at room temperature for 16 hours. When the reaction was completed, the reaction solution was diluted with dimethyl sulfoxide (5 mL) and filtered. The filtrate was purified by Prep-HPLC (waters-xbridge-C18-10um-19*250mm, mobile phase: 0.1% FA/H₂O B:CH₃CN, Gradient: 55% B - 85% B, retention time 8.5 min) to obtain **Compound 167** as a white solid (38.56 mg, 0.08 mmol, 29.43% yield) MS *m/z* (ESI): 482.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.53 (d, *J* = 2.0 Hz, 1H), 8.27 (s, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 8.20–8.16 (m, 2H), 7.89 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.28 (s, 2H), 4.83 (s, 2H), 4.77–4.64 (m, 2H), 4.42 (s, 3H), 4.38–4.26 (m, 2H).

Example 23

Synthesis of Compound 901



Step 1

Under nitrogen atmosphere protection, a solution of **Intermediate 167-3** (1.3 g, 3.64 mmol) in methanol (10 mL) was cooled to $0\text{ }^\circ\text{C}$, and lithium borohydride (3.17 g, 14.55 mmol) was carefully and slowly added thereto, and then the reaction solution was heated to room temperature and stirred for 2 hours. After the reaction was completed, the reaction solution was added saturated aqueous ammonium chloride solution (10 mL), extracted with ethyl acetate

(10 mL), and dried with anhydrous sodium sulfate. The combined organic phase was filtered and concentrated under reduced pressure. The obtained residue was purified by column chromatography (ethyl acetate/petroleum ether = 1/3) to give **Intermediate 901-1** as a light yellow solid (1 g, 2.77 mmol, 76% yield).

Step 2

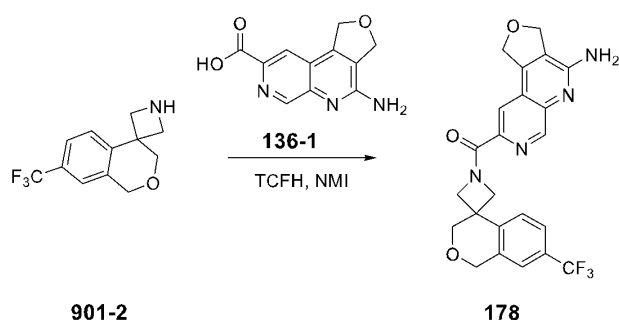
Under nitrogen atmosphere protection, concentrated sulfuric acid (217 mg, 2.21 mmol) was added dropwise to toluene solution (5 mL) of **Intermediate 901-1** (200 mg, 0.55 mmol). After the addition was completed, the mixture was heated to 110 °C and stirred for 16 hours. The reaction solution was then cooled to room temperature and concentrated under reduced pressure to obtain crude **Intermediate 901-2** (134 mg, 0.55 mmol, 100% yield) as a yellow solid. The crude product was used directly in the next step.

Step 3

Under nitrogen atmosphere protection, the solution of **Intermediate 84-11** (80 mg, 0.33 mmol), chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (138 mg, 0.49 mmol) and N-methylimidazole (162 mg, 1.97 mmol) in acetonitrile (2 mL) was stirred at room temperature for 30 minutes, and then **Intermediate 901-2** (80 mg, 0.33 mmol) was added to the reaction solution. The mixture was stirred at room temperature for 16 hours. When the reaction was completed, the reaction solution was diluted with dimethyl sulfoxide (5 mL) and filtered. The filtrate was purified by Prep-HPLC (waters-xbridge-C18-10um-19*250mm, Mobile phase: 0.1% NH₄HCO₃/H₂O B:CH₃CN, Gradient: 55% B - 85% B, Ret 9.5 min) to obtain **Compound 901** as a white solid (24.68 mg, 0.06 mmol, 17.22 % yield) MS m/z (ESI): 467.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.54 (d, *J* = 2.0 Hz, 1H), 8.26 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.89 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.50 (s, 1H), 7.23 (s, 2H), 4.82 (s, 2H), 4.57 (d, *J* = 36.8 Hz, 2H), 4.42 (s, 3H), 4.18 (s, 2H), 4.10 (s, 2H).

Example 24

Synthesis of Compound 178

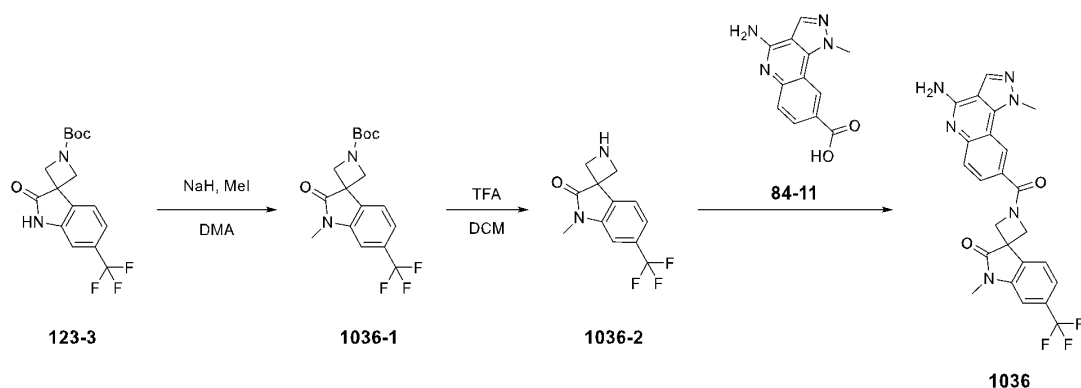


Step 1

Under nitrogen atmosphere protection, a solution of **Intermediate 136-1** (76 mg, 0.33 mmol), chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (138 mg, 0.49 mmol), and *N*-methylimidazole (162 mg, 1.97 mmol) in acetonitrile (2 mL) was stirred at room temperature for 30 minutes, and then **Intermediate 901-2** (80 mg, 0.33 mmol) was added to the reaction solution. The mixture was stirred at room temperature for 16 hours. When the reaction was completed, the reaction solution was diluted with dimethyl sulfoxide (5 mL) and filtered. The filtrate was purified by Prep-HPLC (waters-xbridge-C18-10um-19*250mm, Mobile phase: 0.1% $\text{NH}_4\text{HCO}_3/\text{H}_2\text{O}$ B: CH_3CN , Gradient: 55% B - 85% B, Ret 9.5 min) to obtain **Compound 178** as a white solid (14.18 mg, 0.03 mmol, 9.41 % yield) MS m/z (ESI): 457.2 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.84 (s, 1H), 8.10 (s, 1H), 7.95 (d, $J = 8.4$ Hz, 1H), 7.67 (dd, $J = 2.0, 8.4$ Hz, 1H), 7.50 (d, $J = 2.0$ Hz, 1H), 7.13 (s, 2H), 5.45 – 5.36 (m, 2H), 5.10 – 5.01 (m, 2H), 4.82 (s, 2H), 4.80 – 4.69 (m, 2H), 4.22 – 4.12 (m, 2H), 4.10 (s, 2H).

Example 25

Synthesis of Compound 1036



Step 1

Under nitrogen atmosphere protection, sodium hydrogen (21.03 mg, 0.88 mmol) was added to a solution of **Intermediate 123-3** (200 mg, 0.58 mmol) in dimethylacetamide (4 mL) at 0 °C, and the mixture was stirred for 0.5 hours. The reaction solution was added methyl iodide (55 µL, 0.88 mmol) dropwise and stirred at 0°C for an addition 0.5 hours, and the temperature was then raised to room temperature for stirring for an additional 1 hour. After the reaction was completed, the reaction solution was added with water (10 mL) and extracted with ethyl acetate (10 mL). The combined organic layers were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 1036-1** (160 mg, 0.45 mmol, 76.85%) as a yellow oil.

Step 2

To a solution of **Intermediate 1036-1** (160 mg, 0.45 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) and the solution was stirred at room temperature for 3 hours. After the reaction was completed, the reaction solution was concentrated under reduced pressure. Sodium bicarbonate aqueous solution (5 mL) was added and the resulting solution was extracted with dichloromethane (5 mL). The combined organic layers were washed with saturated brine (5 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude **Intermediate 1036-2** (110 mg, 0.43 mmol, 95.61%) as a yellow solid. The crude product was directly used in the subsequent step.

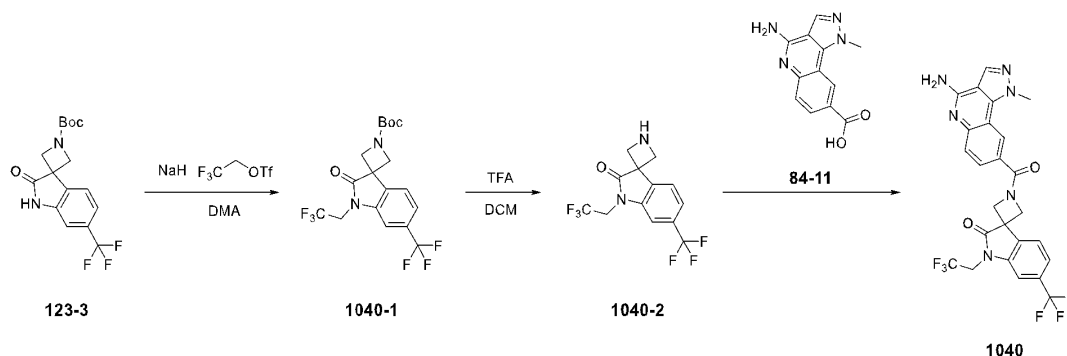
Step 3

Under nitrogen atmosphere protection, a solution of **Intermediate 84-11** (100 mg, 0.39 mmol), chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (219.01 mg, 0.78 mmol), and *N*-methylimidazole (0.19 mL, 2.34 mmol) in acetonitrile (1.5 mL) was stirred at room temperature for 30 minutes, and then **Intermediate 1036-2** (113.45 mg, 0.47 mmol) was added to the reaction solution; the mixture was stirred at room temperature for 3 hours. When the reaction was completed, the reaction solution was diluted with DMSO (5 mL) and filtered. The filter cake was washed with DMSO (2 mL), and then the filtrate was concentrated under reduced pressure. The crude product was purified by HPLC (waters-xbridge-C18-10um-19*250mm, Mobile phase: 0.1% NH₄HCO₃/H₂O B:CH₃CN, Gradient: 55% B - 85% B, Ret 8.5 min) to obtain **Compound 1036** as a white solid (35 mg, 0.07 mmol, 18.67%). MS *m/z* (ESI): 481.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.54 (d, *J* = 2.0 Hz, 1H), 8.27 (s, 1H),

8.00 (d, $J = 7.6$ Hz, 1H), 7.90 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.62 (d, $J = 8.8$ Hz, 1H), 7.53 (d, $J = 7.6$ Hz, 1H), 7.39 (s, 1H), 7.26 (s, 2H), 4.82 - 4.66 (m, 2H), 4.42 (s, 3H), 4.41 - 4.28 (m, 2H), 3.21 (s, 3H).

Example 26

Synthesis of Compound 1040



Step 1

Under nitrogen atmosphere protection, sodium hydrogen (32 mg, 1.31 mmol) was added to a solution of **Intermediate 123-3** (300 mg, 0.88 mmol) in dimethylacetamide (4 mL) at 0 °C, and the mixture was stirred at 0 °C for 0.5 hours. 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.19 mL, 1.31 mmol) was added dropwise into the reaction solution and the resulting solution was stirred at 0°C for 0.5 hours, followed by raising the temperature to room temperature and stirring for additional 1 hour. After the reaction was completed, the reaction solution was added with water (10 mL) and extracted with ethyl acetate (10 mL). The combined organic layers were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 1040-1** (270 mg, 0.64 mmol, 72.60%) as a yellow solid.

Step 2

To a solution of **Intermediate 1040-1** (270 mg, 0.64 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) at room temperature and the solution was stirred for 3 hours. After the reaction was completed, the reaction solution was concentrated under reduced pressure. The obtained crude product was added with saturated aqueous sodium bicarbonate solution (5 mL) for stirring and extracted with dichloromethane (5 mL). The combined organic

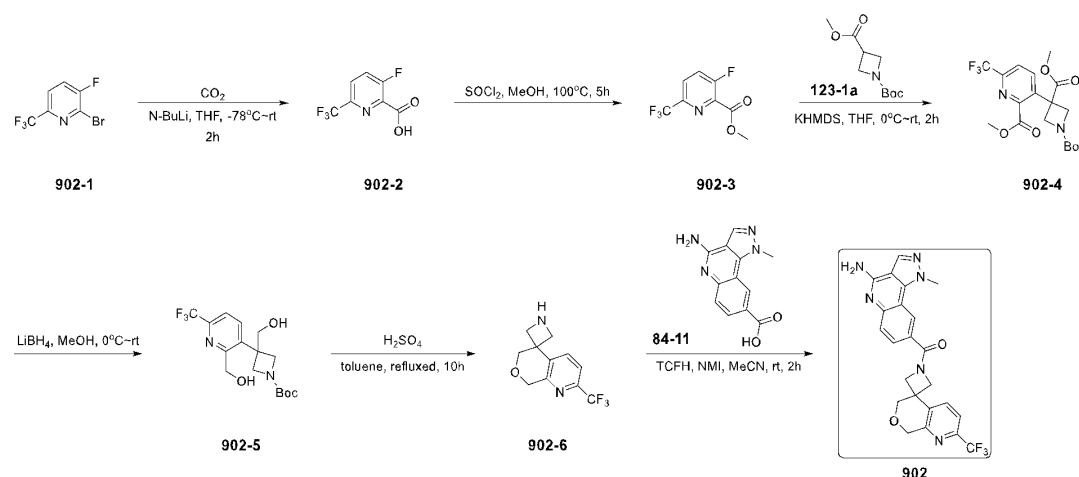
layers were washed with saturated brine (5 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude **Intermediate 1040-2** (170 mg, 0.52 mmol, 89.00%) as a yellow solid. The crude product was used directly in the next step.

Step 3

Under nitrogen atmosphere protection, a solution of **Intermediate 84-11** (90 mg, 0.31 mmol), chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (173.96 mg, 0.62 mmol) and *N*-methylimidazole (0.15 mL, 1.86 mmol) in acetonitrile (5 mL) was stirred at room temperature for 30 minutes, and then **Intermediate 1040-2** (100 mg, 0.47 mmol) was added to the reaction solution; the mixture was stirred at room temperature for 3 hours. When the reaction was completed, the reaction solution was diluted with DMSO (5 mL) and filtered. The filter cake was washed with DMSO (2 mL) and the filtrate is concentrated under reduced pressure. The crude product was purified by HPLC (waters-xbridge-C18-10um-19*250mm, Mobile phase: 0.1% $\text{NH}_4\text{HCO}_3/\text{H}_2\text{O}$ B: CH_3CN , Gradient: 55% B - 85% B, Ret 8.5 min) to obtain **Compound 1040** (16 mg, 0.03 mmol, 9.46%) as a white solid. MS m/z (ESI): 549.3 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.54 (d, $J = 2.0$ Hz, 1H), 8.27 (s, 1H), 8.07 (d, $J = 7.6$ Hz, 1H), 7.90 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.67 – 7.56 (m, 3H), 7.26 (s, 2H), 4.93 – 4.62 (m, 4H), 4.42 (s, 3H), 4.40 – 4.31 (m, 2H).

Example 27

Synthesis of Compound 902



Step 1

To a solution of **Intermediate 902-1** (1.00 g, 4.10 mmol) in tetrahydrofuran (10 mL) was added n-butyllithium (2 mL, 5.0 mmol, 2.5M n-hexane solution) dropwise at -78°C under nitrogen atmosphere. The reaction solution was stirred at -78°C for 2 hours. Then the atmosphere was replaced with carbon dioxide three times, followed by an additional 2 hours stirring at room temperature. The reaction solution was added with sodium sulfate decahydrate and filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by column chromatography (dichloromethane/methanol = 8/1) to obtain **Intermediate 902-2** (1.00 g, 4.78 mmol, 116.69% yield)

Step 2

A solution of **Intermediate 902-2** (500 mg, 2.39 mmol) in thionyl chloride (3 mL) was heated to reflux for 3 hours. The reaction solution was cooled then distilled under pressure. The obtained concentrated solution was added to methanol (3 mL) slowly and dropwise, and stirred at room temperature for 10 minutes. The reaction solution was added with water (10 mL) and extracted with ethyl acetate (5 mL). The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure. The crude product was purified by column chromatography. (ethyl acetate/petroleum ether = 1/4) gave compound 902-3 (290 mg, 1.30 mmol, 74.19% yield).

Step 3

To a solution of **Intermediate 902-3** (290 mg, 1.30 mmol) and **Intermediate 123-1a** (280 mg, 1.30 mmol) in tetrahydrofuran (5 mL) was added potassium bis(trimethylsilyl)amide (1.43 mL, 1.43 mmol, 1 N) dropwise in an ice bath under nitrogen atmosphere. The reaction solution was stirred in an ice bath for 1 hour and then at room temperature for 1 hour, followed by addition of water (10 mL). The solution was extracted with ethyl acetate (5 mL) and the organic layers were combined. The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 1/3) to obtain **Intermediate 902-4** (60 mg, 0.14 mmol, 11.03% yield).

Step 4

Under ice bath, a solution of **Intermediate 902-4** (60 mg, 0.14 mmol) in methanol (2 mL) was slowly added with lithium borohydride (12 mg, 0.56 mmol) and the solution was stirred

for 30 minutes at room temperature. The reaction solution was added with sodium sulfate decahydrate and filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by column chromatography (dichloromethane/methanol = 10/1) to obtain **Intermediate 902-5** (40 mg, 0.11 mmol, 76.97% yield).

Step 5

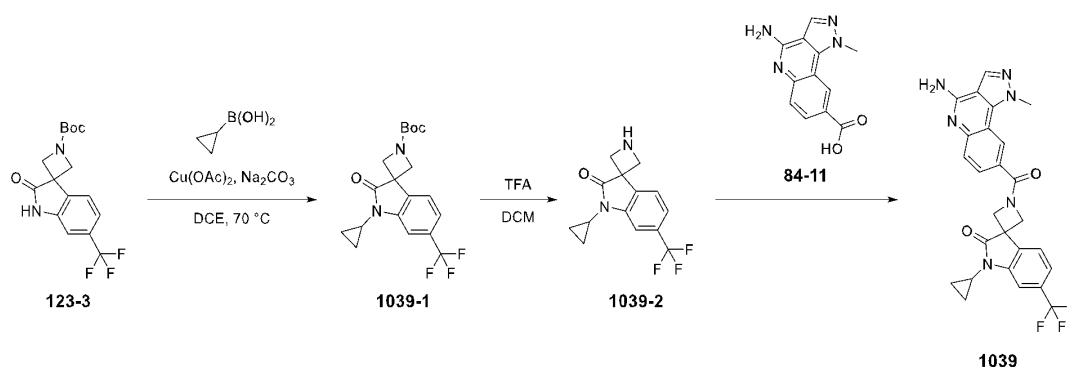
To a solution of **Intermediate 902-5** (40 mg, 0.11 mmol) in toluene (2 mL) was added concentrated sulfuric acid (43 mg, 0.44 mmol) then the solution was refluxed for 10 hours. The reaction solution was concentrated under reduced pressure to obtain crude **Intermediate 902-6** and used directly in the next step.

Step 6

To a solution of **Intermediate 902-5** (20 mg, 0.08 mmol) and **Intermediate 84-11** (40 mg, 0.08 mmol) in acetonitrile (2 mL) were added chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (34 mg, 0.12 mmol) and N-methylimidazole (67 mg, 0.82 mmol) at room temperature and the solution was stirred for 2 hours. Water (10 mL) was added to the reaction solution, and the mixture was extracted with ethyl acetate (5 mL). The combined organic layers were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10mM NH₄HCO₃; B: ACN, gradient: 10-95%, retention time: 10 min) Compound 902 (6.73 mg, 0.01mmol, 17.54% yield) MS m/z (ESI): 468.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.23 (s, 1H), 8.55 (d, *J* = 2.0 Hz, 1H), 8.27 (s, 1H), 7.91 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.71 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.30 (s, 2H), 4.92 – 4.70 (m, 3H), 4.55 – 4.44 (m, 1H), 4.43 (s, 3H), 4.37 – 4.28 (m, 1H), 4.23 – 4.13 (m, 1H), 4.11 (s, 2H)。

Example 28

Synthesis of Compound 1039



Step 1

A solution of **Intermediate 123-3** (500 mg, 1.46 mmol), cyclopropylboronic acid (1000 mg, 11.64 mmol), sodium carbonate (310 mg, 2.92 mmol), copper acetate (530 mg, 2.92 mmol) in dichloroethane (40 mL) was stirred at 70 °C for 2 hours. The reaction solution was concentrated, and the crude product was purified by column chromatography (petroleum ether/ethyl acetate = 2/1) to obtain **Intermediate 1039-1** (190 mg, 0.50 mmol, 34.02%) as a white solid.

Step 2

A solution of **Intermediate 1039-1** (130 mg, 0.34 mmol) in dichloromethane (3 mL) and trifluoroacetic acid (0.5 mL) was stirred at 25 °C for 2 hours. The reaction solution was concentrated, quenched with saturated aqueous sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (10 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to obtain crude **Intermediate 1039-2** (100 mg, 0.35 mmol, 104.20%) as a brown solid which is used directly in the next step.

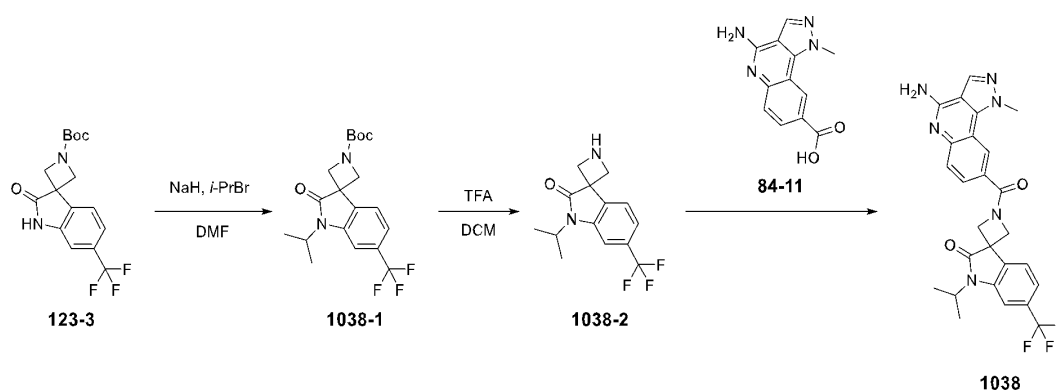
Step 3

A solution of **Intermediate 84-11** (100 mg, 0.41 mmol), chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (170 mg, 0.61 mmol) and *N*-methylimidazole (0.10 mL, 1.20 mmol) in acetonitrile (10 mL) was stirred at 25 °C for 30 minutes. **Intermediate 1039-2** (113 mg, 0.40 mmol) was then added there to and the reaction solution was stirred at 25 °C for 2 hours. The reaction solution was concentrated and diluted with dimethyl sulfoxide (3 mL). The crude product was purified by Prep-HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium bicarbonate/water B: acetonitrile; flow rate: 25) to obtain **Compound 1039** (10.67 mg, 0.02 mmol, 5.26%) as a white solid. MS *m/z* (ESI):

507.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.53 (d, *J* = 2.0 Hz, 1H), 8.27 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.88 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.31 (s, 1H), 7.26 (s, 2H), 4.83 – 4.71 (m, 1H), 4.68 – 4.54 (m, 1H), 4.42 (s, 3H), 4.39 – 4.33 (m, 1H), 4.31 – 4.22 (m, 1H), 2.76 – 2.70 (m, 1H), 1.08 – 0.97 (m, 2H), 0.89 – 0.79 (m, 2H).

Example 29

Synthesis of Compound 1038



Step 1

To a solution of **Intermediate 123-3** (200 mg, 0.58 mmol) and sodium hydride (60 mg, 1.50 mmol, 60% w%) in N,N-dimethylformamide (10 mL) was added 2-bromopropane (0.2 mL, 2.13 mmol) and the solution was stirred at 50°C for 2 hours. The reaction solution was quenched by water (10 mL) and extracted with ethyl acetate (10 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to obtain crude **Intermediate 1038-1** (250 mg, 0.65 mmol, 111.31%) as a white solid, which was directly used in the subsequent step.

Step 2

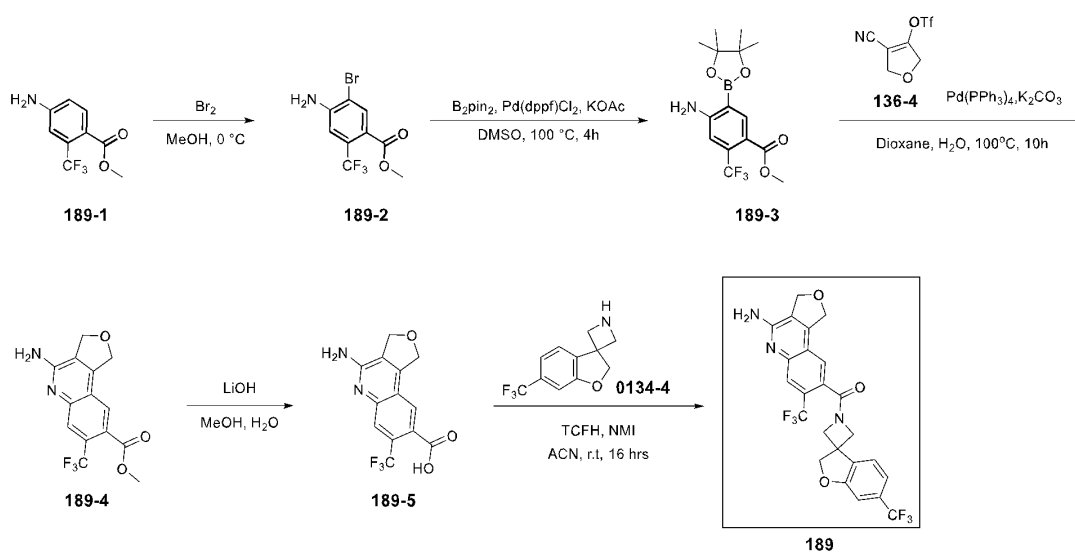
A solution of **Intermediate 1038-1** (250 mg, 0.65 mmol) in trifluoroacetic acid (1 mL) and dichloromethane (5 mL) was stirred at 25 °C for 2 hours. The reaction solution was quenched with saturated aqueous sodium bicarbonate solution (30 mL), extracted with ethyl acetate (20 mL), and the combined organic layers were dried over anhydrous sodium sulfate and concentrated to obtain crude **Intermediate 1038-2** (240 mg, 0.84 mmol, 129.81%) as a brown solid, which was directly used in the subsequent step.

Step 3

A solution of **Intermediate 84-11** (100 mg, 0.41 mmol), chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (175 mg, 0.62 mmol) and *N*-methylimidazole (0.10 mL, 1.24 mmol) in acetonitrile (10 mL) was stirred at 25 °C for 30 min. **Intermediate 1038-2** (110 mg, 0.39 mmol) was then added and reaction solution was stirred at 25°C for 2 hours. The reaction solution was concentrated, and the crude product was purified by Prep-HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium bicarbonate/water B: acetonitrile; flow rate: 25) to obtain **Compound 1038** (14.95 mg, 0.03 mmol, 6.73%) as a white solid. MS *m/z* (ESI): 509.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.54 (d, *J* = 2.0 Hz, 1H), 8.27 (s, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.89 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.43 (s, 1H), 7.26 (s, 2H), 4.85 – 4.76 (m, 1H), 4.70 – 4.62 (m, 1H), 4.62 – 4.50 (m, 1H), 4.42 (s, 3H), 4.42 – 4.35 (m, 1H), 4.33 – 4.23 (m, 1H), 1.42 (d, *J* = 6.8 Hz, 6H).

Example 30

Synthesis of Compound 189



Step 1

Under nitrogen atmosphere protection, to a solution of **Intermediate 189-1** (4.7 g, 21.45 mmol) in methanol (40 mL) solution was added liquid bromine (1.10 mL, 21.45 mmol) dropwise and slowly at $0\text{ }^\circ\text{C}$ and the solution was stirred at $0\text{ }^\circ\text{C}$ for 1 hour. After the reaction

was completed, the reaction was added with water (30 mL) and then extracted with ethyl acetate (30 mL). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (petroleum ether/ethyl acetate = 10/1) to obtain **Intermediate 189-2** (2.8 g, 9.39 mmol, 43.80%) as a yellow solid.

Step 2

Under nitrogen atmosphere protection, to a solution of **Intermediate 189-2** (500 mg, 1.68 mmol) in 1,4-dioxane (5 mL) were added bis(pinacolato)diboron (638.98 mg, 2.52 mmol), potassium acetate (411.58 mg, 4.19 mmol) and Pd(dppf)Cl₂ (136.21 mg, 0.17 mmol). The reaction solution was stirred at 80 °C for 2 hours. After the reaction was completed, the reaction solution was filtered and concentrated under reduced pressure to obtain crude **Intermediate 189-3** (400 mg, 1.16 mmol, 69.09%) as a yellow solid, which was directly used in the subsequent step.

Step 3

Under nitrogen atmosphere protection, to a solution of **Intermediate 189-3** (300 mg, 1.23 mmol) in 1,4-dioxane (8 mL) and water (0.8 mL) were added **Intermediate 136-4** (553 mg, 1.60 mmol), tetrakis(triphenylphosphine) palladium (0) (14 mg, 0.01 mmol) and potassium carbonate (51 mg, 0.37 mmol) and the solution was stirred at 80°C for 18 hours. After the reaction was completed, the reaction solution was added with water (30 mL), and then extracted with ethyl acetate (30 mL). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (petroleum ether/ethyl acetate = 10/1) to obtain **Intermediate 189-4** (350 mg, 1.12 mmol, 90.85%) as a yellow solid.

Step 4

To a solution of **Intermediate 189-4** (200 mg, 0.64 mmol) in methanol (2 mL), tetrahydrofuran (2 mL) and water (2 mL) was added lithium hydroxide (54 mg, 1.28 mmol) and the reaction solution was heated at 75 °C and stirred for 3 hours. After the reaction was completed, the reaction solution was adjusted to pH~6 with 1M dilute hydrochloric acid. The reaction solution was concentrated under reduced pressure and then lyophilized to obtain **Intermediate 189-5** (237 mg, 0.64 mmol, 99.26%) as a yellow solid, which was directly used

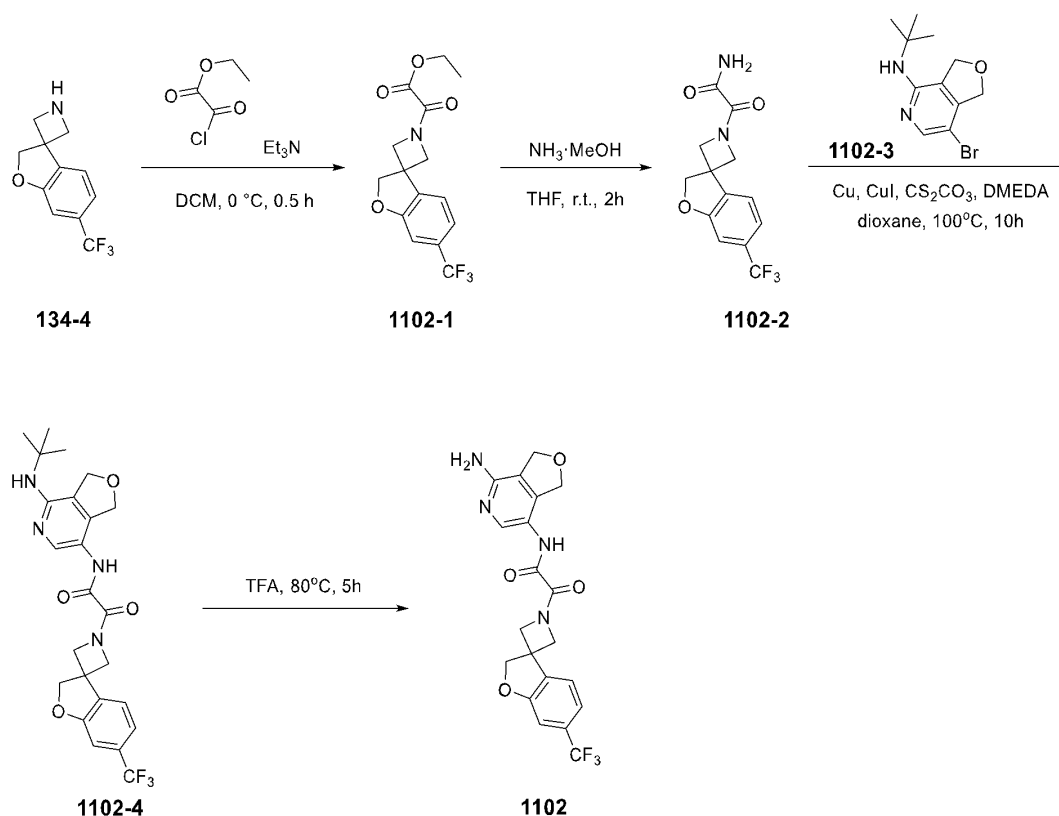
in the subsequent step.

Step 5

Under nitrogen atmosphere protection, a solution of **Intermediate 189-5** (100 mg, 0.27 mmol), chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (150 mg, 0.54 mmol), and *N*-methylimidazole (0.13 mL, 1.61 mmol) in acetonitrile (5 mL) was stirred at room temperature for 30 minutes, then **Intermediate 134-4** (74 mg, 0.32 mmol) was added to the reaction solution, and the mixture was stirred at room temperature for 16 hours. When the reaction was completed, the reaction solution was diluted with DMSO (5 mL) and filtered. The filter cake was washed with DMSO (2 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by HPLC (waters-xbridge-C18-10um-19*250mm, Mobile phase: 0.1% $\text{NH}_4\text{HCO}_3/\text{H}_2\text{O}$ B: CH_3CN , Gradient: 55% B - 85% B, Ret 8.5 min) to obtain **Compound 189** as a white solid (27.22 mg, 0.05 mmol, 19.92%).

Example 31

Synthesis of Compound 1102



Step 1

To a solution of **Intermediate 134-4** (250 mg, 1.10 mmol) and triethylamine (0.46 mL, 3.30 mmol) in dichloromethane (3 mL) in an ice bath was added mono-ethyl chlorooxoacetate (180 mg, 1.32 mmol). The reaction solution was stirred at room temperature for 0.5 hours, then quenched with water (10 mL) and extracted with ethyl acetate (3 mL). The combined organic layers were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to obtain crude **Intermediate 1102-1** (250 mg, 0.76 mmol, 69.43% yield) as a yellow oil. The crude product was used directly in the next step without further purification.

Step 2

A solution of **Intermediate 1102-1** (200 mg, 0.61 mmol) in tetrahydrofuran (1 mL) and ammonia-methanol (1 mL, 7M) was stirred at room temperature for 2 hrs. The reaction solution was concentrated under reduced pressure. The crude product was purified by column chromatography (dichloromethane/methanol = 10/1) to obtain **Intermediate 1102-2** as a yellow solid (160 mg, 0.54 mmol, 87.79% yield).

Step 3

To a solution of **Intermediate 1102-2** (100 mg, 0.37 mmol) in 1,4-dioxane (2 mL) were added **Intermediate 1102-3** (111 mg, 0.37 mmol), copper powder (5 mg, 0.07 mmol), cuprous iodide (105 mg, 0.55 mmol) and cesium carbonate (360 mg, 1.11 mmol) at room temperature under nitrogen atmosphere and the reaction solution was stirred at 100°C for 10 hours. Water (10 mL) was added to the reaction solution, and the mixture was extracted with ethyl acetate (5 mL). The combined organic layers were washed with saturated brine (10 mL) and dried over anhydrous sodium sulfate. After concentrated under reduced pressure, the obtained residue was purified by column chromatography (ethyl acetate/petroleum ether = 1/3) to obtain black liquid **Intermediate 1102-4** (0.1 g, 0.20 mmol, 55.29% yield).

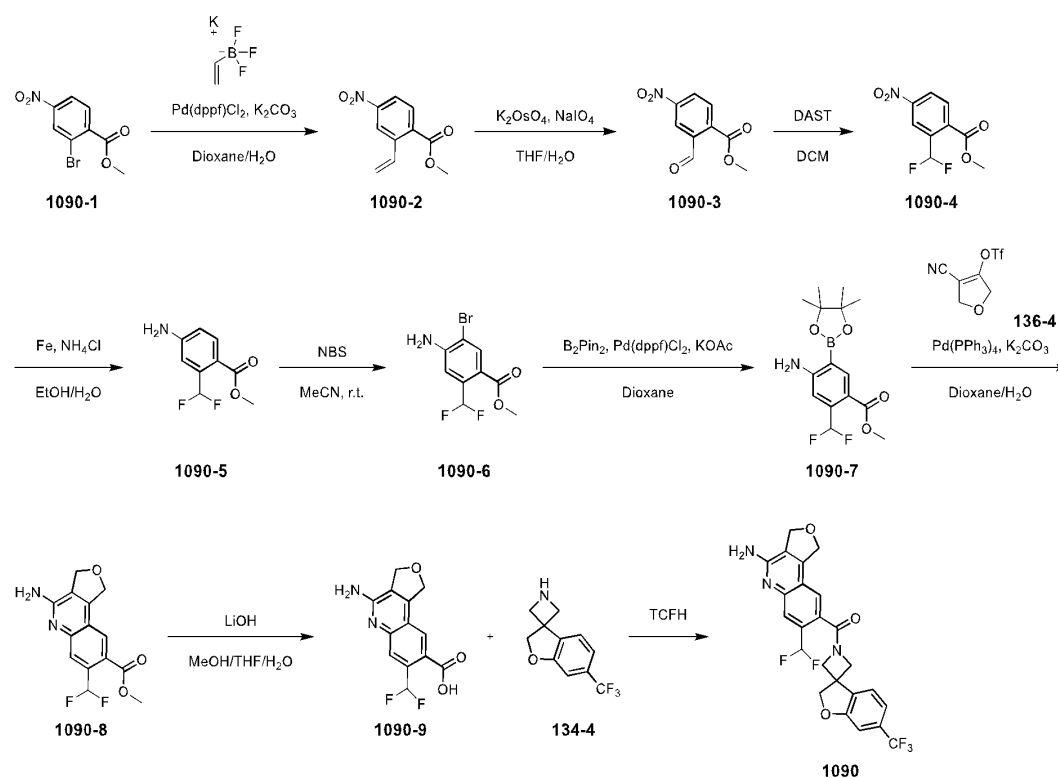
Step 4

At room temperature, a solution of **Intermediate 1102-4** (100 mg, 0.20 mmol) in trifluoroacetic acid (2 mL) was stirred at 80°C for 5 hours. The reaction solution was concentrated under reduced pressure, and the crude product was purified by HPLC (Waters-Xbridge-C18-10μm-19*250mm, mobile phase: A: 10mM NH₄HCO₃; B: ACN, gradient: 5-

21%, retention time: 9 min) was purified to obtain a white solid **Compound 1102** (13.23 mg, 0.03 mmol, 14.94% yield) MS m/z (ESI): 435.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 10.35 (s, 1H), 7.87 (d, $J = 7.6$ Hz, 1H), 7.81 (s, 1H), 7.35 – 7.28 (m, 1H), 7.14 (d, $J = 1.6$ Hz, 1H), 5.96 (s, 2H), 4.90 – 4.85 (m, 4H), 4.84 – 4.81 (m, 2H), 4.81 – 4.70 (m, 2H), 4.36 – 4.18 (m, 2H).

Example 32

Synthesis of Compound 1090



Step 1

To a solution of **Intermediate 1090-1** (10 g, 38.46 mmol) in water (40 mL) and dioxane (200 mL) were added potassium vinyltrifluoroborate (15 g, 111.98 mmol), $Pd(dppf)Cl_2$ (1.57 g, 1.92 mmol) and potassium carbonate (16 g, 115.77 mmol) and the mixture was stirred at 100 °C for 18 hours. After the reaction was completed, water (50 mL) was added and the aqueous layer was extracted with ethyl acetate (200 mL). The combined organic layers were washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column

chromatography (ethyl acetate: petroleum ether = 1:100 to 1:10) to obtain **Intermediate 1090-2** (7.6 g, 36.68 mmol, 95.39%) as a white solid.

Step 2

To a solution of **Intermediate 1090-2** (8.5 g, 41.03 mmol) in water (150 mL) and tetrahydrofuran (300 mL) were added potassium osmate dihydrate (0.76 g, 2.05 mmol), sodium periodate (35.10 g, 164.10 mmol), and the mixture was stirred at 25°C for 1 hour. After the reaction was completed, water (200 mL) was added and the aqueous layer was extracted with ethyl acetate (400 mL). The combined organic layers were washed with aqueous brine solution (200 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate: petroleum ether = 1:100 to 1:10) to obtain **Intermediate 1090-3** (5.8 g, 27.73 mmol, 67.59%) as a white solid.

Step 3

To a solution of **Intermediate 1090-3** (5.8 g, 27.73 mmol) in dichloromethane (100 mL) was added DAST (15 mL, 138.65 mmol) at -78 °C, and the reaction solution was slowly heated from -78 °C to room temperature then stirred for 2 hours. After the reaction was completed, water (50 mL) was added and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (ethyl acetate: petroleum ether = 1:100 to 1:10) to obtain white solid **Intermediate 1090-4** (6 g, 1.51 mmol, 5.46%)

Step 4

To solution of **Intermediate 1090-4** (6.1 g, 26.39 mmol) in ethanol (70 mL) and water (35 mL) were added iron powder (7.37 g, 131.95 mmol) and ammonium chloride (7.06 g, 131.95 mmol) and the reaction solution was stirred at 80°C for 2 hours. After that the reaction was completed, the reaction mixture was filtered through Celite while hot and the filter cake was washed with methanol. The filtrate was concentrated under reduced pressure, and the mixture was diluted with water (50 mL) and extracted with ethyl acetate (100 mL). The combined organic layers were washed with saturated brine (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude **Intermediate 1090-5**, which was directly used in the subsequent step.

Step 5

To a solution of **Intermediate 1090-5** (4.8 g, 23.86 mmol) in acetonitrile (100 mL) was added N-bromosuccinimide (4.25 g, 23.86 mmol), and the reaction solution was stirred at 20°C for 1 hour under nitrogen atmosphere protection. After the reaction was completed, water (30 mL) was added to the reaction solution, and the aqueous layer was extracted with ethyl acetate (60 mL). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (ethyl acetate: petroleum ether = 1:100 to 1:5) to obtain **Intermediate 1090-6** (5.8 g, 20.71 mmol, 86.79%) as a white solid.

Step 6

To a solution of **Intermediate 1090-6** (500 mg, 1.79 mmol) in dioxane (15 mL) were added bis(pinacolato)diboron (545 mg, 2.15 mmol), potassium acetate (525 mg, 5.35 mmol), and Pd(dppf)Cl₂ (145 mg, 0.18 mmol). The mixture was stirred at 100 °C for 1.5 h. After the reaction was completed, the reaction mixture was filtered through Celite while hot and the filter cake was washed with ethyl acetate. The filtrate was concentrated under reduced pressure to obtain crude **Intermediate 1090-7**, which was directly used in the next step.

Step 7

To solution of **Intermediate 136-4** (250 mg, 1.03 mmol) and **Intermediate 1090-7** (336 mg, 1.03 mmol) in water (1 mL) and dioxane (10 mL) were added tetrakis(triphenylphosphine) palladium (0) (115 mg, 0.10 mmol) and potassium carbonate (426 mg, 3.08 mmol) and the reaction solution was stirred at 80°C for 18 hours. After the reaction was completed, the reaction mixture was filtered through Celite while hot and washed with methanol/dichloromethane. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (dichloromethane: methanol = 100:1 to 10:1) to obtain **Intermediate 1090-8** (600 mg, 1.02 mmol, 99.16%) as a black solid.

Step 8

To a solution of **Intermediate 1090-8** (400 mg, 0.68 mmol) in tetrahydrofuran (2 mL) and water (2 mL) and methanol (2 mL) was added lithium hydroxide (90 mg, 3.76 mmol) and the mixture was stirred for 3 hours at 75 °C. After the reaction was completed, the pH of the reaction solution was adjusted to 3 with 2M dilute hydrochloric acid. The aqueous layer was

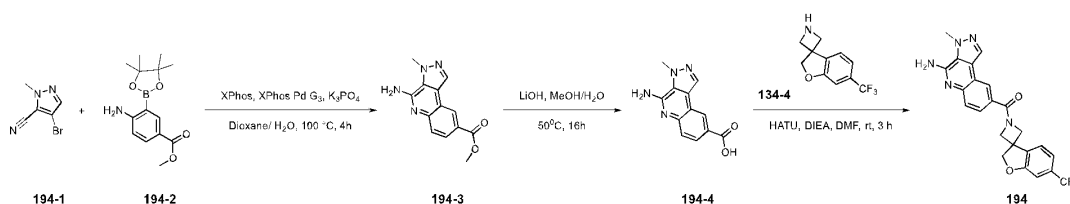
extracted with ethyl acetate (20 mL), and then the aqueous layer was lyophilized to obtain crude **Intermediate 1090-9**, which was used directly in the next step.

Step 9

To a solution of **Intermediate 1090-9** (200 mg, 0.23 mmol) in dimethyl sulfoxide (1 mL) were added **Intermediate 134-4** (74 mg, 0.32 mmol), 1-methylimidazole (0.14 mL, 1.71 mmol) and TCFH (90 mg, 0.32 mmol), and the mixture was stirred at 25 °C for 1 h. After the reaction was completed, the reaction solution was filtered and purified by Prep-HPLC (SunFire-C18-10μm-19*250mm, flow rate: 25 mL/min, mobile phase: A: 0.1% FA/H₂O B: ACN) to obtain white solid **Compound 1090** (46.3 mg, 0.09 mmol, 43.56%) MS m/z (ESI): 492.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.80 (d, *J* = 7.2 Hz, 2H), 7.75 (s, 1H), 7.54 – 7.21 (m, 2H), 7.15 (d, *J* = 1.6 Hz, 1H), 6.91 (s, 2H), 5.37 (t, *J* = 3.2 Hz, 2H), 5.02 (t, *J* = 3.2 Hz, 2H), 4.94 – 4.79 (m, 2H), 4.50 – 4.22 (m, 4H).

Example 33

Synthesis of Compound 194



Step 1

At room temperature, to a solution of **Intermediate 194-1** (137 mg, 0.74 mmol) in dioxane (3 mL) and water (0.3 mL) were added **Intermediate 194-2** (213 mg, 0.81 mmol), tripotassium phosphate (312 mg, 1.47 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (70 mg, 0.07 mmol) and XPhos Pd G3 (70 mg, 0.15 mmol) and the reaction solution was stirred at 100°C for 16 hours. After the reaction was completed, the reaction solution was filtered. The filtrate was added water (20 mL) and extracted with ethyl acetate (10 mL). The organic layers were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and the filtrate was concentrated under reduced pressure. The crude product was washed with dichloromethane (10 mL) to obtain **Intermediate 194-3** (80 mg, 0.31 mmol, 42.39% yield).

Step 2

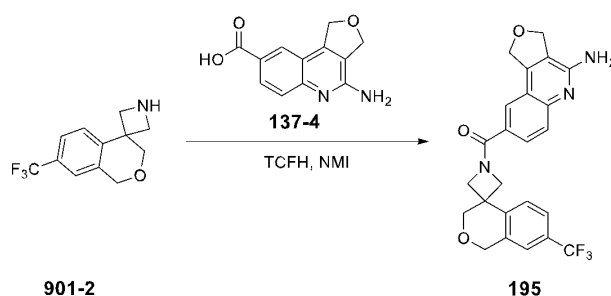
At room temperature, to a solution of **Intermediate 194-3** (60 mg, 0.23 mmol) in methanol (3 mL) and water (1 mL) was added lithium hydroxide (27 mg, 1.15 mmol) and the reaction solution was stirred at 50°C under nitrogen atmosphere for 16 hours. The reaction solution then was cooled to room temperature and concentrated under reduced pressure. 1M dilute hydrochloric acid was added to adjust the pH to 5 and the solid was collected and dried to obtain **Intermediate 194-4** (40 mg, 0.17 mmol, 70.52% yield).

Step 3

At room temperature, to a solution of **Intermediate 194-4** (60 mg, 0.25 mmol), **Intermediate 134-4** (57 mg, 0.25 mmol) in N,N-dimethylformamide (3 mL) were added N,N-diisopropylethylamine (90 mg, 0.74 mmol), hexafluorophosphate azabenzotriazole tetramethyl uronium (122 mg, 0.32 mmol) and the reaction solution was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, and the crude product was purified by Prep-HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10mM NH₄HCO₃; B: ACN, gradient: 5-70%, retention time: 8.1 min) to obtain **Compound 194** (6.6 mg, 0.01 mmol, 5.88% yield). MS m/z (ESI): 454.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 8.59 (s, 1H), 8.39 (d, J = 2.0 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.16 (t, J = 1.2 Hz, 1H), 6.96 (s, 2H), 4.89 (s, 2H), 4.83 – 4.62 (m, 2H), 4.46 – 4.24 (m, 5H).

Example 34

Synthesis of Compound 195



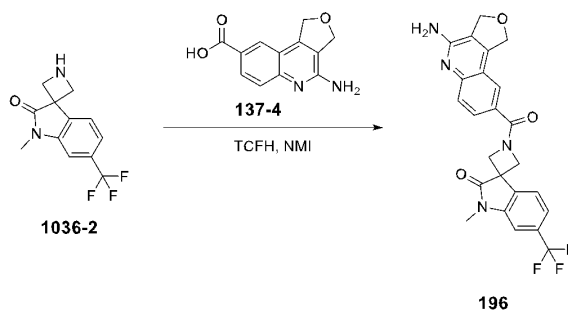
Step 1

Under nitrogen atmosphere protection, a solution of **Intermediate 137-4** (95 mg, 0.41 mmol), chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (173 mg,

0.62mmol), N-methyl imidazole (203 mg, 2.47mmol) in acetonitrile (2 mL) was stirred at room temperature for 30 minutes, then **Intermediate 901-2** (100 mg, 0.41mmol) was added to the reaction solution, and the mixture was stirred at room temperature for 16 hours. When the reaction is completed, the reaction solution was diluted with dimethyl sulfoxide (5 mL) and filtered. The filtrate was purified by Prep-HPLC (waters-xbridge-C18-10um-19*250mm, Mobile phase: 0.1% $\text{NH}_4\text{HCO}_3/\text{H}_2\text{O}$ B: CH_3CN , Gradient: 55% B - 85% B, Ret 9.5 min) to obtain **Compound 195** as a white solid (14.18 mg, 0.06 mmol, 14.94 % yield). MS m/z (ESI): 456.2 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.99 (d, $J = 8.4$ Hz, 1H), 7.88 – 7.79 (m, 2H), 7.73 – 7.66 (m, 1H), 7.61 – 7.53 (m, 1H), 7.49 (s, 1H), 6.78 (s, 2H), 5.37 (t, $J = 3.6$ Hz, 2H), 5.01 (t, $J = 3.6$ Hz, 2H), 4.81 (s, 2H), 4.63 – 4.37 (m, 2H), 4.28 – 4.00 (m, 4H).

Example 35

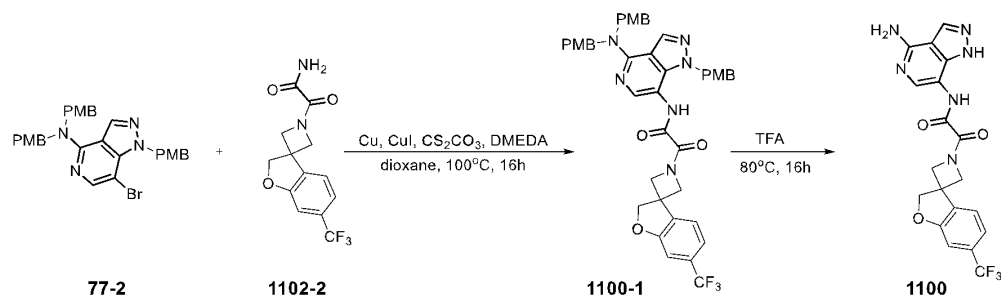
Synthesis of Compound 196



1H), 7.38 (s, 1H), 6.81 (s, 2H), 5.38 (s, 2H), 5.02 (s, 2H), 4.78 – 4.20 (m, 4H), 3.20 (s, 3H).

Example 36

Synthesis of Compound 1100

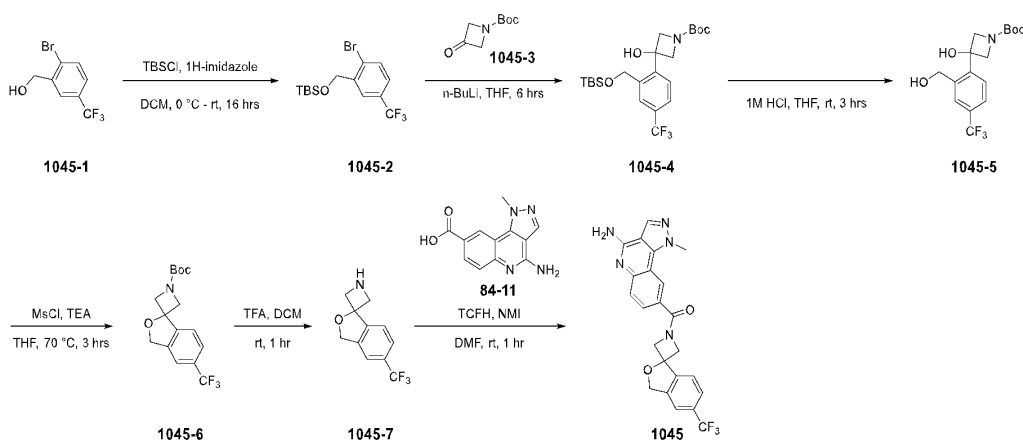


Step 1

To a solution of **Intermediate 77-2** (58 mg, 0.10 mmol) in dioxane (2 mL) were added **Intermediate 1102-2** (30 mg, 0.10 mmol), cesium carbonate (66 mg, 0.20 mmol), N,N'-dimethylethylenediamine (13 mg, 0.15 mmol), cuprous iodide (29 mg, 0.15 mmol), and copper powder (8 mg, 0.12 mmol) at room temperature. The reaction solution was stirred at 100°C for 16 hours under nitrogen atmosphere protection, then the reaction solution was concentrated under reduced pressure. The crude product was purified by column chromatography (dichloromethane/methanol = 18/1) to obtain **Intermediate 1100-1** (10.00 mg, 12.61 μmol , 12.47% yield) as a yellow solid.

Example 37

Synthesis of Compound 1045



Step 1

To a solution of compound 1045-1 (1.0 g, 3.92 mmol) and imidazole (590 mg, 8.63 mmol) in dichloromethane (10 mL) was added tert-butyldimethylsilyl chloride (710 mg, 4.71 mmol) at 0 °C. The mixture was slowly raised to room temperature and stirred for 16 hours. After the reaction was completed, the reaction solution was diluted with water (50 mL) and extracted with dichloromethane (30 mL). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 1/50) to obtain **Intermediate 1045-2** (1.4 g, 3.79 mmol, 96.68% yield) as a colorless oil.

Step 2

Under nitrogen atmosphere protection, to a solution of **Intermediate 1045-2** (1.0 g, 2.71 mmol) in tetrahydrofuran (15 mL) was added n-butyllithium solution (1.62 mL, 4.06 mmol) at -78 °C and stirred for 0.5 hours. Then **Intermediate 1045-3** (0.70 g, 4.06 mmol) in tetrahydrofuran (7 mL) was added to the reaction solution, and the mixture was stirred in a nitrogen atmosphere at room temperature for 6 hours. After the reaction was completed, the reaction solution was quenched with water (50 mL) and extracted with ethyl acetate (50 mL). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 1/4) to obtain **Intermediate 1045-4** (330 mg, 0.71 mmol, 26.40% yield) as a colorless oil.

Step 3

To a solution of **Intermediate 1045-4** (330 mg, 0.71 mmol) in tetrahydrofuran (15 mL) was added hydrochloric acid (7.15 mL, 7.15 mmol), and the mixture was stirred at room temperature for 3 hours. After the reaction was completed, the reaction solution was diluted with water (50 mL) and extracted with ethyl acetate (30 mL). The organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 1/4) to obtain colorless oily **Intermediate 1045-5** (200 mg, 0.58 mmol, 80.54% yield).

Step 4

To a solution of **Intermediate 1045-5** (150 mg, 0.43 mmol) in tetrahydrofuran (6 mL) were added triethylamine (87.4 mg, 0.86 mmol) and methanesulfonyl chloride (34.63 mg, 0.3 mmol), and the reaction solution was stirred at 70 °C for 3 hours. When the reaction was completed, the reaction solution was diluted with water (30 mL) and extracted with ethyl acetate (20 mL). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 1/4) to obtain **Intermediate 1045-6** (76 mg, 0.23 mmol, 53.44% yield) as a colorless oil.

Step 5

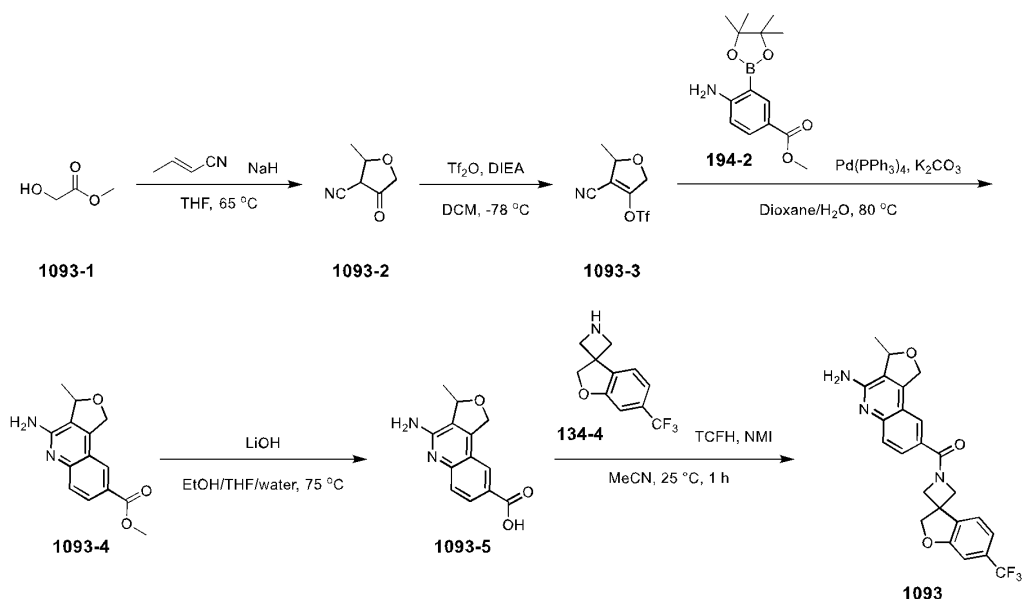
To a solution of **Intermediate 1045-6** (76 mg, 0.23 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (2 mL) and the reaction solution was stirred at room temperature for 30 minutes. After the reaction was completed, the reaction solution was concentrated under reduced pressure to obtain crude **Intermediate 1045-7** (50 mg) which was directly used in the subsequent step.

Step 6

To a solution of **Intermediate 1045-7** (50 mg, 0.23 mmol) and **Intermediatae 84-11** (50 mg, 0.23 mmol) in N,N-dimethylformamide (2 mL) were added N-methylimidazole (151 mg, 1.83 mmol) and chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (128 mg, 0.46 mmol). The reaction solution was stirred at room temperature for 1 hour. After the reaction was completed, the reaction solution was concentrated under reduced pressure, and the obtained residue was dissolved in dimethyl sulfoxide (3 mL) and filtered. The filtrate was purified by Prep-HPLC (mobile phase: A: 0.1% FA; B: ACN, gradient: 16- 56%, retention time: 9.2 min) to obtain **Compound 1045** as a white solid (31.4 mg, 0.07 mmol, 31.74 %yield) MS *m/z* (ESI): 453.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.53 (d, *J* = 2.0 Hz, 1H), 8.27 (s, 1H), 7.93 – 7.86 (m, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.75 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.29 (s, 2H), 5.17 (s, 2H), 4.80 – 4.45 (m, 4H), 4.43 (s, 3H).

Example 38

Synthesis of Compound 1093



Step 1

To a solution of sodium hydride (2.23 g, 55.85 mmol, 60%) in tetrahydrofuran (100 mL) was added **Intermediate 1093-1** (8.6 mL, 111.70 mmol) under nitrogen atmosphere protection at room temperature, and then crotononitrile (11 mL, 134.45 mmol) was slowly dripped into the reaction solution at 65 °C. The reaction continued under stirring at 65 °C for 2 hours. After the reaction was completed, the reaction was cooled and quenched with sodium hydroxide aqueous solution (50 mL, 2M), extracted with methyl tert-butyl ether (50 mL), and the aqueous phase was acidified with concentrated hydrochloric acid to pH~1 and then further extracted with dichloromethane (50 mL). The combined organic layers were washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 10:1) to obtain **Intermediate 1093-2** (3.4 g, 27.17 mmol, 24.33%) as a colorless oil.

Step 2

To a solution of **Intermediate 1093-2** (3.5 g, 27.97 mmol) and diisopropylethylamine (9.27 mL, 55.94 mmol) in dichloromethane (10 mL) was added trifluoromethanesulfonic anhydride (6.50 mL, 39.16 mmol) dropwise at -78 °C. The reaction solution was stirred at -78 °C for 2 hours. After the reaction was completed, the reaction was quenched with saturated aqueous sodium bicarbonate solution (50 mL) and extracted with dichloromethane (50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and

concentrated under reduced pressure to obtain crude **Intermediate 1093-3** (7.0 g, 27.22 mmol, crude) as a black solid, which was directly used in the subsequent step.

Step 3

A solution of **Intermediate 1093-3** (200 mg, 0.78 mmol), **Intermediate 194-2** (646.54 mg, 2.33 mmol), tetrakis(triphenylphosphine)palladium (0) (89.9 mg, 0.08 mmol), potassium carbonate (322.4 mg, 2.33 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was stirred at 90°C for 18 hours under nitrogen atmosphere protection. After the reaction was completed, the reaction solution was filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 2:1) to obtain **Intermediate 1093-4** (200 mg, 0.39 mmol, 49.79%) as a yellow solid.

Step 4

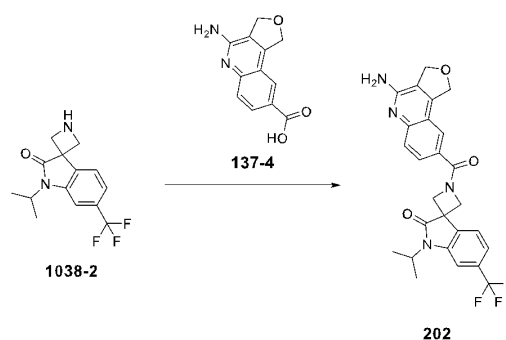
A solution of **Intermediate 1093-4** (180 mg, 0.70 mmol) and lithium hydroxide (69 mg, 2.86 mmol) in water (5 mL), tetrahydrofuran (5 mL) and ethanol (5 mL) was stirred at 75°C for 3 hours. After the reaction was completed, the reaction solution was quenched with hydrochloric acid (2.8 mL, 1M) and filtered, and the filter cake was dried under vacuum to obtain **Intermediate 1093-5** (80 mg, 0.33 mmol, 47.00%) as a yellow solid.

Step 5

To a solution of **Intermediate 1093-5** (70 mg, 0.29 mmol), chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (120 mg, 0.43 mmol), and *N*-methylimidazole (0.11 mL, 1.43 mmol) in acetonitrile (7 mL) was added **Intermediate 134-4** (120 mg, 0.52 mmol) at room temperature and the solution was stirred for 1 hour. After the reaction was completed, the reaction solution was concentrated and diluted with dimethyl sulfoxide (3 mL). The crude product was purified by HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium bicarbonate/water B: acetonitrile; flow rate: 25;) to obtain **Compound 1093** (16.98 mg, 0.04 mmol, 12.46%) as a white solid. MS *m/z* (ESI): 455.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.88 – 7.79 (m, 3H), 7.60 – 7.53 (m, 1H), 7.38 – 7.31 (m, 1H), 7.16 (d, *J* = 1.6 Hz, 1H), 6.70 (s, 2H), 5.47 – 5.25 (m, 3H), 4.88 (s, 2H), 4.66 (br s, 2H), 4.35 – 4.27 (m, 2H), 1.41 (d, *J* = 6.0 Hz, 3H)

Example 39

Synthesis of Compound 202

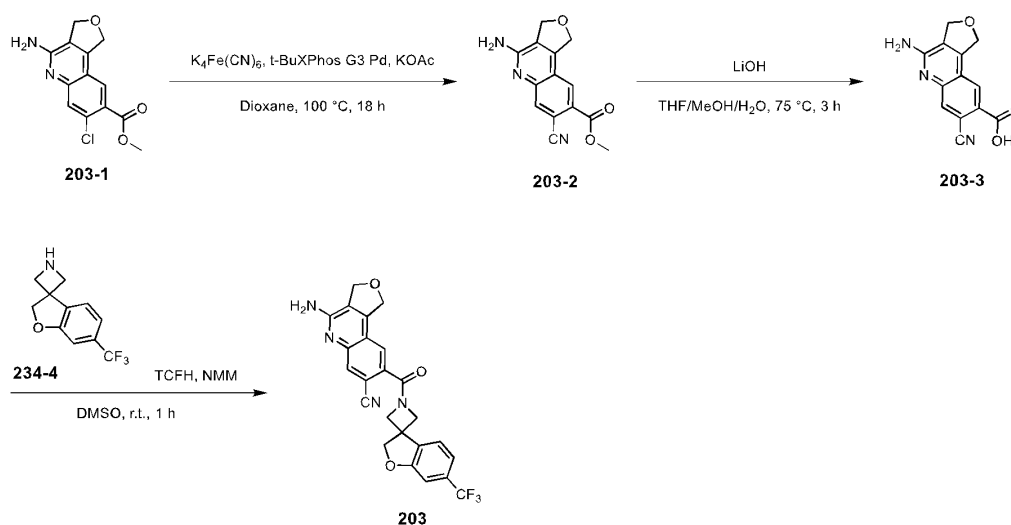


Step 1

To a solution of **Intermediate 1038-2** (50 mg, 0.22 mmol), chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (75 mg, 0.27 mmol), and *N*-methylimidazole (0.04 mL, 0.53 mmol) in acetonitrile (5 mL) was added **Intermediate 137-4** (50 mg, 0.18 mmol) at room temperature and stirred for 2 hours. After the reaction was completed, the reaction solution was concentrated and diluted with dimethyl sulfoxide (3 mL). The crude product was purified by Prep-HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium bicarbonate/water B: acetonitrile; flow rate: 25) to obtain **Compound 202** (13.02 mg, 0.03 mmol, 14.91%) as a white solid. MS *m/z* (ESI): 497.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.97 (d, *J* = 7.6 Hz, 1H), 7.89 – 7.81 (m, 2H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 1.6 Hz, 1H), 6.80 (s, 2H), 5.38 (t, *J* = 3.6 Hz, 2H), 5.02 (t, *J* = 3.6 Hz, 2H), 4.73 – 4.69 (m, 1H), 4.61 – 4.47 (m, 2H), 4.36 – 4.23 (m, 2H), 1.42 (d, *J* = 6.8 Hz, 6H).

Example 40

Synthesis of Compound 203



Step 1

To a solution of Intermediate **203-1** (180 mg, 0.39 mmol) in dioxane (2 mL) were added potassium ferrocyanide (145 mg, 0.39 mmol), potassium acetate (95 mg, 0.97 mmol), tBuXPhos (32 mg, 0.08 mmol) and tBuXPhos-Pd-G3 (46 mg, 0.06 mmol) and the solution was stirred at 100°C for 18 hours. After the reaction was completed, the reaction solution was cooled to room temperature and then filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (dichloromethane: methanol = 100:1 to 10:1) to obtain **Intermediate 203-2** (100 mg, 0.37 mmol, 95.83%) as a white solid.

Step 2

To a solution of **Intermediate 203-2** (80 mg, 0.30 mmol) in tetrahydrofuran (2 mL), water (2 mL) and methanol (2 mL) was added lithium hydroxide (45 mg, 1.88 mmol), and the reaction solution was stirred at 75 °C for 3 hours. After reaction was completed, the pH of the reaction solution was adjusted to 3 with dilute hydrochloric acid (2M). The aqueous layer was extracted with ethyl acetate (20 mL), and then the aqueous layer was lyophilized to obtain the crude **Intermediate 203-3**, which was directly used in the subsequent step.

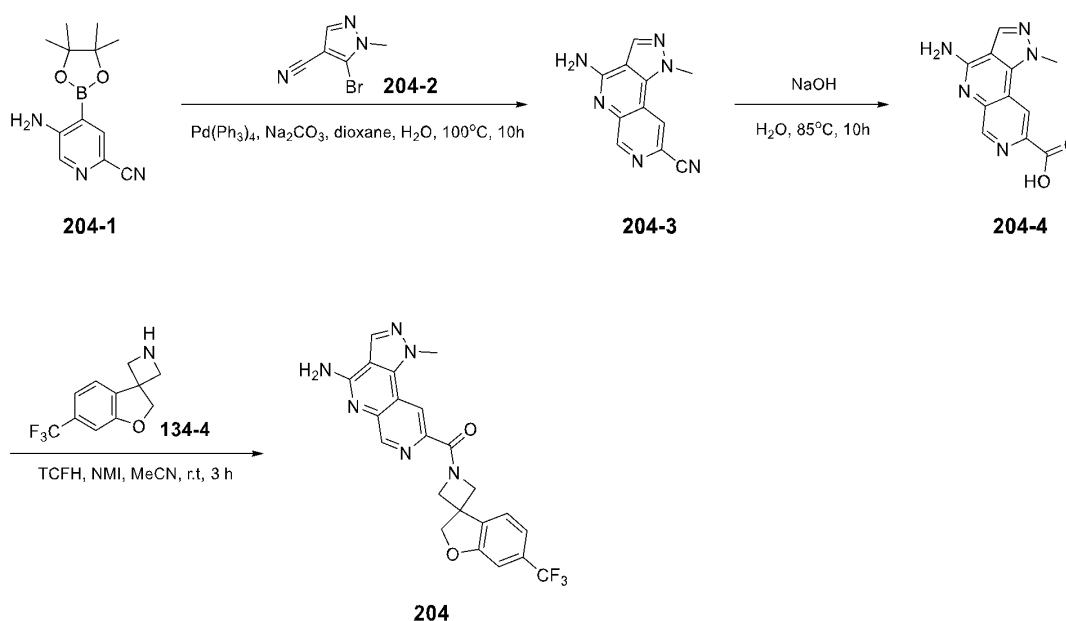
Step 3

To a solution of **Intermediate 203-3** (90 mg, 0.09 mmol) in dimethyl sulfoxide (1 mL) were added **Intermediate 134-4** (30 mg, 0.13 mmol), chloro-*N,N,N',N'*-

tetramethylformamidine hexafluorophosphate (37.10 mg, 0.13 mmol) and N-methylimidazole (43 mg, 0.53 mmol), and the reaction solution was stirred at 25°C for 1 hour. After reaction was completed, the crude product was purified by Prep-HPLC (SunFire-C18-10 μ m-19*250mm, flow rate: 25 mL/min, mobile phase: A: 0.1% FA/H₂O B: ACN) to obtain **Compound 203** (5.38 mg, 0.01 mmol, 11.91%) as a light yellow solid. MS m/z (ESI): 467.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.03 (s, 1H), δ 7.94 – 7.79 (m, 2H), 7.43 – 7.33 (m, 1H), 7.20 – 7.07 (m, 3H), 5.44 – 5.35 (m, 2H), 5.03 (t, *J* = 3.6 Hz, 2H), δ 4.94 – 4.80 (m, 2H), 4.51 (s, 2H), 4.36 (dd, *J* = 10.4, 49.2 Hz, 2H).

Example 41

Synthesis of Compound 204



Step 1

At room temperature, to a solution of **Intermediate 204-1** (500 mg, 2.04 mmol) in dioxane (5 mL) and water (0.5 mL) were added **Intermediate 204-2** (380 mg, 2.04 mmol), tetrakis(triphenylphosphine)palladium (0) (236 mg, 0.2 mmol) and potassium carbonate (0.56 g, 4.08 mmol) at 100 °C for 10 hours under nitrogen atmosphere. Then the reaction solution was cooled to room temperature, and solid precipitated. The mixture was filtered, and the filter cake was washed with water (10 mL) and dried to obtain **Intermediate 204-3** (200 mg, 0.89 mmol, 43.72% yield).

Step 2

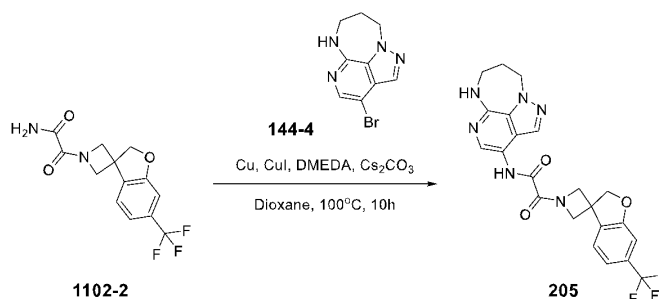
A solution of **Intermediate 204-3** (200 mg, 0.89 mmol) and sodium hydroxide (143 mg, 3.57 mmol) in water (2 mL) was stirred at 85 °C for 10 hours. After the reaction solution was cooled to room temperature, diluted hydrochloric acid (1 M) was added to adjust pH to 3 and solid precipitated. The mixture was filtered and the filter cake was dried to obtain crude **Intermediate 204-4** (150 mg, 0.62 mmol, 69.14% yield) which was directly used in the subsequent step.

Step 3

At room temperature, to a solution of **Intermediate 204-4** (100 mg, 0.41 mmol) and **Intermediate 134-4** (94 mg, 0.41 mmol) in acetonitrile (2 mL) were added chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (172 mg, 0.61 mmol) and *N*-methylimidazole (236 mg, 2.87 mmol). The reaction solution was stirred at room temperature for 2 hours then quenched with water (10 mL) and extracted with ethyl acetate (5 mL). The combined organic layers were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by Prep-HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10mM FA; B: ACN, gradient: 10-60%, retention time: 10 min) to obtain the **Compound 204** (2.36 mg, 0.01mmol, 1.26% yield) MS *m/z* (ESI): 454.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.84 (s, 1H), 8.72 (s, 1H), 8.37 (s, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.57 (s, 2H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.16 (s, 1H), 4.99 (d, *J* = 10.4 Hz, 1H), 4.94 – 4.86 (m, 3H), 4.46 (s, 3H), 4.42 (d, *J* = 10.0 Hz, 1H), 4.32 (d, *J* = 10.0 Hz, 1H).

Example 42:

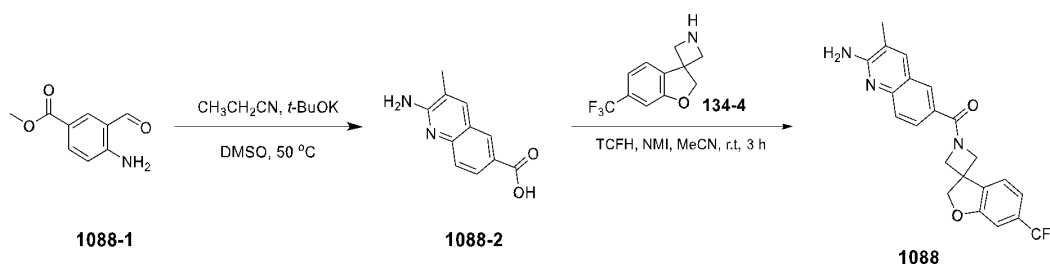
Synthesis of Compound 205



At room temperature, to a solution of **Compound 1102-2** (100 mg, 0.33 mmol) 1,4-dioxane (2 mL) were added **Compound 144-4** (84 mg, 0.33 mmol), copper powder (4.0 mg, 0.06 mmol), cuprous iodide (90 mg, 0.06 mmol) and cesium carbonate (311 mg, 0.96 mmol). The atmosphere was purged with nitrogen three times and stirred at 100 °C for 10 hours. The reaction solution was added with water (10 mL) and extracted with ethyl acetate (5 mL). The collected organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10mM NH₄HCO₃; B: ACN, gradient: 5-85%, retention time: 7 min) to obtain **Compound 205** (18.27 mg, 0.04 mmol, 11.61% yield). MS m/z (ESI): 472.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-_d6) δ 10.52 (s, 1H), 7.96 (s, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.71 (s, 1H), 7.33 (d, *J* = 1.6, 8.4 Hz, 1H), 7.22 (t, *J* = 3.2 Hz, 1H), 7.15 (d, *J* = 1.6 Hz, 1H), 4.89 (s, 2H), 4.86 – 4.75 (m, 2H), 4.49 – 4.42 (m, 2H), 4.39 – 4.22 (m, 2H), 3.46 – 3.38 (m, 2H), 2.22 – 2.15 (m, 2H).

EXAMPLE 43:

Synthesis of Compound 1088



Step 1;

At 0°C and under nitrogen atmosphere, to a solution of propionitrile (7.9 mL, 112 mmol) in DMSO (80 mL) was added a solution of potassium tert-butyl oxide in tetrahydrofuran (112 mL, 112 mmol, 1.0 M). The mixture was stirred for 15 minutes, followed by addition of **Compound 1088-1** (10.0 g, 55.8 mmol), and then heated at 50 °C for 16 hours. The reaction mixture was cooled to room temperature, diluted with water (400 mL) and washed with ethyl acetate (800 mL). The pH of the aqueous layer was adjusted to close to 6.5 by using 1.5 M HCl solution. The solid obtained by filtering was washed with water (1000 mL) then with acetone (1000 mL), and dried under vacuum. The obtained solid was stirred in MTBE (1000 mL) for 12 h, filtered, and dried under vacuum to obtain **Compound 1088-2** (4.6 g, 22.8 mmol, 40.8%

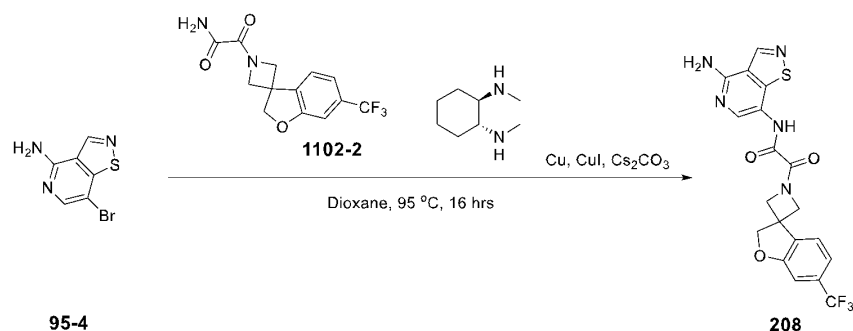
yield) as a brown solid.

Step 2;

Under nitrogen atmosphere, a solution of **Compound 134-4** (50 mg, 0.25 mmol), chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (104 mg, 0.37 mmol) and *N*-methylimidazole (99.65 μ L, 1.25 mmol) in acetonitrile (3 mL) was stirred at room temperature for 30 minutes, and then was added with **Compound 1088-2** (57 mg, 0.25 mmol). The mixture was stirred at room temperature for 3 hours. After the reaction was completed, the reaction solution was diluted with DMSO (5 mL) and filtered, and the solid was washed with DMSO (2 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by preparative HPLC (waters-xbridge-C18-10 μ m-19*250mm, Mobile phase: 0.1% $\text{NH}_4\text{HCO}_3/\text{H}_2\text{O}$ B: CH_3CN , Gradient: 55% B - 85% B, Ret 8.5 min) to obtain **Compound 1088** (16 mg, 0.03 mmol, 15.64%). 5.64%) as a white solid. MS m/z (ESI): 413.9 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.00 (d, $J = 2.0$ Hz, 1H), 7.89 – 7.80 (m, 2H), 7.75 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.47 (d, $J = 8.8$ Hz, 1H), 7.34 (d, $J = 7.6$ Hz, 1H), 7.16 (d, $J = 1.6$ Hz, 1H), 6.58 (s, 2H), 4.88 (s, 2H), 4.67 (s, 2H), 4.32 (d, $J = 44.3$ Hz, 2H), 2.22 (s, 3H).

Example 44:

Synthesis of Compound 208

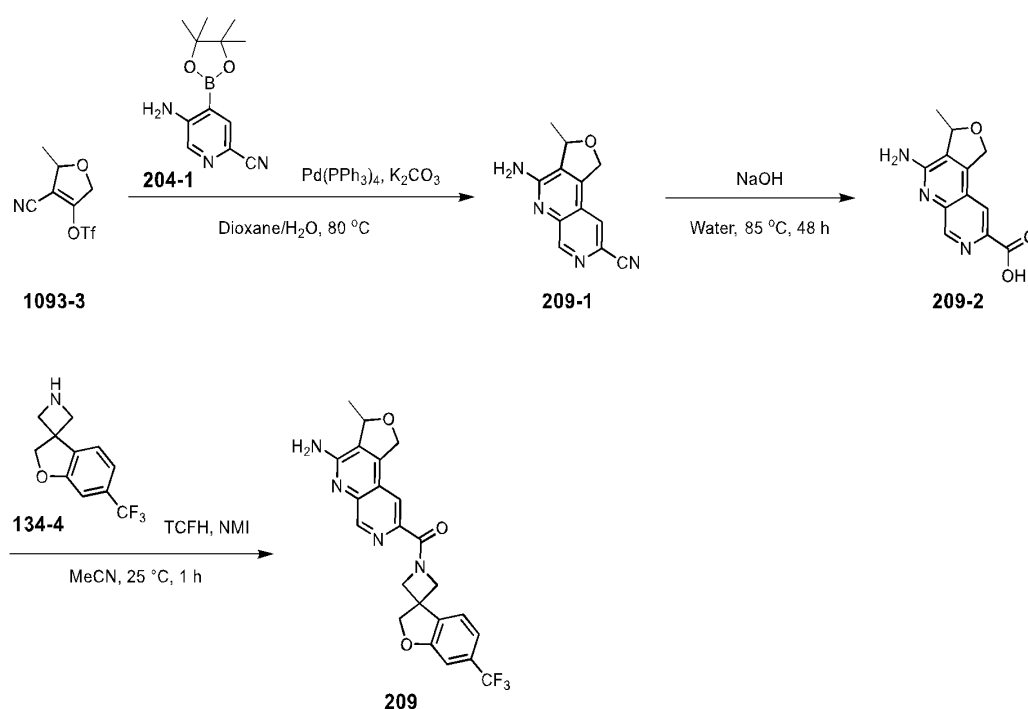


A solution of **Compound 95-4** (80 mg, 0.35 mmol), **Compound 1102-2** (104 mg, 0.35 mmol), copper powder (26 mg, 0.42 mmol), cuprous iodide (99 mg, 0.52 mmol), cesium carbonate (227 mg, 0.70 mmol) and (*R,R*)-(-)-*N,N'*-dimethyl-1,2-cyclohexanediamine (99 mg, 0.70 mmol) in 1,4-dioxane (1.5 mL) was purged with nitrogen three times, heated to 95 °C in a sealed tube and stirred for 16 hours. After the reaction solution was cooled to room

temperature, it was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by preparative HPLC (mobile phase: A: 10 mM NH_4HCO_3 ; B: ACN, gradient: 40-50%, retention time: 8.5 min) to obtain **Compound 208** (1.87 mg, 0.004 mmol, 1.2% yield) as a white solid. MS m/z (ESI): 450.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.93 (s, 1H), 9.20 (s, 1H), 7.94 – 7.88 (m, 2H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.19 (s, 2H), 7.15 (d, $J = 1.6$ Hz, 1H), 4.89 (s, 2H), 4.87 – 4.74 (m, 2H), 4.41 – 4.18 (m, 2H).

Example 45:

Synthesis of Compound 209



Step 1:

Compound 204-1 (200 mg, 0.82 mmol), **Compound 1093-3** (630 mg, 2.45 mmol), potassium carbonate (340 mg, 2.46 mmol) and tetrakis(triphenylphosphine) palladium (94 mg, 0.08 mmol) were dissolved in a mixed solution of water (1 mL) and 1,4-dioxane (10 mL). The mixture was stirred at $90\text{ }^\circ\text{C}$ under nitrogen atmosphere for 18 hours. After the reaction was completed, the reaction solution was filtered and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 1:1) to obtain compound 209-1 (200 mg, 0.44 mmol, 54.17% yield) as a yellow solid.

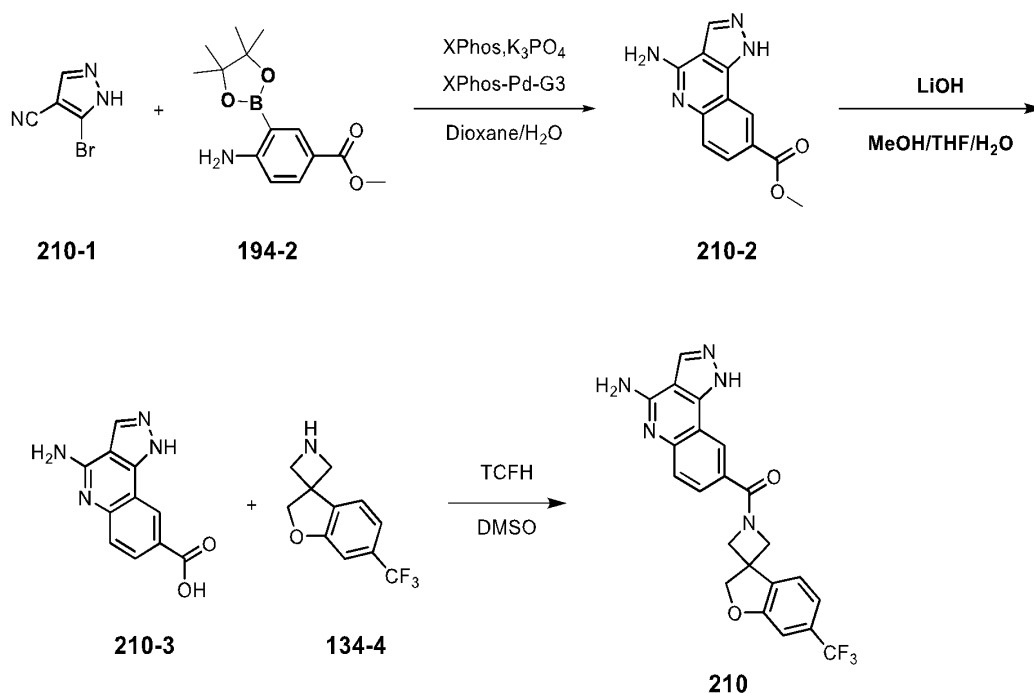
Step 2:

A solution of **Compound 209-1** (300 mg, 1.33 mmol) and sodium hydroxide (320 mg, 8.00 mmol) in water (10 mL) was stirred at 85 °C for 18 hours. After the reaction was completed, the reaction solution was filtered. The aqueous phase was acidified to pH = 4 with hydrochloric acid (1M) and filtered again. The filter cake was washed with water (10 mL) and dried under vacuum to obtain **Compound 209-2** (84 mg, 0.34 mmol, 25.83% yield) as a yellow solid.

Step 3:

A solution of **Compound 209-2** (100 mg, 0.41 mmol), Chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (172 mg, 0.61 mmol), and N-methylimidazole (0.10 mL, 1.22 mmol) in dimethylformamide (3 mL) was stirred at 25 °C for 10 minutes, added with **Compound 134-4** (200 mg, 0.87 mmol) and then stirred for 2 hours. After the reaction was completed, the reaction solution was filtered. The crude product was purified by preparative HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM formic acid/water B: acetonitrile; flow rate: 25;) to obtain **Compound 209** (1.56 mg, 0.00 mmol, 0.80%) as a white solid. MS m/z (ESI): 457.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.87 (s, 1H), 8.13 (s, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.33 – 7.22 (m, 3H), 7.16 (s, 1H), 5.52 – 5.32 (m, 3H), 5.00 – 4.80 (m, 4H), 4.41 (d, *J* = 10.4 Hz, 1H), 4.30 (d, *J* = 10.4 Hz, 1H), 1.43 (d, *J* = 6.0 Hz, 3H).

Example 46:**Synthesis of Compound 210**

**Step 1:**

To a solution of **Compound 210-1** (400 mg, 2.33 mmol) in water (2 mL) and dioxane (20 mL) were added **Compound 194-2** (2500 mg, 2.71 mmol), XPhos Pd G3 (195 mg, 0.23 mmol), XPhos (165 mg, 0.35 mmol) and potassium phosphate (1480 mg, 6.97 mmol). The mixture was stirred at 100°C for 18 hours. After the reaction was completed, the reaction solution was filtered through celite and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (dichloromethane: methanol = 100: 1 to 10: 1) to obtain **Compound 210-2** (900 mg, 1.86 mmol, 79.88%) as a black solid.

Step 2:

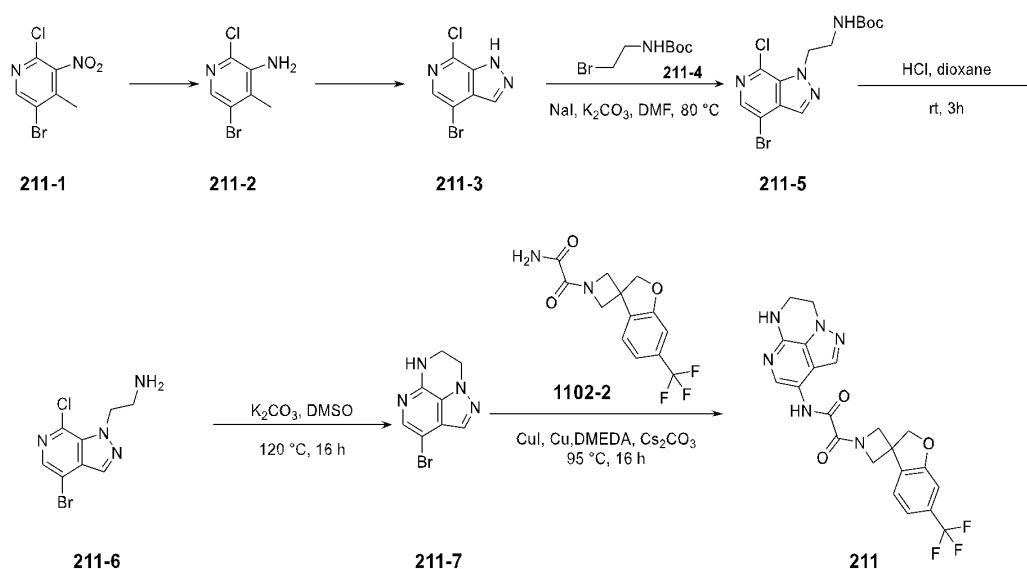
To a solution of **Compound 210-2** (800 mg, 1.65 mmol) in tetrahydrofuran (4 mL), water (45 mL) and methanol (4 mL) was added lithium hydroxide (400 mg, 9.53 mmol). The mixture was stirred at 75°C for 3 hours. After the reaction was completed, the pH of the reaction solution was adjusted to 3 with dilute hydrochloric acid (2M). The aqueous layer was washed with ethyl acetate (20 mL), and then lyophilized to obtain the crude product **Compound 210-3**, which was directly used in the subsequent step.

Step 3:

To a solution of **Compound 210-3** (500 mg, 0.44 mmol) in dimethyl sulfoxide (2 mL) were added **Compound 134-4** (150 mg, 0.65 mmol), TCFH (184 mg, 0.66 mmol), and 1-methylimidazole (210.00 μ L, 2.63 mmol). The mixture was stirred at 25°C for 1 hour. After the reaction was completed, the reaction solution was filtered and purified by HPLC (SunFire-C18-10 μ m-19*250mm, flow rate: 25 mL/min, mobile phase: A: 10 mM NH_4HCO_3 / H_2O B: ACN) to obtain compound 210 (2.1 mg, 0.00 mmol, 1.09% yield) as a white solid. MS m/z (ESI): 440.2 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.50 (d, J = 2.0 Hz, 1H), 8.32 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.81 (dd, J = 2.0, 8.8 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.22 (s, 2H), 7.17 (s, 1H), 4.88 (s, 2H), 4.77 – 4.70 (m, 2H), 4.41 – 4.31 (m, 2H).

Example 47:

Synthesis of Compound 211



Step 1:

To a solution of **Compound 211-1** (25.0 g, 99.42 mmol) in methanol (250 mL) and water (25 mL) were added ammonium chloride (53.2 g, 994.19 mmol) and iron powder (27.3 g, 55.84 mmol). The mixture was purged with nitrogen three times, and was stirred at 80 °C for 5 hours. The reaction solution was filtered. The filtrate was added with water (200 mL) and extracted with ethyl acetate (150 mL). The collected organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate =

5/1) to obtain **Compound 211-2** (20.1 g, 90.75 mmol, 91.28% yield) as a white solid.

Step 2:

At room temperature, to a solution of **Compound 211-2** (19.0 g, 85.79 mmol) in chloroform (250 mL) were added potassium acetate (8.4 g, 85.79 mmol) and acetic anhydride (13.1 g, 128.68 mmol) under stirring. The reaction solution was purged with nitrogen three times and then stirred at 65 °C for 2 hours. The reaction solution was cooled to 0 °C, and added with isoamyl nitrite (10.05 g, 85.79 mmol) and 1,4,7,10,13,16-hexaoxacyclooctadecane (2.72 g, 10.29 mmol) and then stirred at 65 °C for 18 hours. The reaction solution was cooled to room temperature, adjusted its pH to 7 with a saturated aqueous solution of sodium bicarbonate, and extracted with dichloromethane (150 mL). The collected organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 2/1) to obtain a yellow solid compound, which was washed with (petroleum ether/dichloromethane = 15/1, 200 mL) to obtain **Compound 211-3** (14.0 g, 60.22 mmol, 70.20 % yield) as a white solid.

Step 3:

At room temperature, to a solution of **Compound 211-3** (300 mg, 1.29 mmol) and **Compound 211-4** (434 mg, 1.94 mmol) in N,N-dimethylformamide (7 mL) were added sodium iodide (193 mg, 1.29 mmol) and potassium carbonate (445 mg, 3.23 mmol). The mixture was stirred at 80°C for 3 hours. The reaction solution was diluted with water (20 mL) and extracted with ethyl acetate (15 mL). The collected organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to obtain **Compound 211-5** (150 mg, 0.40 mmol, 30.94% yield) as a white solid.

Step 4:

At room temperature, **Compound 211-5** (150 mg, 0.40 mmol) was added with a solution of hydrogen chloride and 1,4-dioxane (4.0 M, 5 mL). The reaction solution was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, diluted with water, adjusted to pH = 8 with saturated sodium bicarbonate solution, and then extracted with ethyl acetate (5 mL). The collected organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to obtain **Compound**

211-6 (130 mg, 0.47 mmol,) as a yellow solid, which was directly used in the subsequent step.

Step 5:

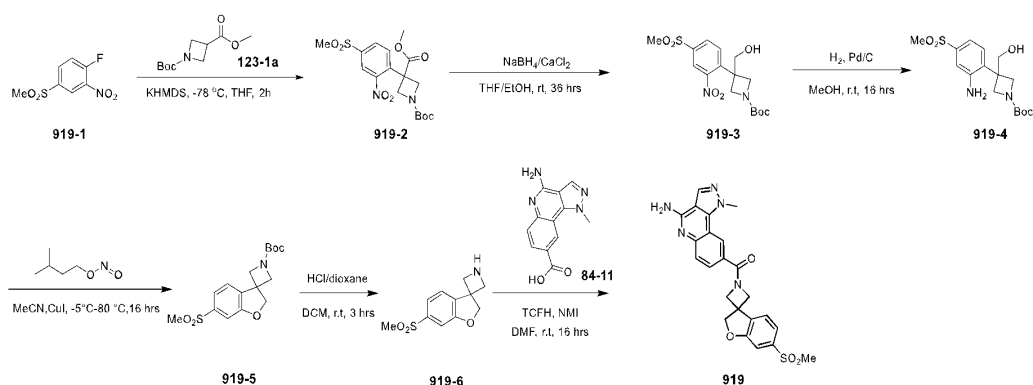
At room temperature, **Compound 211-6** (130 mg, 0.47 mmol) in dimethyl sulfoxide (5 mL) was added potassium carbonate (195 mg, 1.41 mmol). The reaction solution was purged with nitrogen three times, and then stirred at 120 °C for 16 hours. The reaction solution was added with water (20 mL) and extracted with ethyl acetate (10 mL). The collected organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to obtain **Compound 211-7** (60 mg, 0.25 mmol, 53.19% yield) as a white solid.

Step 6:

At room temperature, a mixture of **Compound 211-7** (60 mg, 0.25 mmol), **Compound 1102-2** (90 mg, 0.30 mmol), copper powder (19 mg, 0.30 mmol), cuprous iodide (95 mg, 0.50 mmol), cesium carbonate (245 mg, 0.75 mmol) and N,N'-dimethylethylenediamine (44 mg, 0.50 mmol) in 1,4-dioxane (3 mL) was stirred at 90 °C under nitrogen atmosphere for 16 hours. The reaction solution was filtered through celite, and the filtrate was purified by preparative HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10mM NH₄HCO₃; B: ACN, gradient: 40-50%, retention time: 8.5 min) to obtain **Compound 211** (1.79 mg, 0.004 mmol, 1.55% yield) as a white solid. MS m/z (ESI): 459.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.68 (s, 1H), 8.41 (s, 1H), 7.92 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.68 (s, 1H), 7.35 – 7.28 (m, 2H), 7.15 (s, 1H), 4.89 (d, *J* = 7.2 Hz, 2H), 4.86 – 4.77 (m, 2H), 4.41 – 4.34 (m, 3H), 4.26 (d, *J* = 10.8 Hz, 1H), 3.72 (s, 2H).

Example 48:

Synthesis of Compound 919



Step 1:

At -78°C and under nitrogen atmosphere, to a solution of **Compound 919-1** (25 g, 114 mmol) and **Compound 123-1a** (36.5 g, 1.71 mol) in THF (500 mL) was added dropwise KHMDS (342 mL). The mixture was reacted at -78°C for 1 hour and then heated to room temperature for 2 hours. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The collected organic layers were washed with brine (1000 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to obtain a crude product, which was further purified by reverse phase column chromatography (acetonitrile/water (trifluoroacetic acid 0.1%) = 35%) to obtain **Compound 919-2** (1.1 g, 2.65 mmol, 2.33% yield) as a yellow solid.

Step 2:

At 0°C and under nitrogen atmosphere, to a solution of **Compound 919-2** (110 mg, 2.65 mmol) and CaCl_2 (552 mg, 10.6 mmol) in THF (10 mL) and EtOH (5 mL) was added sodium borohydride (261 mg, 7.95 mmol). The mixture was stirred at 0°C for 0.5 hour and then heated to room temperature for 2 hours. The reaction was quenched with water and extracted with ethyl acetate (50 mL). The collected organic layers were washed with brine (70 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4/1) to obtain **Compound 919-3** (495 mg, 1.28 mmol, 48.03% yield) as a white solid.

Step 3:

Under nitrogen atmosphere, to a solution of **Compound 919-3** (495 mg, 1.28 mmol) in

methanol (5 mL) was added 10% Pd/C (50 mg). The mixture was stirred at room temperature for 2 hours. The reaction solution was filtered and concentrated to obtain **Compound 919-4** (440 mg, 1.25 mmol, 97.46% yield) as a white oil.

Step 4:

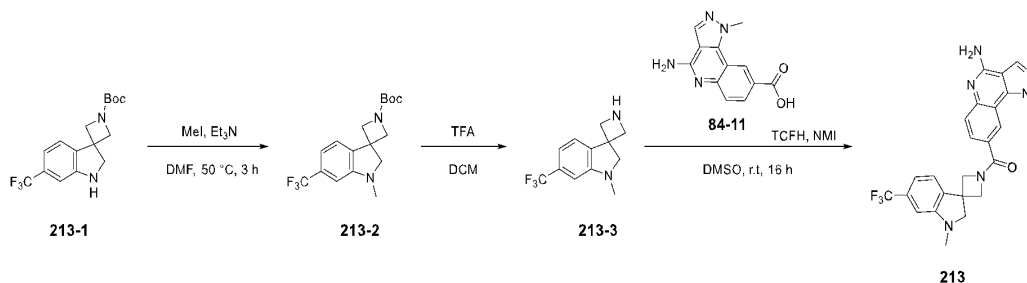
To a solution of **Compound 919-4** (440 mg, 1.25 mmol) and CuI (481 mg, 2.50 mmol) in MeCN (20 mL) was added dropwise isoamyl nitrite (177 mg, 1.51 mmol). The mixture was reacted at room temperature for 0.5 hour and then heated to 80 °C for 16 hours. The reaction solution was diluted with water and extracted with ethyl acetate. The collected organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to obtain **Compound 919-5** (230 mg, 0.68 mmol, 53.68% yield) as a colorless oil.

Step 5:

To a solution of **Compound 919-5** (495 mg, 1.28 mmol) in dichloromethane (5 mL) was added a solution of HCl and 1,4-dioxane (3 mL). The mixture was stirred at room temperature for 2 hours and then concentrated to obtain **Compound 919-6** (150 mg, 0.63 mmol, 92.50% yield) as a white solid.

Step 6:

To a solution of **Compound 919-6** (70 mg, 0.29 mmol) and **Compound 84-11** (84 mg, 0.35 mmol) in DMF (2 mL) were added TCFH (121 mg, 0.43 mmol) and N-methylimidazole (59 mg, 0.72 mmol). The mixture was reacted at room temperature for 16 hours. The reaction solution was diluted with water (20 mL) and extracted with ethyl acetate (30 mL). The collected organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by preparative TLC (dichloromethane/methanol = 10/1) and then by preparative HPLC (column: Welch ultimate XB-NH2 250*50*10um, mobile phase: [Heptane-EtOH(0.1%NH₃H:O)]; B% 10%-10%, 10 min) to obtain **Compound 919** (27.28 mg, 0.06 mmol, 20.37% yield). MS m/z (ESI): 464.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.53 – 8.51 (m, 1H), 8.26 (s, 1H), 7.95 – 7.90 (m, 1H), 7.85 (s, 1H), 7.62 – 7.59 (m, 1H), 7.57 – 7.53 (m, 1H), 7.32 – 7.31 (m, 1H), 7.24 (s, 2H), 4.92 (s, 2H), 4.75 (brs, 2H), 4.42 (s, 4H), 4.36 – 4.28 (m, 1H), 3.21 (s, 3H).

Example 49:**Synthesis of Compound 213****Step 1:**

To a solution of **Compound 213-1** (48 mg, 0.15 mmol) and triethylamine (0.06 mL, 0.44 mmol) in dimethylformamide (2 mL) was added iodomethane (0.05 mL, 0.73 mmol). The reaction solution was stirred at 50 °C for 3 hours. After the reaction was completed, the reaction solution was diluted with water (10 mL) and extracted with ethyl acetate (10 mL). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 6:1) to obtain **Compound 5** (60 mg, 0.15 mmol, 100.70% yield) as a white solid.

Step 2:

A solution of **Compound 213-2** (60 mg, 0.18 mmol) in dichloromethane (5 mL) and trifluoroacetic acid (1 mL) was stirred at 25 °C for 2 hours. Using TLC (dichloromethane: methanol = 20:1) to determine whether the reaction was completed and a new point appeared on the plate. The reaction solution was then concentrated to obtain a crude product **Compound 213-3** (60 mg, 0.17 mmol, 96.10% yield) as a red solid.

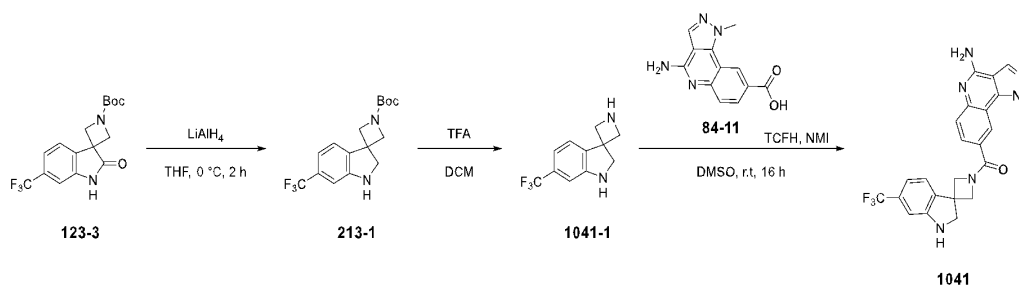
Step 3:

A solution of **Compound 84-11** (40 mg, 0.17 mmol), chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (70 mg, 0.25 mmol), and *N*-methylimidazole (0.05 mL, 0.66 mmol) in dimethyl sulfoxide (1 mL) was stirred at 25 °C for 10 minutes and then added with **Compound 213-3** (40.00 mg, 0.17 mmol). The mixture was stirred at 25 °C for 2 hours. After the reaction was completed, the reaction solution was filtered and purified by HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium

bicarbonate/water B: acetonitrile; flow rate: 25;) to obtain **Compound 213** (10.68 mg, 0.02 mmol, 13.86% yield) as a white solid. MS m/z (ESI): = 467.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 8.53 (d, J = 2.0 Hz, 1H), 8.27 (s, 1H), 7.88 (dd, J = 8.4, 2.0 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.24 (s, 2H), 7.03 (d, J = 7.6 Hz, 1H), 6.80 (s, 1H), 4.66 (s, 2H), 4.43 (s, 3H), 4.27 (d, J = 29.2 Hz, 2H), 3.71 (s, 2H), 2.81 (s, 3H).

Example 50:

Synthesis of Compound 1041



Step 1:

At 0 °C, to a solution of **Compound 123-3** (780 mg, 2.28 mmol) in tetrahydrofuran (50 mL) was added dropwise a solution of lithium aluminum tetrahydride in tetrahydrofuran (2.5N, 0.91 mL, 2.28 mmol). The reaction solution was stirred at 0 °C for 2 hours. After the reaction was completed, the reaction solution was quenched with sodium sulfate decahydrate and filtered. The organic layer was concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 5:1) to obtain **Compound 213-1** (140 mg, 0.43 mmol, 18.71% yield) as a white solid.

Step 2:

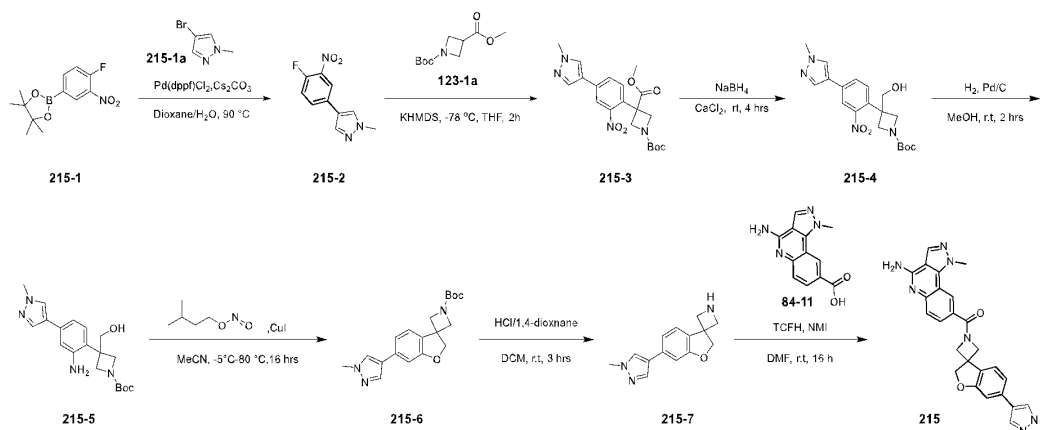
A solution of **Compound 213-1** (120 mg, 0.37 mmol) in dichloromethane (5 mL) and trifluoroacetic acid (1 mL) was stirred at 25 °C for 2 hours. Using TLC (dichloromethane: methanol = 20:1) to determine whether the reaction was completed and a new point appeared on the plate. The reaction solution was then concentrated to obtain a crude product **Compound 1041-1** (80 mg, 0.35 mmol, 95.91% yield) as a red solid.

Step 3:

A solution of **Compound 84-11** (100 mg, 0.41 mmol), chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (170 mg, 0.61 mmol) and *N*-methylimidazole (0.16 mL, 2.06 mmol) in dimethyl sulfoxide (1 mL) was stirred at 25 °C for 30 minutes, and then added with **Compound 1041-1** (100 mg, 0.44 mmol). The mixture was stirred at 25 °C for 2 hours. After the reaction was completed, the reaction solution was concentrated and dissolved in dimethyl sulfoxide (3 mL). The crude product was purified by HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium bicarbonate/water B: acetonitrile; flow rate: 25) to obtain **Compound 1041** (34.1 mg, 0.07 mmol, 18.12% yield) as a white solid. MS *m/z* (ESI): = 453.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.52 (d, *J* = 2.0 Hz, 1H), 8.27 (s, 1H), 7.87 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.23 (s, 2H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 1.6 Hz, 1H), 6.11 (s, 1H), 4.64 (s, 2H), 4.43 (s, 3H), 4.26 (s, 2H), 3.82 (d, *J* = 1.7 Hz, 2H).

Example 51:

Synthesis of Compound 215



Step 1:

To a solution of **Compound 215-1** (2 g, 7.49 mmol) and **Compound 215-1a** (1.81 g, 11.23 mmol) in 1,4-dioxane (40 mL) and water (10 mL) were added cesium carbonate (4.88 g, 14.98 mmol) and Pd(dppf)Cl₂ (0.55 g, 0.75 mmol). The mixture was reacted at 100 °C under nitrogen atmosphere for 3 hours. The reaction solution was diluted with water and extracted with ethyl acetate. The collected organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by column

chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to obtain **Compound 215-2** (1.1 g, 4.97 mmol, 66.41% yield) as a yellow solid.

Step 2:

At -78 °C and under nitrogen atmosphere, to a solution of **Compound 215-2** (1 g, 2.4 mmol) and **Compound 123-1a** (1.03 g, 4.8 mmol) in THF (50 mL) was added dropwise KMHDMS (7.2 mL). The mixture was reacted at -78 °C for 1 hour and then heated to room temperature for 2 hours. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The collected organic layers were washed with brine (1000 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by column chromatography on silica gel (SiO₂, PE/EA=3/1) to obtain a crude product, which was purified by liquid column chromatography (MeCN/H₂O(TFA 0.1%)=35%) to obtain **Compound 215-3** (143 mg, 0.36 mmol, 15.0% yield) as a yellow solid.

Step 3:

At 0 °C and under nitrogen atmosphere, to a solution of **Compound 215-3** (890 mg, 2.14 mmol) and CaCl₂ (948.75 mg, 8.55 mmol) in THF (10 mL) and EtOH (5 mL) was added sodium borohydride (242.55 mg, 6.41 mmol) batchwise. The mixture was stirred at 0 °C for 0.5 hour, and then heated to room temperature for 2 hours. The reaction was quenched with water and extracted with ethyl acetate (50 mL). The collected organic layers were washed with brine (70 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by column chromatography (PE/EA = 1/4) to obtain **Compound 215-4** (440 mg, 1.13 mmol, 53.0% yield) as a white solid.

Step 4:

Under nitrogen atmosphere, to a solution of **Compound 215-4** (440 mg, 1.13 mmol) in methanol (5 mL) was added Pd/C (50 mg). The mixture was stirred at room temperature for 2 hours. The reaction solution was filtered and concentrated to obtain **Compound 215-5** (348 mg, 0.97 mmol, 86.0% yield) as a white oil.

Step 5:

To a solution of **Compound 215-5** (348 mg, 0.97 mmol) and CuI (361 mg, 1.9 mmol) in MeCN (20 mL) was added dropwise isoamyl nitrite (133 mg, 1.14 mmol). The mixture was reacted at room temperature for 0.5 h and then heated to 80 °C for 16 h. The reaction solution

was diluted with water and extracted with ethyl acetate. The collected organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by column chromatography on silica gel (SiO₂, PE/EA=1/1) to obtain **Compound 215-6** (110 mg, 0.32 mmol, 33.97% yield) as a colorless oil.

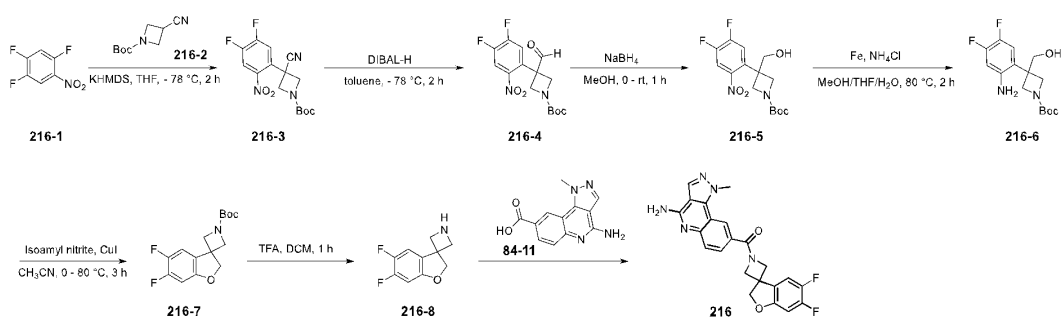
Step 6:

To a solution of **Compound 215-6** (110 mg, 0.32 mmol) in dichloromethane (5 mL) was added HCl in 1,4-dioxane (3 mL). The mixture was stirred at room temperature for 2 hours. The reaction solution was concentrated to obtain **Compound 215-7** (70 mg, 0.29 mmol, 90.62% yield) as a white solid.

Step 7:

To a solution of **Compound 215-7** (70 mg, 0.29 mmol) and **Compound 84-11** (84 mg, 0.29 mmol) in DMF (2 mL) were added TCFH (121 mg, 0.43 mmol) and N-methylimidazole (59 mg, 0.72 mmol). The mixture was reacted at room temperature for 16 hours. The reaction solution was diluted with water (20 mL) and extracted with ethyl acetate (30 mL). The collected organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by preparative TLC (dichloromethane/methanol = 10/1) and then by preparative HPLC (column: Welch ultimate XB-NH2 250*50*10um, mobile phase: [Heptane-EtOH(0.1%NH₃H:O)]; B% 10%-10%, 10 min) to obtain **Compound 215** (6.5 mg, 0.01 mmol, 4.81% yield). MS m/z (ESI): 466.0 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.52 (d, *J* = 2.0 Hz, 1H), 8.26 (s, 1H), 8.12 (s, 1H), 7.88 – 7.82 (m, 2H), 7.62 – 7.56 (m, 2H), 7.25 – 7.17 (m, 3H), 7.02 (d, *J* = 1.4 Hz, 1H), 4.80 (s, 2H), 4.70 (d, *J* = 15.3 Hz, 2H), 4.42 (s, 3H), 4.33 (d, *J* = 33.1 Hz, 2H), 3.84 (s, 3H).

Example 52:**Synthesis of Compound 216**

**Step 1:**

Under nitrogen atmosphere and at -78 °C, to a solution of **Compound 216-1** (20.0 g, 109.76 mmol) and **Compound 216-2** (19.4 g, 110 mmol) in tetrahydrofuran (100 mL) was added dropwise potassium bis(trimethylsilyl)amide (1.0 M, 165 mL, 165 mmol). After the addition was completed, the mixture was stirred at -78 °C for 2 hours. After the reaction was completed, the reaction solution was quenched with saturated ammonium chloride (100 mL), diluted with water (200 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4) to obtain **Compound 216-3** (3.22 g, 9.49 mmol, 8.65% yield) as a yellow oil.

Step 2:

Under nitrogen atmosphere and at -78 °C, to a solution of **Compound 216-3** (3.22 g, 9.49 mmol) in toluene (20 mL) was added diisobutylaluminum hydride (1.0 M, 28 mL, 28 mmol). The mixture was stirred at -78 °C for 2 hours. After the reaction was completed, the reaction solution was quenched with methanol (20 mL) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (methanol/dichloromethane = 1/10) to obtain **Compound 216-4** (1.5 g, 4.38 mmol, 46.18% yield) as a yellow solid.

Step 3:

At 0 °C, to a solution of **Compound 216-4** (1.5 g, 4.38 mmol) in methanol (20 mL) was added sodium borohydride (0.25 g, 6.57 mmol). The mixture was stirred at room temperature for 1 hour. After the reaction was completed, the reaction solution was quenched with saturated ammonium chloride (50 mL) and extracted with ethyl acetate (30 mL). The organic phase was

washed with brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4) to obtain compound 216-5 (150 mg, 0.44 mmol, 9.94% yield) as a yellow oil.

Step 4:

To a solution of **Compound 216-5** (150 mg, 0.44 mmol) in methanol (1.5 mL), tetrahydrofuran (1.5 mL) and water (1.5 mL) were added ammonium chloride (235 mg, 4.4 mmol) and iron powder (123 mg, 2.2 mmol). The mixture was stirred at 80 °C for 1 hour. After the reaction was completed, the reaction solution was filtered. The filtrate was diluted with water (30 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (methanol/dichloromethane = 1/10) to obtain **Compound 216-6** (140 mg, 0.23 mmol, 100% yield) as a white solid.

Step 5:

At 0 °C, to a solution of **Compound 216-6** (140 mg, 0.23 mmol) in acetonitrile (5 mL) were added cuprous iodide (170 mg, 0.89 mmol) and isoamyl nitrite (62 mg, 0.53 mmol). The reaction solution was stirred at 0 °C for 1 hour, and then heated to 80 °C for 2 hours. After the reaction was completed, the reaction solution was filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/3) to obtain **Compound 216-7** (17 mg, 0.06 mmol, 12.84% yield) as a light yellow oil.

Step 6:

To a solution of **Compound 216-7** (17 mg, 0.06 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL). The mixture was stirred at room temperature for 30 minutes. After the reaction was completed, the reaction solution was concentrated under reduced pressure to obtain a crude **Compound 216-8** (10 mg, crude), which was directly used in the subsequent step without further purification.

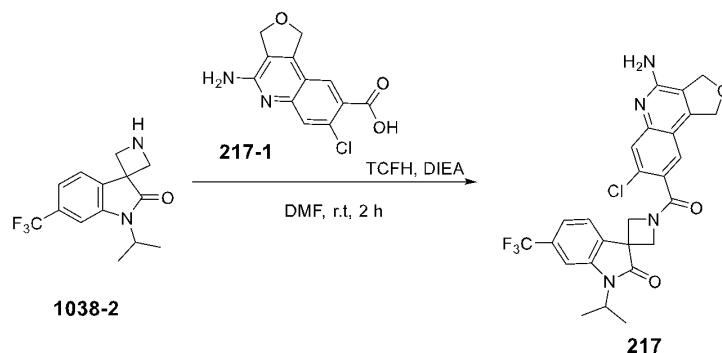
Step 7:

To a solution of **Compound 216-8** (10 mg, 0.05 mmol) and **Compound 84-11** (13 mg,

0.06 mmol) in *N,N*-dimethylformamide (1 mL) were added *N*-methylimidazole (25 mg, 0.3 mmol) and chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (21 mg, 0.08 mmol). The mixture was stirred at room temperature for 1 hour. After the reaction was completed, the reaction solution was filtered. The filtrate was purified by preparative HPLC (mobile phase: A: 0.1% FA; B: ACN, gradient: 16-56%, retention time: 9.2 min) to obtain **Compound 216** (13.53 mg, 0.03 mmol, 63.31% yield) as a white solid. MS *m/z* (ESI): 422.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO-*d*₆) δ 8.51 (d, *J* = 2.0 Hz, 1H), 8.28 (s, 1H), 8.14 (s, 0.6H), 7.93 – 7.74 (m, 2H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.40 – 7.20 (m, 2H), 7.01 – 6.97 (m, 1H), 4.86 (s, 2H), 4.70 (brs, 2H), 4.42 (s, 3H), 4.38 – 4.30 (m, 2H).

Example 53:

Synthesis of compound 217

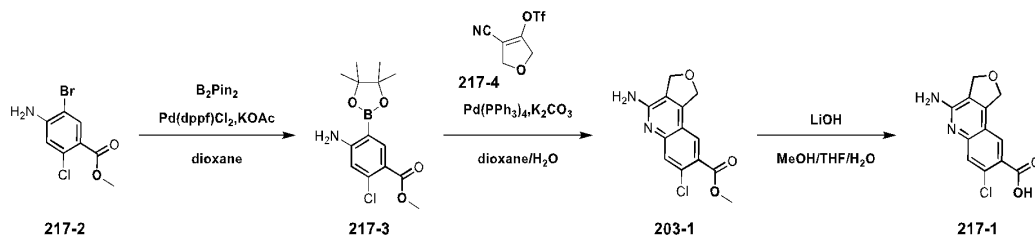


Step 1

A solution of **Intermediate 217-1** (50 mg, 0.19 mmol), *N,N,N',N'*-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate ("HATU") (110 mg, 0.29 mmol) and *N,N*-Diisopropylethylamine (0.16 mL, 0.94 mmol) dissolved in *N,N*-Dimethylformamide ("DMF") (1.5 mL) was stirred at 25°C for 10 minutes. **Intermediate 1038-2** (100 mg, 0.35 mmol) was then added to the solution and stirring continued for 2 hours at 25 °C. After the reaction was completed, the reaction solution was filtered. The crude product was separated by high-pressure liquid chromatography mass spectrometry (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium bicarbonate/water B: acetonitrile; flow rate: 25) to obtain **Compound 217** (35.35 mg, 0.07 mmol, 34.78%) as a white solid. MS *m/z* (ESI): = 530.9 $[M+H]^+$; 1H NMR (400 MHz, DMSO-*d*₆) δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.72 (s, 1H), 7.62 (s, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.41 (s, 1H), 6.90 (s, 2H), 5.36 (q, *J* = 3.2 Hz, 2H), 5.00 (t, *J* = 3.6 Hz, 2H), 4.54 (p, *J* = 6.8 Hz, 1H), 4.36 – 4.23 (m, 2H), 4.22 – 4.10 (m, 2H), 1.41 (d, *J* =

6.8 Hz, 6H).

Synthesis of Intermediate 217-1



Step 1:

To a solution of **Intermediate 217-2** (3.00 g, 11.34 mmol) in 1,4-dioxane (60 mL) were added bis(pinacolato)diboron (3.46 g, 13.61 mmol), potassium acetate (3.34 g, 34.03 mmol), and $Pd(dppf)Cl_2$ (0.5 g, 0.68 mmol). The mixture was stirred at 100 °C for 2 hours. After the reaction was completed, the reaction solution was filtered through celite and washed with ethyl acetate. The solvent was removed under reduced pressure to obtain crude **Intermediate 217-3** which was directly used in the subsequent step.

Step 2:

To a solution of **Intermediate 217-4** (1 g, 4.11 mmol) in 1,4-dioxane (60 mL) and water (4 mL) were added **Intermediate 217-3** (1.92 g, 6.17 mmol), tetrakis(triphenylphosphine)palladium (0.48 g, 0.41 mmol) and potassium carbonate (1.71 g, 12.34 mmol). The mixed solution was stirred and reacted at 80 °C for 18 hours. After the reaction was completed, the reaction solution was filtered through celite and washed with methanol and dichloromethane. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (dichloromethane: methanol = 100:1 to 10:1) to obtain **Intermediate 203-1** (1.1 g, 3.95 mmol, 95.98% yield) as a black solid.

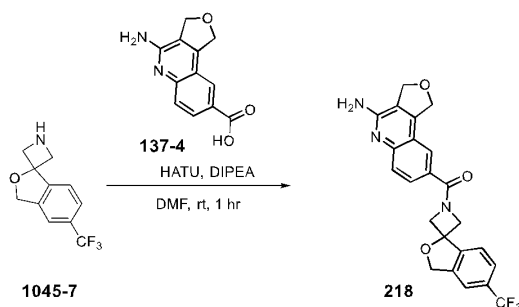
Step 3;

To a mixed solution of **Intermediate 203-1** (550 mg, 1.97 mmol) in tetrahydrofuran (5 mL), water (5 mL) and methanol (5 mL) was added lithium hydroxide (350 mg, 15.87 mmol). The mixture was stirred at 75 °C for 3 hours. After the reaction was completed, the reaction solution was adjusted to pH=3 with diluted hydrochloric acid (2 M). The aqueous layer was

washed with ethyl acetate (20 mL) and lyophilized to obtain crude **Intermediate 217-1**, which was directly used in the subsequent synthesis procedures.

Example 54:

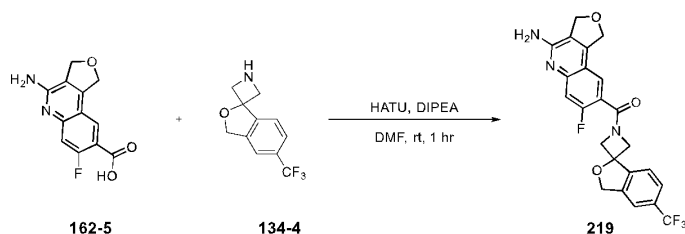
Synthesis of Compound 218



To a solution of **Intermediate 1045-7** (30 mg, 0.13 mmol) and **Intermediate 137-4** (30 mg, 0.13 mmol) in *N,N*-dimethylformamide (2 mL) were added HATU (74 mg, 0.2 mmol) and DIPEA (34 mg, 0.26 mmol). The reaction solution was stirred at room temperature for 1 hour, and then concentrated under reduced pressure after the reaction was completed. The residue was dissolved in dimethyl sulfoxide (3 mL) and filtered. The filtrate was purified by preparative HPLC (mobile phase: A: 0.1% NH_4HCO_3 ; B: ACN, gradient: 16-56%, retention time: 9.2 min) to obtain **Compound 218** (6.58 mg, 0.01 mmol, 11.44% yield) as a white solid. MS m/z (ESI): 442.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.96 – 7.81 (m, 3H), 7.81 – 7.73 (m, 2H), 7.59 – 7.54 (m, 1H), 6.78 (s, 2H), 5.42 – 5.34 (m, 2H), 5.15 (s, 2H), 5.08 – 4.97 (m, 2H), 4.82 – 4.31 (m, 4H).

Example 55:

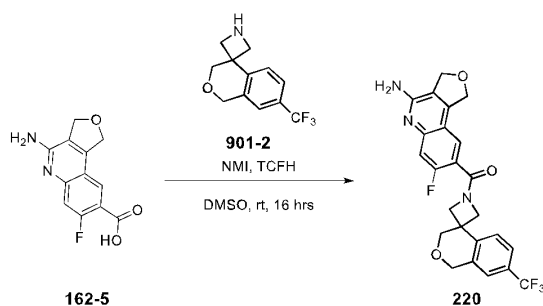
Synthesis of Compound 219



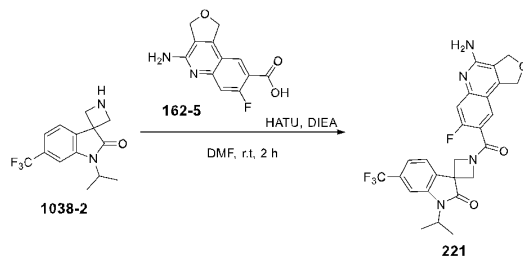
To a solution of **Intermediate 162-5** (30 mg, 0.13 mmol) and **Intermediate 134-4** (28 mg, 0.13 mmol) in *N,N*-dimethylformamide (2 mL) were added HATU (74 mg, 0.2 mmol) and DIPEA (34 mg, 0.26 mmol). The reaction solution was stirred at room temperature for 1 hour, and then concentrated under reduced pressure after the reaction was completed. The crude product was dissolved in dimethyl sulfoxide (3 mL) and filtered. The filtrate was purified by preparative HPLC (mobile phase: A: 0.1% NH_4HCO_3 ; B: ACN, gradient: 16-56%, retention time: 9.1 min) to obtain compound 219 (18.19 mg, 0.04 mmol, 30.48% yield) as a white solid. MS m/z (ESI): 460.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.84 – 7.80 (m, 1H), 7.78 – 7.71 (m, 2H), 7.63 (s, 1H), 7.36 – 7.31 (m, 1H), 5.45 – 5.41 (m, 2H), 5.24 – 5.16 (m, 2H), 5.12 – 5.08 (m, 2H), 4.54 (s, 1H), 4.52 – 4.49 (m, 2H), 4.45 (s, 1H).

Example 56:

Synthesis of Compound 220

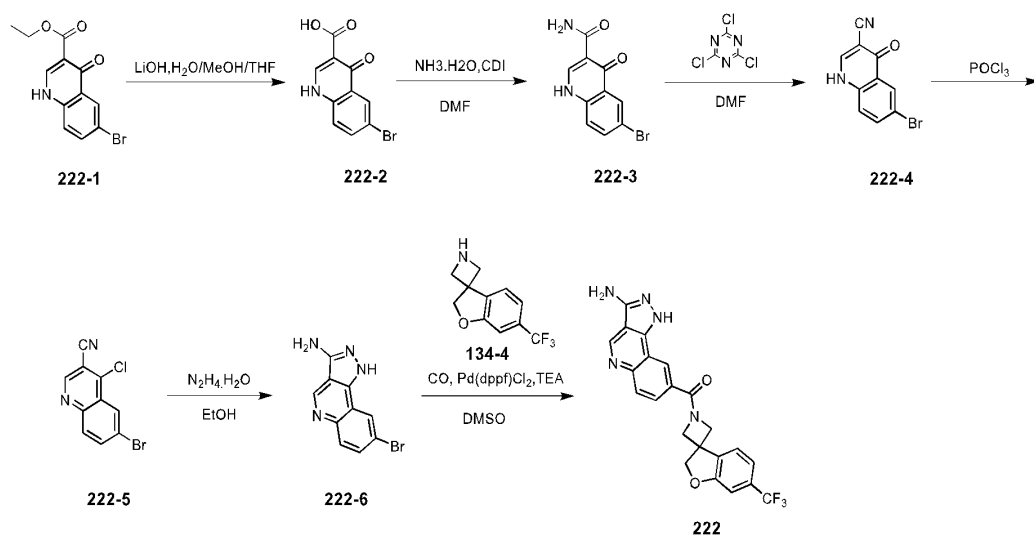


At room temperature, to a solution of **Intermediate 162-5** (50 mg, 0.20 mmol) and **Intermediate 901-2** (63 mg, 0.26 mmol) in dimethyl sulfoxide (2 mL) were added *N*-methylimidazole (82 mg, 1.01 mmol) and chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (113 mg, 0.40 mmol). The reaction solution was stirred at room temperature for 16 hours and then concentrated under reduced pressure. The crude product was purified by preparative HPLC (Waters-Xbridge-C18-10 μm -19*250mm, mobile phase: A: 10mM NH_4HCO_3 ; B: ACN, gradient: 5-70%, retention time: 8.1 min) to obtain **Compound 220** (12 mg, 0.03 mmol, 12.58% yield). MS m/z (ESI): 473.9 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.94 - 7.92 (m, 1H), 7.88 - 7.83 (m, 1H), 7.73 - 7.70 (m, 1H), 7.50 - 7.49 (m, 1H), 7.40 - 7.37 (m, 1H), 5.39 - 5.38 (m, 2H), 5.02 - 5.01 (m, 2H), 4.80 - 4.79 (m, 2H), 4.21 - 4.05 (m, 6H).

Example 57:**Synthesis of Compound 221**

A solution of **Intermediate 162-5** (50 mg, 0.20 mmol), HATU (120 mg, 0.32 mmol) and *N,N*-Diisopropylethylamine (0.18 mL, 1.01 mmol) in *N,N*-dimethylformamide (1 mL) was stirred at 25 °C for 10 minutes. **Intermediate 1038-2** (100 mg, 0.35 mmol) was further added, and stirring continued at 25 °C for 2 hours. After the reaction was completed, the reaction solution was filtered. The filtrate was purified by HPLC-MS (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM formic acid/water B: acetonitrile; flow rate: 25;) to obtain **Compound 221** (10 mg, 0.02 mmol, 9.58%) as a white solid. MS *m/z* (ESI): 515.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.41 (s, 1H), 7.31 (d, *J* = 12.4 Hz, 1H), 6.94 (s, 2H), 5.37 (d, *J* = 4.2 Hz, 2H), 5.00 (s, 2H), 4.60 – 4.45 (m, 1H), 4.39 – 4.22 (m, 4H), 1.41 (d, *J* = 6.8 Hz, 6H).

Example 58:**Synthesis of Compound 222**

**Step 1:**

To a solution of **Intermediate 222-1** (8.50 g, 28.70 mmol) in water (30 mL), methanol (30 mL) and tetrahydrofuran (30 mL) was added lithium hydroxide (4 g, 95.33 mmol). The mixture was stirred at 75 °C for 18 hours. After the reaction was completed, the reaction solution was adjusted to pH=3 with diluted hydrochloric acid (2 M) and solids formed in the solution. The solution was filtered. The filtered cake was washed with 100 mL of water and dried under vacuum to obtain the crude **Intermediate 222-2**, which was directly used in the subsequent step.

Step 2:

A solution of **Intermediate 222-2** (8 g, 29.84 mmol) and CDI (9.68 g, 59.69 mmol) in *N,N*-dimethylformamide (100 mL) was stirred at 65 °C for 2 hours. When the reaction solution was cooled to room temperature, it was added to aqueous ammonia (1500 mL, 33% purity) at 0 °C. The mixture was stirred at room temperature for 18 hours. After the reaction was completed, the reaction solution was concentrated under vacuum and filtered. The filter cake was washed with water (200 mL) and dried under vacuum to obtain **Intermediate 222-3**.

Step 3:

To a solution of **Intermediate 222-3** (8 g, 29.95 mmol) in *N,N*-dimethylformamide (100 mL) was added cyanuric chloride (3.3 g, 17.90 mmol). The mixture was stirred at 65 °C for 18 hours. After the reaction was completed, water (50 mL) was added. The solution was adjusted

to pH=9 with saturated sodium bicarbonate solution and then filtered. The filter cake was washed with water (200 mL) and dried under vacuum to obtain **Intermediate 222-4**.

Step 4:

A solution of **Intermediate 222-4** (7.5 g, 30.11 mmol) in phosphorus oxychloride (70 mL) solution was stirred at 100 °C for 18 hours. After the reaction was completed, the reaction solution was concentrated under vacuum, and then added with water (100 mL). The solution was adjusted to pH=9 with saturated sodium bicarbonate solution and then extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate and purified by column chromatography (ethyl acetate: petroleum ether = 1/100 to 1/10) to obtain **Intermediate 222-5** (7.5 g, 28.04 mmol, 93.11%) as a white solid.

Step 5:

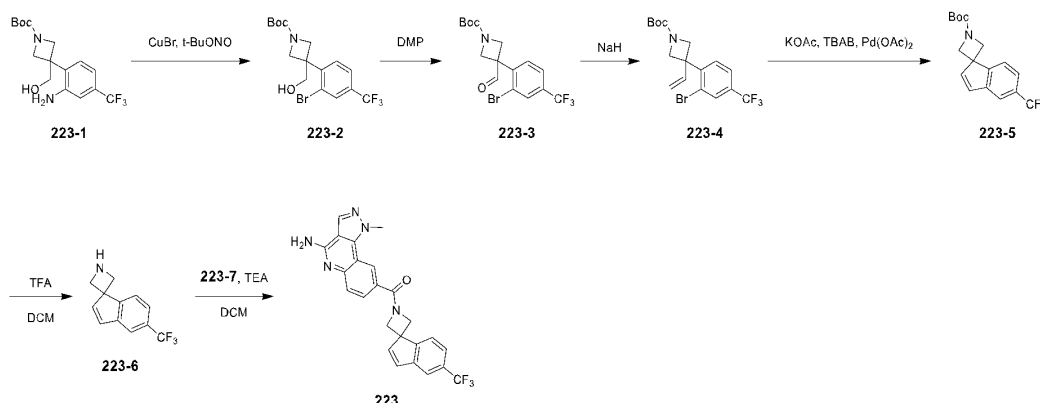
To **Intermediate 222-5** (6.5 g, 24.30 mmol) in ethanol (65 mL) was added hydrazine hydrate (52 mL). The mixture was stirred at 80 °C for 0.5 hours. After the reaction was completed, the reaction solution was filtered to obtain **Intermediate 222-6** (5.00 g, 19.00 mmol, 78.21%) as a white solid.

Step 6:

To a solution of **Intermediate 222-6** (50 mg, 0.19 mmol) in dimethyl sulfoxide (2 mL) were added **Intermediate 134-4** (65 mg, 0.28 mmol), triethylamine (80 μ L, 0.58 mmol) and Pd(dppf)Cl₂ dichloromethane complex (16 mg, 0.02 mmol). The mixture was stirred at 100°C for 18 hours and then filtered after the reaction was completed. The crude product was purified by preparative HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10mM NH₄HCO₃; B: ACN, gradient: 5-70%, retention time: 8.1 min) to obtain **Compound 222** (10.9 mg, 0.02 mmol, 11.82%) as a yellow solid. MS *m/z* (ESI) = 439.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.98 (s, 1H), 9.16 (s, 1H), 8.62 (d, *J* = 1.9 Hz, 1H), 8.16 (s, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 7.99 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.17 (d, *J* = 1.6 Hz, 1H), 5.94 (s, 2H), 4.89 (d, *J* = 4.0 Hz, 2H), 4.75 (d, *J* = 17.4 Hz, 2H), 4.49 – 4.27 (m, 2H).

Example 59:

Synthesis of Compound 223



Step 1:

To a solution of **Intermediate 223-1** (2 g, 5.77 mmol) and cuprous bromide (1.7 g, 11.85 mmol) in acetonitrile (20 mL) was added tert-butyl nitrite (1.1 mL, 9.17 mmol). The reaction solution was stirred at 80 °C for 4 hours, diluted with water (100 mL) and ammonia (2 mL), and extracted with ethyl acetate (50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, and then concentrated. The crude product was purified by column chromatography on silica gel (tetrahydrofuran: petroleum ether = 0-10%) to obtain **Intermediate 223-2** (1.28 g, 2.03 mmol, 35.11% yield, 65% purity) as a light-yellow colloid.

Step 2:

To a solution of **Intermediate 223-2** (1 g, 2.44 mmol) in dichloromethane (10 mL) was added Dess-Martin periodinane (1.1 g, 2.59 mmol). The reaction solution was stirred at 25 °C for 12 hours. The reaction solution was diluted with water (30 mL) and extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, and concentrated to obtain **Intermediate 223-3** (1.59 g, 2.45 mmol, 100.66%), as a light-yellow solid, which was directly used in the next step.

Step 3:

To a solution of methyltriphenylphosphonium bromide (4 g, 11.20 mmol) in tetrahydrofuran (15 mL) was added sodium hydride (0.43 g, 10.80 mmol, 60% purity). After the reaction solution was stirred at 20 °C for 30 minutes, **Intermediate 223-3** (1.59 g, 2.45 mmol) was added. The reaction solution was stirred at 60 °C for 6 hours, quenched with

saturated ammonium chloride solution (50 mL) and extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and then concentrated. The crude product was purified by column chromatography on silica gel (ethyl acetate: petroleum ether = 0-5%) to obtain **Intermediate 223-4** (500 mg, 1.23 mmol, 50.16%) as a light-yellow oil.

Step 4:

Under nitrogen atmosphere, to a solution of **Intermediate 223-4** (500 mg, 1.23 mmol), potassium acetate (365 mg, 3.72 mmol) and tetrabutylammonium bromide (480 mg, 1.49 mmol) in *N,N*-dimethylformamide (6 mL) was added palladium acetate (28 mg, 0.12 mmol). The reaction solution was stirred at 100 °C for 8 hours, diluted with water (50 mL) and extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and then concentrated. The crude product was purified by column chromatography on silica gel (ethyl acetate: petroleum ether = 0-5%) to obtain **Intermediate 223-5** (200 mg, 0.31 mmol, 24.97%) as a light-yellow oil.

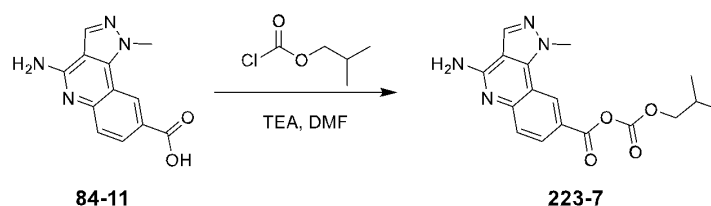
Step 5:

To a solution of **Intermediate 223-5** (50 mg, 0.15 mmol) in dichloromethane (0.5 mL) was added trifluoroacetic acid (120 µL, 1.57 mmol). The reaction solution was stirred at 20 °C for 2 hours, and then concentrated to obtain **Intermediate 223-6** (34.61 mg, 0.15 mmol, 99.99%) as a light-yellow oil.

Step 6:

A mixed solution of **Intermediate 223-6** (34.61 mg, 0.15 mmol), **Intermediate 223-7** (60 mg, 0.18 mmol) and triethylamine (65 µL, 0.47 mmol) in tetrahydrofuran (1 mL) was stirred at 20 °C for 2 hours and then concentrated. The crude product was purified by preparative HPLC (C18, 0.05% ammonium bicarbonate solution/acetonitrile) to obtain **Intermediate 223** (2.8 mg, 0.01 mmol, 4.05%) as a white solid. MS *m/z* (ESI): 450.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.56 (d, *J* = 2.0 Hz, 1H), 8.26 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.91 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.71 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.23 (s, 2H), 7.02 (d, *J* = 5.2 Hz, 1H), 6.91 (d, *J* = 5.6 Hz, 1H), 5.04 - 4.63 (m, 2H), 4.61 - 4.24 (m, 5H).

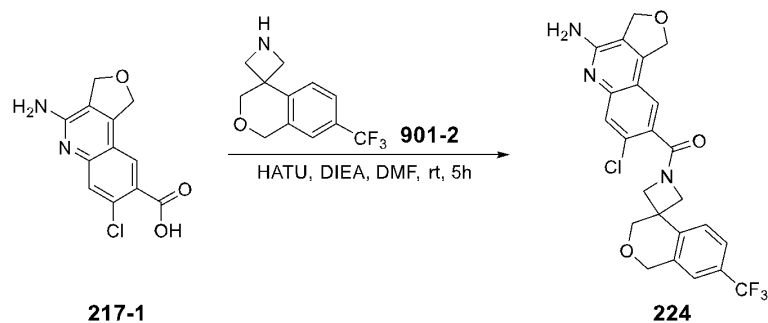
Synthesis of Intermediate 223-7



To a solution of **Intermediate 84-11** (500 mg, 2.06 mmol) and triethylamine (350 μL , 2.52 mmol) in *N,N*-dimethylformamide (5 mL) was added isobutyl chloroformate (270 μL , 2.08 mmol). The reaction solution was stirred at 20 °C for 2 hours, diluted with water (50 mL) and ethyl acetate (50 mL), and then filtered out the solid. The filtrate was extracted with ethyl acetate (50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and then concentrated to obtain **Intermediate 223-7** (200 mg, 0.58 mmol, 28.30%) as a light brown solid. MS m/z (ESI): 343.2 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.84 (d, $J = 2.4$ Hz, 1H), 8.30 (s, 1H), 8.04 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.64 (d, $J = 8.8$ Hz, 1H), 7.58 (s, 2H), 4.44 (s, 3H), 4.15 (d, $J = 6.8$ Hz, 2H), 2.02 (d, $J = 6.8$ Hz, 2H), 0.96 (d, $J = 6.4$ Hz, 6H).

Example 60:

Synthesis of Compound 224

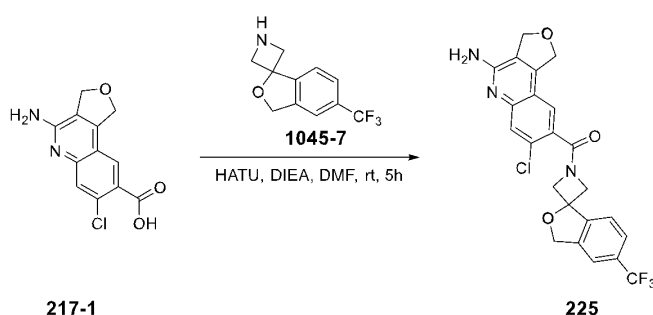


At room temperature, to a solution of **Intermediate 217-1** (30 mg, 0.11 mmol) in *N,N*-dimethylformamide (1 mL) were added **Intermediate 901-2** (41 mg, 0.17 mmol), *N,N*-diisopropylethylamine (44 mg, 0.34 mmol) and HATU (65 mg, 0.17 mmol). The reaction solution was stirred at room temperature for 3 hours and then filtered. The filtrate was added with water (3 mL) and then extracted with ethyl acetate (1 mL). The organic layer was washed with brine (3 mL), dried over anhydrous sodium sulfate, and concentrated under reduced

pressure. The residue was purified by HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10mM NH₄HCO₃; B: ACN, gradient: 10-65%, retention time: 14 min) to obtain **Compound 224** (9.73 mg, 0.02 mmol, 17.52% yield). MS m/z (ESI): 489.9, 491.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.93 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.68 (s, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 6.88 (s, 2H), 5.34 (t, *J* = 3.6 Hz, 2H), 4.99 (t, *J* = 3.6 Hz, 2H), 4.84 – 4.74 (m, 2H), 4.20 – 4.10 (m, 2H), 4.09 – 4.01 (m, 3H), 3.97 – 3.89 (m, 1H).

Example 61:

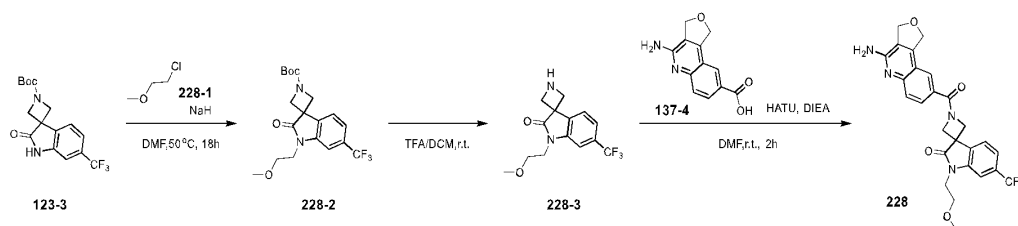
Synthesis of compound 225



At room temperature, to a solution of **Intermediate 217-1** (30 mg, 0.11 mmol) in *N,N*-dimethylformamide (1 mL) were added **Intermediate 1045-7** (39 mg, 0.17 mmol), *N,N*-diisopropylethylamine (44 mg, 0.34 mmol), HATU (65 mg, 0.17 mmol). The reaction solution was stirred at room temperature for 3 hours, and then filtered. The filtrate was added with water (3 mL) and then extracted with ethyl acetate (1 mL). The organic layer was washed with brine (3 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by HPLC (Welch-Xtimate-C18-5 μ m-21.2*150mm, mobile phase: A: 10mM NH₄HCO₃; B: ACN, gradient: 10-65%, retention time: 11.4 min) to obtain **Compound 205** (28.25 mg, 0.06 mmol, 52.38% yield). MS *m/z* (ESI): 475.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.82 (d, *J* = 1.2 Hz, 2H), 7.74 (s, 1H), 7.71 (s, 1H), 7.60 (s, 1H), 6.88 (s, 2H), 5.39 – 5.28 (m, 2H), 5.19 – 5.08 (m, 2H), 4.99 (t, *J* = 3.6 Hz, 2H), 4.43 – 4.34 (m, 2H), 4.32 – 4.17 (m, 2H).

Example 62:

Synthesis of compound 228



Step 1:

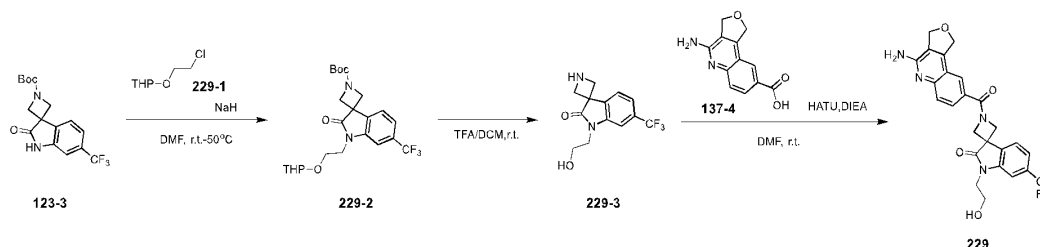
To a solution of **Intermediate 123-3** (300 mg, 0.88 mmol) and sodium hydride (100 mg, 2.50 mmol) in *N,N*-dimethylformamide (10 mL) was added **Intermediate 228-1** (0.16 mL, 1.75 mmol). The mixture was stirred at 50 °C for 18 hours. After the reaction was completed, the reaction solution was added with water (30 mL) and then extracted with ethyl acetate (20 mL). The organic layer was washed with brine (50 mL) and then concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 228-2** (350 mg, 0.87 mmol, 99.74%) as a white solid.

Step 2:

A solution of **Intermediate 228-2** (350 mg, 0.87 mmol) in dichloromethane (5 mL) and trifluoroacetic acid (2 mL) was stirred at 25 °C for 2 hours. After the reaction was completed, the reaction solution was concentrated to obtain a crude **Intermediate 228-3** (340 mg, 0.82 mmol, 93.88%) as a red oil, which was directly used in the subsequent step.

Step 3:

A solution of **Intermediate 137-4** (50 mg, 0.22 mmol), HATU (130 mg, 0.34 mmol), and *N,N*-diisopropylethylamine (0.19 mL, 1.09 mmol) in *N,N*-dimethylformamide (1 mL) was stirred at 25 °C for 30 minutes. **Intermediate 228-3** (70 mg, 0.23 mmol) was added and stirring continued at 25 °C for 2 hours. After the reaction was completed, the reaction solution was filtered. The filtrate was purified by HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium bicarbonate/water B: acetonitrile; flow rate: 25;) to obtain **Compound 228** (8.52 mg, 0.02 mmol, 7.57%) as a white solid. MS *m/z* (ESI): 513.0 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.94 (d, *J* = 7.6 Hz, 1H), 7.86 – 7.79 (m, 2H), 7.57 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.51 – 7.45 (m, 1H), 7.43 (s, 1H), 6.78 (s, 2H), 5.36 (t, *J* = 3.6 Hz, 2H), 4.99 (t, *J* = 3.6 Hz, 2H), 4.72 (s, 1H), 4.55 (s, 1H), 4.33 – 4.28 (m, 2H), 3.90 (t, *J* = 5.6 Hz, 2H), 3.53 (t, *J* = 5.6 Hz, 2H), 3.20 (s, 3H).

Example 63:**Synthesis of compound 229****Step 1:**

To a solution of **Intermediate 123-3** (500 mg, 1.46 mmol) and sodium hydride (120 mg, 3.00 mmol) in *N,N*-dimethylformamide (10 mL) was added **Intermediate 229-1** (0.65 mL, 4.38 mmol). The reaction solution was stirred at 50 °C for 18 hours. After the reaction was completed, the reaction solution was added with water (30 mL) and extracted with ethyl acetate (10 mL). The combined organic layers were dried over anhydrous sodium sulfate and then concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to obtain **Intermediate 229-2** (489 mg, 1.04 mmol, 71.16%) as a colorless oil.

Step 2:

A solution of **Intermediate 229-2** (200 mg, 0.43 mmol) in dichloromethane (5 mL) and trifluoroacetic acid (2.5 mL) was stirred at 25 °C for 2 hours. After the reaction was completed, the reaction solution was concentrated to obtain a crude **Intermediate 229-3** (110 mg, 0.38 mmol, 52.46%) as a yellow solid, which was directly used in the subsequent step.

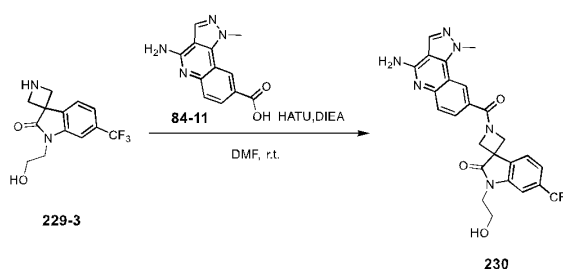
Step 3:

A solution of **Intermediate 229-3** (40 mg, 0.17 mmol), HATU (100 mg, 0.26 mmol) and diisopropylethylamine (0.15 mL, 0.87 mmol) in *N,N*-dimethylformamide (1 mL) was stirred at 25 °C for 10 minutes. The reaction solution was added with **Intermediate 137-4** (40 mg, 0.14 mmol) and continued stirring at 25 °C for 2 hours. After the reaction was completed, the reaction solution was filtered. The filtrate was purified by HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM formic acid/water B: acetonitrile; flow rate: 25;) to obtain **Compound 229** (2.24 mg, 0.00 mmol, 2.49%) as a white solid. MS *m/z* (ESI): 499.0 [*M*+*H*]⁺;

^1H NMR (400 MHz, DMSO- d_6) δ 7.96 (d, J = 7.6 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.86 – 7.84 (m, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.44 (s, 1H), 6.81 (s, 2H), 5.40 – 5.36 (m, 2H), 5.04 – 4.99 (m, 2H), 4.84 (t, J = 6.0 Hz, 1H), 4.77 – 4.71 (m, 1H), 4.61 – 4.54 (m, 1H), 4.39 – 4.24 (m, 2H), 3.83 – 3.77 (m, 2H), 3.64 – 3.58 (m, 2H).

Example 64:

Synthesis of compound 230

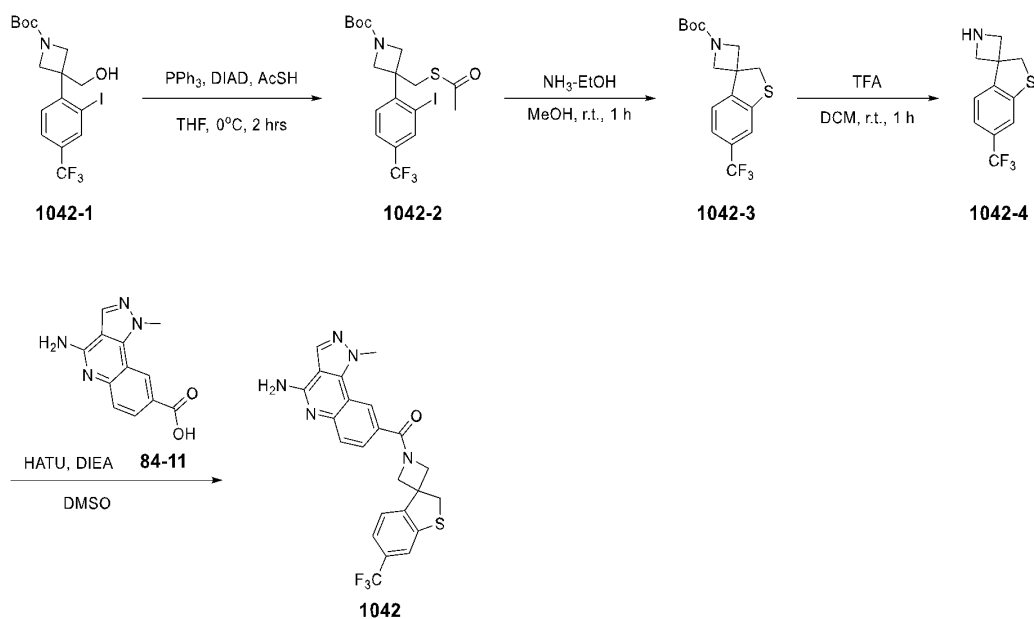


Step 1

A solution of **Intermediate 229-3** (40 mg, 0.17 mmol), HATU (100 mg, 0.26 mmol) and diisopropylethylamine (0.14 mL, 0.80 mmol) in *N,N*-dimethylformamide (0.5 mL) was stirred at 25 °C for 10 minutes. **Intermediate 84-11** (40 mg, 0.14 mmol) was added, and the reaction solution was further stirred at 25 °C for 2 hours. After the reaction was completed, the reaction solution was filtered. The filtrate was purified by HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium bicarbonate/water B: acetonitrile; flow rate: 25;) to obtain **Compound 230** (3.88 mg, 0.01 mmol, 4.73%) as a white solid. MS m/z (ESI): 511.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 8.55 (d, J = 2.0 Hz, 1H), 8.27 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.90 (dd, J = 2.0, 8.8 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.45 (s, 1H), 7.26 (s, 2H), 4.85 (t, J = 6.0 Hz, 1H), 4.83 – 4.78 (m, 1H), 4.71 – 4.62 (m, 1H), 4.43 (s, 3H), 4.40 – 4.37 (m, 1H), 4.35 – 4.29 (m, 1H), 3.85 – 3.78 (m, 2H), 3.66 – 3.58 (m, 2H).

Example 65:

Synthesis of Compound 1042

**Step 1:**

At 0 °C and under nitrogen atmosphere, to a solution of triphenylphosphine (103 mg, 0.39 mmol) in tetrahydrofuran (1.5 mL) was added DIAD (78 μ L, 0.40 mmol), and then a solution of **Intermediate 1042-1** (150 mg, 0.28 mmol) and thioacetic acid (28 μ L, 0.39 mmol) in tetrahydrofuran (1.5 mL) was added dropwise to the reaction solution. The mixture was stirred at 0 °C for 2 hours. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography on silica gel (petroleum ether: ethyl acetate and petroleum ether = 0-10%) to obtain **Intermediate 1042-2** (90 mg, 0.17 mmol, 62.63%) as a light yellow oil.

Step 2:

At 25 °C and under nitrogen atmosphere, to a solution of **Intermediate 1042-2** (99 mg, 0.19 mmol) in methanol (20 mL) was added amine ethanol solution (1.0 mL, 2.0 mol/L). The mixture was stirred at 25 °C for 2 hours. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography on silica gel (petroleum ether: ethyl acetate and petroleum ether = 0-10%) to obtain **Intermediate 1042-3** (932 mg, 0.07 mmol, 38.58%) as a light yellow oil.

Step 3:

At 25 °C and under nitrogen atmosphere, to a solution of **Intermediate 1042-3** (13 mg,

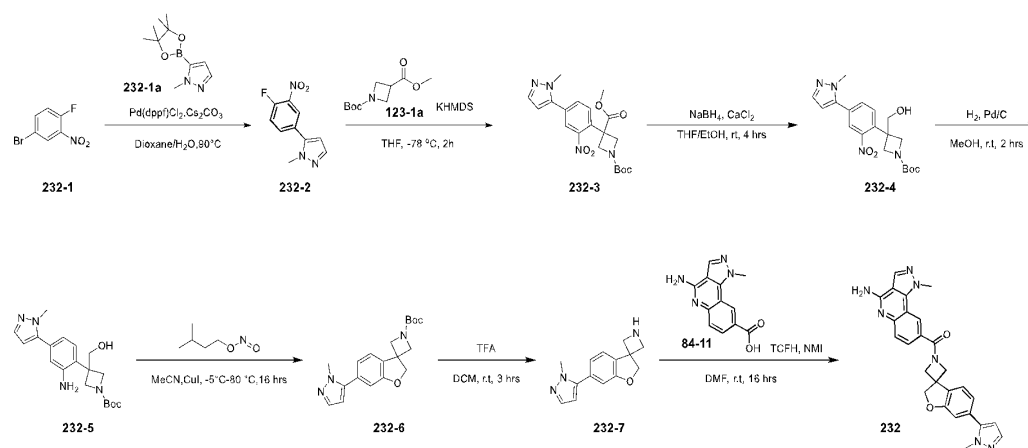
0.03 mmol) in dichloromethane (2.0 mL) was added trifluoroacetic acid (0.4 mL, 5.23 mmol). The mixture was stirred at 25 °C for 1 hour. After the reaction was completed, the reaction solution was concentrated to obtain crude **Intermediate 1042-4** (17 mg, 0.03 mmol, 98.98% yield) as a yellow oil, which was directly used in the subsequent step without further purification.

Step 4

At 25 °C and under nitrogen atmosphere, to a solution of **Intermediate 84-11** (13 mg, 0.03 mmol) and HATU (33 mg, 0.09 mmol) in DMSO (1.0 mL) was added DIEA (11 mg, 0.09 mmol). The mixture was stirred at 25 °C for half an hour. The reaction solution was added with a solution of **Intermediate 1042-4** (17 mg, 0.03 mmol) in DMSO (1.0 mL), and continued stirring at 25 °C for 1.5 hours. After the reaction was completed, the reaction solution was added with water (20 mL) and filtered. The filter cake was purified by plate chromatography on silica gel (CH₂Cl₂/MeOH = 15/1) to obtain **Compound 1042** (4.44 mg, 0.01 mmol, 16.04% yield) as a white solid. MS m/z (ESI): 470.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.53 (d, *J* = 2.0 Hz, 1H), 8.29 (s, 1H), 7.92 – 7.86 (m, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.46 – 7.19 (m, 2H), 4.78 – 4.57 (m, 2H), 4.43 (s, 3H), 4.41 – 4.16 (m, 2H), 3.82 (s, 2H).

Example 66:

Synthesis of Compound 232



Step 1:

To a solution of **Intermediate 232-1** (10 g, 37.45 mmol) and **Intermediate 232-1a** (13 g, 44.94 mmol) in 1,4-dioxane (160 mL) and water (40 mL) were added potassium carbonate (29.3 g, 74.9 mmol) and Pd(dppf)Cl₂ (3.3 g, 3.74 mmol). The mixture was stirred at 100 °C under nitrogen for 3 hours. After the reaction was completed, the reaction solution was diluted with water (200 mL) and extracted with ethyl acetate (200 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to obtain **Compound 232-2** (8.0 g, 36.20 mmol, yield 96% yield) as a yellow solid.

Step 2:

At -78 °C and under nitrogen atmosphere, to a solution of **Intermediate 232-2** (5.6 g, 13.44 mmol) and **Intermediate 123-1a** (5.4 g, 13.44 mmol) in tetrahydrofuran (250 mL) was added dropwise LiHMDS (3.0 M, 13 mL, 40.32 mmol). The mixture was stirred at -78 °C for 1 hour, and then stirred at room temperature for 2 hours. The reaction was quenched with saturated aqueous ammonium chloride solution (100 mL) and extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 2/3) to obtain **Intermediate 232-3** (1.5 g, 3.6 mmol, 26.78% yield) as a yellow solid.

Step 3:

At 0°C and under nitrogen atmosphere, to a solution of **Intermediate 232-3** (450 mg, 1.0 mmol), calcium chloride (474 mg, 4.27 mmol) in tetrahydrofuran (10 mL)/ethanol (5 mL) was added sodium borohydride (121 mg, 3.20 mmol). The mixture was stirred at 0°C for 0.5 hours, and then stirred at room temperature for 2 hours. The reaction was quenched with water and extracted with ethyl acetate (50 mL). The combined organic layers were washed with brine (70 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by column chromatography (petroleum ether/ethyl acetate = 1/4) to obtain **Intermediate 232-4** (220 mg, 0.56 mmol, 53.0% yield) as a white solid.

Step 4:

Under nitrogen atmosphere, to a solution of **Intermediate 232-4** (90 mg, 0.23 mmol) in methanol (5 mL) was added Pd/C (10%, 20 mg). The mixture was stirred at room temperature

for 2 hours. The reaction solution was filtered and concentrated to obtain **Intermediate 232-5** (80 mg, 0.22 mmol, 95% yield) as a white oil.

Step 5:

To a solution of **Intermediate 232-5** (50 mg, 0.14 mmol) and cuprous iodide (63 mg, 0.28 mmol) in acetonitrile (5 mL) was added dropwise isoamyl nitrite (24 mg, 0.03 mmol). The mixture was stirred at room temperature for 0.5 hours, and then heated to 80 °C and continued stirring for 16 hours. The reaction was diluted with water (10 mL), and extracted with ethyl acetate (5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to obtain **Intermediate 232-6** (30 mg, 0.09 mmol, 62% yield) as a colorless oil.

Step 6:

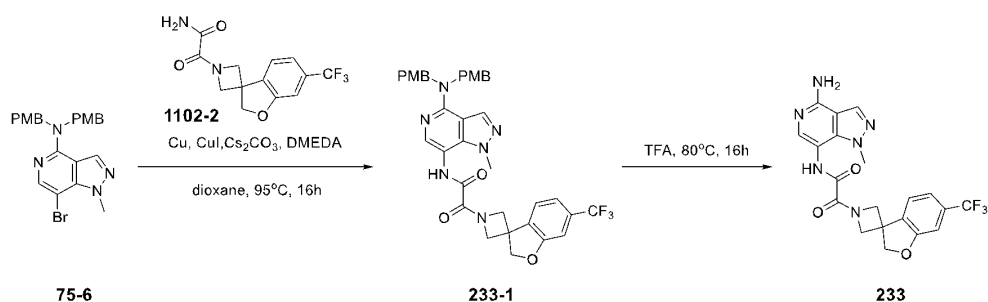
To a solution of **Intermediate 232-6** (30 mg, 0.09 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at room temperature for 2 hours, and then concentrated under reduced pressure to obtain **Intermediate 232-7** (20 mg, 0.08 mmol, 92% yield) as a white solid.

Step 7:

To a solution of **Intermediate 232-7** (20 mg, 0.08 mmol) and **Intermediate 5a** (20 mg, 0.08 mmol) in DMF (2 mL) were added TCFH (35 mg, 0.12 mmol) and N-methylimidazole (17 mg, 0.2 mmol). The mixture was stirred at room temperature for 16 hours. The reaction solution was diluted with water (20 mL) and extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by preparative HPLC (column: Welch ultimate XB-NH2 250*50*10um, mobile phase: [heptane-EtOH (0.1% NH₃H:O)]; B% 10%-10%, 10min) to obtain **Compound 232** (9.8 mg, 0.02 mmol, 26% yield). MS m/z (ESI): 466.0 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 8.70 – 8.63 (m, 1H), 8.22 (s, 1H), 7.96 – 7.89 (m, 1H), 7.74 – 7.65 (m, 2H), 7.51 – 7.46 (m, 1H), 7.16 – 7.07 (m, 1H), 6.95 – 6.86 (m, 1H), 6.38 – 6.27 (m, 1H), 4.87 – 4.85 (m, 2H), 4.84 – 4.71 (m, 4H), 4.49 (s, 3H), 3.85 (s, 3H).

Example 67:

Synthesis of Compound 233



Step 1:

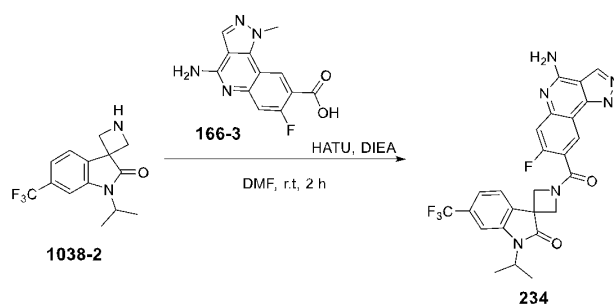
At room temperature, to a solution of **Intermediate 75-6** (300 mg, 0.64 mmol) in 1,4-dioxane (3 mL) were added **Intermediate 1102-2** (193 mg, 0.64 mmol), cesium carbonate (418 mg, 1.28 mmol), N,N'-dimethylethylenediamine (112 mg, 0.96 mmol), cuprous iodide (184 mg, 0.96 mmol), and copper powder (50 mg, 0.77 mmol). The mixture was stirred at 95 °C under nitrogen atmosphere for 16 hours. The reaction solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to obtain **Intermediate 233-1** (100 mg, 0.15 mmol, 22.69% yield) as a white solid.

Step 2:

At room temperature and under nitrogen atmosphere, a solution of **Intermediate 233-1** (100 mg, 0.15 mmol) in trifluoroacetic acid (2 mL) was stirred for 16 hours. The reaction solution was concentrated and purified by preparative TLC (dichloromethane/methanol = 16/1), followed by preparative HPLC (column: Welch ultimate XB-NH2 250*50*10um, mobile phase: [Heptane-EtOH(0.1%FA)]; B% 10%-10%, 10min) to obtain **Compound 233** (24.5 mg, 0.05 mmol, 37.69% yield) as a white solid. MS m/z (ESI): 447.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.41 (s, 1H), 8.16 - 8.13 (m, 1H), 7.88 - 7.86 (m, 1H), 7.44 (s, 1H), 7.34 - 7.32 (m, 1H), 7.15 (s, 1H), 6.94 (s, 2H), 4.89 - 4.88 (m, 2H), 4.82 - 4.71 (m, 2H), 4.39 - 4.25 (m, 2H), 3.97 (s, 3H).

Example 68:

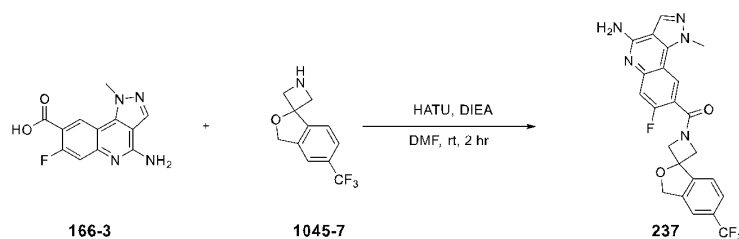
Synthesis of Compound 234



A solution of **Intermediate 166-3** (110 mg, 0.42 mmol), HATU (240 mg, 0.63 mmol), and *N,N*-diisopropylethylamine (0.37 mL, 2.11 mmol) in *N,N*-dimethyl sulfoxide (1 mL) was stirred at 25 °C for 10 minutes. **Intermediate 1038-2** (120.17 mg, 0.42 mmol) was added thereto. The reaction solution was stirred at 25 °C for 2 hours. After the reaction was completed, the reaction solution was filtered and purified by HPLC-MS (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM formic acid/water B: acetonitrile; flow rate: 25) to obtain **Compound 234** (15.24 mg, 0.03 mmol, 6.47% yield) as a white solid. MS m/z (ESI): 527.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 8.44 (d, J = 7.6 Hz, 1H), 8.30 (s, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.43 (s, 1H), 7.36 (d, J = 12.4 Hz, 1H), 4.60 – 4.49 (m, 1H), 4.43 (s, 3H), 4.39 – 4.30 (m, 4H), 1.42 (d, J = 6.9 Hz, 6H).

Example 69:

Synthesis of Compound 237

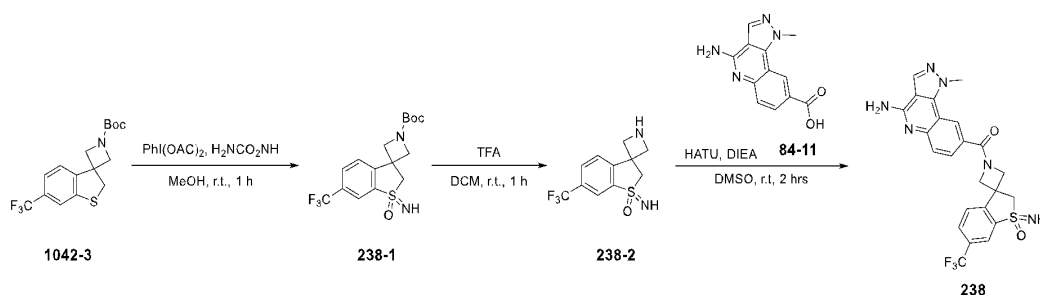


To a solution of **Intermediate 166-3** (50 mg, 0.19 mmol) in *N,N*-dimethylformamide (5 mL) were added HATU (72.0 mg, 0.19 mmol) and *N,N*-Diisopropylethylamine (73 mg, 0.57 mmol). The mixture was stirred at room temperature for 0.5 hours. The reaction solution was added with **Intermediate 1045-7** (50 mg, 0.22 mmol) and further stirred at room temperature for 2 hours. After the reaction was completed, the reaction solution was filtered. The filtrate was purified by preparative HPLC (column: Welch ultimate XB-NH2 250*50*10 μ m, mobile

phase: [Heptane-EtOH (0.1% FA)]; B% 10%-10%, 10min) to obtain **Compound 237** (27.51 mg, 0.06 mmol, 30.74% yield) as a white solid. MS m/z (ESI): 472.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 8.40 (d, J = 7.6 Hz, 1H), 8.26 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.75 (s, 1H), 7.37 (s, 2H), 7.31 (d, J = 12.4 Hz, 1H), 5.15 (d, J = 6.4 Hz, 2H), 4.50 – 4.34 (m, 7H).

Example 70:

Synthesis of Compound 238



Step 1:

Under nitrogen atmosphere, to a solution of **Intermediate 1042-3** (18 mg, 0.05 mmol) in methanol (2.0 mL) were added iodobenzene acetate (56 mg, 0.17 mmol) and ammonium carbamate (14 mg, 0.18 mmol). The mixture was stirred at 25 °C for 1 hour. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography on silica gel (dichloromethane: dichloromethane and methanol = 0-7%) to obtain **Intermediate 238-1** (21 mg, 0.05 mmol, 96.33% yield) as a white solid.

Step 2:

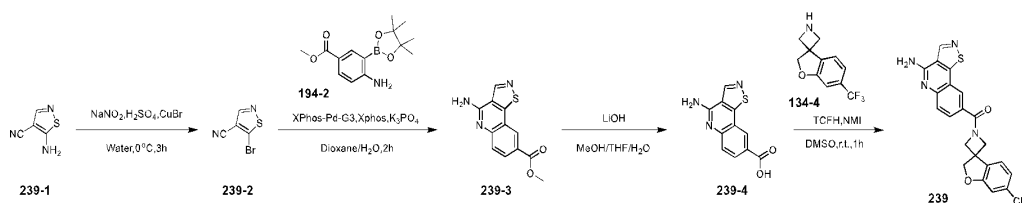
Under nitrogen atmosphere and at 25 °C, to a solution of **Intermediate 238-1** (21 mg, 0.06 mmol) in dichloromethane (2.5 mL) was added trifluoroacetic acid (0.5 mL, 6.53 mmol). The mixture was stirred at 25 °C for 1 hour. After the reaction was completed, the reaction solution was concentrated under reduced pressure to obtain a crude **Intermediate 238-2** (27 mg, 0.05 mmol, 97.31% yield) as a yellow oil, which was used directly in the next step without further purification.

Step 3:

At 25 °C and under nitrogen atmosphere, to a solution of **Intermediate 84-11** (24 mg, 0.05 mmol) and HATU (32 mg, 0.08 mmol) in DMSO (1.0 mL) was added DIEA (10 mg, 0.08 mmol). The mixture was stirred at 25 °C for half an hour, and then added with a solution of **Intermediate 238-2** (27 mg, 0.05 mmol) in DMSO (1.0 mL). The mixture was stirred at 25 °C for one and a half hours. After the reaction was completed, the reaction solution was introduced into water (20 mL) and filtered. The filter cake was purified by column chromatography on silica gel (dichloromethane: dichloromethane and methanol = 0-10%) to obtain **Intermediate 238** (19.68 mg, 0.04 mmol, 69.61% yield) as a light yellow solid. MS m/z (ESI): 500.9 $[M+H]^+$; 1H NMR (500 MHz, DMSO- d_6) δ : 8.55 (d, J = 2.0 Hz, 1H), 8.34 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.11 – 8.06 (m, 1H), 8.02 (s, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 4.96 – 4.75 (m, 3H), 4.51 – 4.30 (m, 5H), 4.12 – 4.00 (m, 2H).

Example 71:

Synthesis of Compound 239



Step 1:

Intermediate 239-1 (20 mg, 0.16 mmol), sodium nitrite (22 mg, 0.32 mmol) and sulfuric acid (20.00 μ L, 0.32 mmol) were added to water (1 mL) in sequence, and then cuprous bromide (46 mg, 0.32 mmol) was added thereto. The mixture was stirred at 0°C for 2 hours. After the reaction was completed, the reaction solution was added with water (5 mL). The aqueous layer was extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous sodium sulfate. The filtrate was concentrated and purified by plate chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to obtain **Intermediate 239-2** (6 mg, 0.03 mmol, 19.9% yield) as a white solid.

Step 2:

To a solution of **Intermediate 239-2** (60 mg, 0.32 mmol) in 1,4-dioxane (6 mL) and water (0.6 mL) were added XPhos Pd G3 (54 mg, 0.06 mmol), XPhos (60 mg, 0.13 mmol), potassium

phosphate (200 mg, 0.094 mmol) and **Intermediate 194-2** (120 mg, 0.43 mmol). The mixture was stirred at 100 °C for 2 hours. After the reaction was completed, the reaction solution was added with water (5 mL). The aqueous layer was extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by thin layer plate chromatography on silica gel (petroleum ether: ethyl acetate = 1:1) to obtain **Intermediate 239-3** (55 mg, 0.21 mmol, 66.83% yield) as a yellow solid.

Step 3:

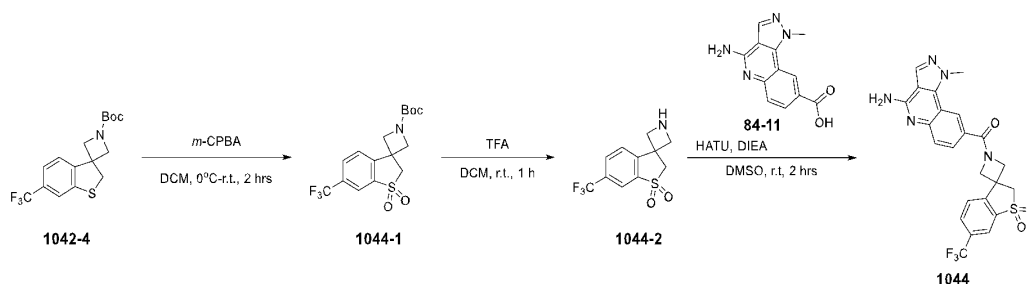
To a solution of **Intermediate 239-3** (45 mg, 0.17 mmol) in water (2.25 mL), tetrahydrofuran (2.25 mL) and methanol (2.25 mL) was added lithium hydroxide (4.16 mg, 0.17 mmol). The mixture was stirred at 75 °C for 1 hour. After the reaction was completed, the reaction solution was adjusted to pH=3 with the diluted hydrochloric acid aqueous solution (2M) to form a solid as crude **Intermediate 239-4**. The aqueous layer was extracted with ethyl acetate (20 mL), and then lyophilized to obtain crude **Intermediate 239-4**. The combined crude **Intermediate 239-4**, which was directly used in the subsequent step.

Step 4:

To a solution of **Intermediate 239-4** (10 mg, 0.04 mmol) in dimethyl sulfoxide (1 mL) were added **Intermediate 134-4** (15 mg, 0.07 mmol), TCFH (18 mg, 0.06 mmol), and 1-methylimidazole (20 µL, 0.25 mmol). The mixture was stirred at 25 °C for 1 hour. After the reaction was completed, the reaction solution was filtered and purified by preparative HPLC (column: Welch ultimate XB-NH2 250*50*10um, mobile phase: [heptane-EtOH (0.1% NH₃H:O)]; B% 10%-10%, 10min) to obtain **Compound 239** (0.4 mg, 0.00 mmol, 2.15% yield) as a white solid. MS m/z (ESI): 457.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.41 (s, 1H), 8.30 (d, *J* = 2.0 Hz, 1H), 7.96 – 7.78 (m, 2H), 7.74 – 7.60 (m, 3H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.16 (s, 1H), 4.89 (s, 2H), 4.70 (brs, 2H), 4.39 – 4.30 (m, 2H).

Example 72:

Synthesis of Compound 1044

**Step 1:**

At 0 °C and under nitrogen atmosphere, to a solution of **Intermediate 1042-4** (40 mg, 0.12 mmol) in dichloromethane (3.0 mL) was added *m*-chloroperbenzoic acid (60 mg, 0.30 mmol). The mixture was stirred at 0 °C for 1 hour. After the temperature was raised to 25 °C, the reaction mixture was stirred for additional 1 hour. After the reaction was completed, the reaction solution was concentrated under reduced pressure, and purified by column chromatography on silica gel (dichloromethane: dichloromethane and methanol = 0-5%) to obtain **Intermediate 1044-1** (28 mg, 0.07 mmol, 64.06% yield) as a light yellow solid.

Step 2:

At 25°C and under nitrogen atmosphere, to a solution of **Intermediate 1044-1** (28 mg, 0.07 mmol) in dichloromethane (3.0 mL) was added trifluoroacetic acid (0.3 mL, 3.92 mmol). The mixture was stirred at 25 °C for 1 hour. After the reaction was completed, the reaction solution was concentrated under reduced pressure to obtain **Intermediate 1044-2** (26 mg, 0.07 mmol, 99.85% yield) as a yellow oil, which was directly used in the subsequent step without further purification.

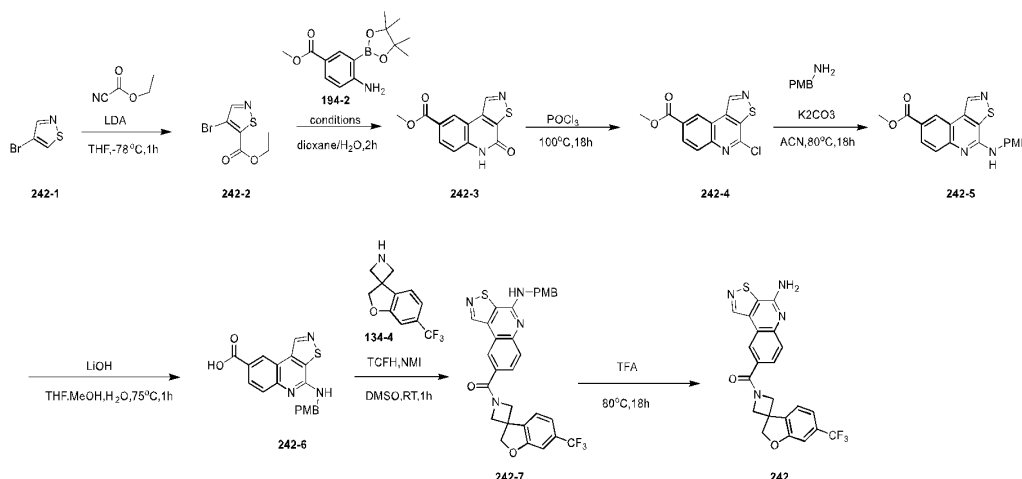
Step 3:

At 25°C and under nitrogen atmosphere, to a solution of **Intermediate 84-11** (29 mg, 0.07 mmol) and HATU (42 mg, 0.11 mmol) in dimethyl sulfoxide (1.0 mL) was added *N,N*-diisopropylethylamine (14 mg, 0.11 mmol). The mixture was stirred at 25 °C for 0.5 hours. A solution of **Intermediate 1044-2** (26 mg, 0.07 mmol) in dimethyl sulfoxide (1.0 mL) was added to the reaction solution, and the solution was stirred at 25 °C for 1.5 hours. After the reaction was completed, the reaction solution was poured into water (20 mL) and filtered. The filter cake was purified by prep-TLC (CH₂Cl₂/MeOH = 10/1) to obtain **Compound 1044** (7.8 mg, 0.02 mmol, 21.65% yield) as a white solid. MS *m/z* (ESI): 501.9 [M+H]⁺; ¹H NMR (500

MHz, DMSO-*d*₆) δ : 8.53 (d, *J* = 2.0 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 8.27 – 8.24 (m, 2H), 8.23 – 8.19 (m, 1H), 7.87 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.25 (s, 2H), 4.92 – 4.73 (m, 2H), 4.57 – 4.35 (m, 2H), 4.41 (s, 3H), 4.23 (s, 2H).

Example 73:

Synthesis of Compound 242



Step 1:

To a solution of **Intermediate 242-1** (2500 mg, 15.24 mmol) in tetrahydrofuran (50 mL) was added LDA (9.15 mL, 18.29 mmol) at -78°C. The mixture was stirred at -78 °C for 30 minutes and then added with a solution of ethyl cyanofornate (1.81 mL, 18.29 mmol) in tetrahydrofuran (10 mL). The solution was stirred at -78 °C for 1 hour under nitrogen atmosphere. After the reaction was completed, the reaction solution was quenched with saturated aqueous ammonium chloride solution (50 mL). The resulting solution was extracted with ethyl acetate (50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20/1) to obtain **Intermediate 242-2** (800 mg, 3.39 mmol, 22.23% yield) as a colorless liquid.

Step 2:

To a solution of **Intermediate 242-2** (1200 mg, 5.08 mmol) in 1,4-dioxane (24 mL) and water (4.8 mL) were added **Intermediate 194-2** (1700 mg, 6.13 mmol),

tetrakis(triphenylphosphine)palladium (450 mg, 0.39 mmol) and potassium carbonate (2107 mg, 15.25 mmol). The mixture was stirred at 100 °C for 18 hours. After the reaction was completed, the reaction solution was cooled to room temperature, and then added with water (5 mL) and ethyl acetate (20 mL) to precipitate a large amount of solid. The solid was filtered and dried under reduced pressure to obtain a crude **Intermediate 242-3** as a brown solid.

Step 3:

A solution of **Intermediate 242-3** (1700 mg, 6.53 mmol) in phosphorus oxychloride (32 mL, 0.38 mmol) was stirred at 10 °C for 18 hours. After the reaction was completed, the reaction solution was concentrated under reduced pressure to remove majority of the phosphorus oxychloride and then slowly added to 200 mL of saturated sodium bicarbonate solution. The solution was extracted with ethyl acetate (50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain **Intermediate 242-4** (1200 mg, 4.31 mmol, 65.92% yield), which was a red solid.

Step 4:

To a solution of **Intermediate 242-4** (800 mg, 2.87 mmol) in acetonitrile (20 mL) were added (4-methoxyphenyl)methylamine (0.94 mL, 7.18 mmol) and potassium carbonate (1190 mg, 8.61 mmol). The mixture was stirred at 80 °C for 18 hours. After the reaction was completed, the reaction solution was added with water (50 mL), and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 242-5** (1000 mg, 1.85 mmol, 64.28% yield) as a yellow solid.

Step 5:

To a solution of **Intermediate 242-5** (300 mg, 0.79 mmol) in methanol (3 mL), water (3 mL) and tetrahydrofuran (3 mL) was added lithium hydroxide (115 mg, 2.74 mmol). The mixture was stirred at 75 °C for 1 hour. After the reaction was completed, the reaction solution was adjusted to pH=6 with a dilute aqueous hydrochloric acid solution (1 M). The solution was concentrated under reduced pressure and then lyophilized to obtain the crude **Intermediate 242-6**, which was directly used in the subsequent step.

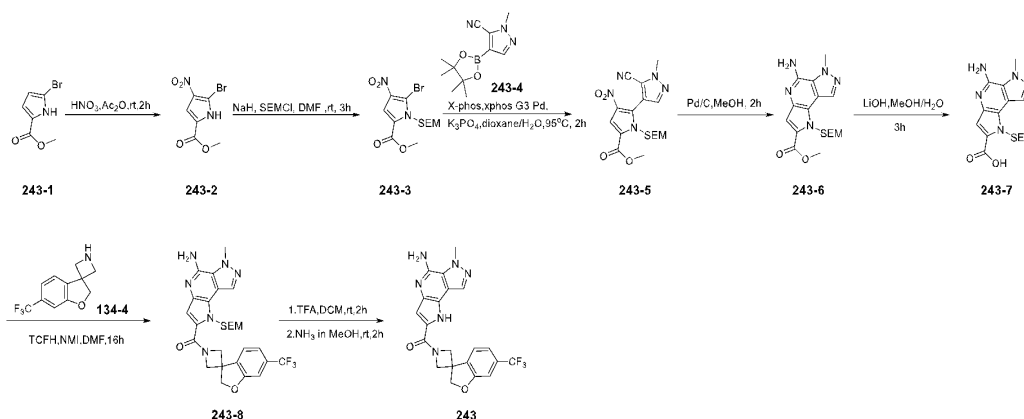
Step 6:

To a solution of **Intermediate 242-6** (280 mg, 0.77 mmol) in dimethyl sulfoxide (10 mL) were added **Intermediate 134-4** (260 mg, 1.13 mmol), TCFH (320 mg, 1.14 mmol) and 1-methylimidazole (380 μ L, 4.77 mmol). The mixture was stirred at 25 °C for 1 hour. After the reaction was completed, the reaction solution was added with water (20 mL). The aqueous layer was extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to obtain **Intermediate 242-7** (60 mg, 0.10 mmol, 13.58% yield), which was a yellow liquid.

Step 7:

At 80 °C and under a nitrogen atmosphere, a solution of **Intermediate 242-7** (60 mg, 0.10 mmol) in trifluoroacetic acid (1 mL, 13.07 mmol) was stirred for 18 hours. After the reaction was completed, the reaction solution was concentrated under reduced pressure. The crude product was purified by preparative HPLC (column: Welch ultimate XB-NH2 250*50*10 μ m, mobile phase: [Heptane-EtOH (0.1% $\text{NH}_3\text{H}_2\text{O}$)]; B% 10%-10%, 10min) to obtain **Intermediate 242** (18.65 mg, 0.04 mmol, 36.35% yield) as a white solid. MS m/z (ESI): 457.1 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.90 (s, 1H), 8.69 (d, $J = 2.0$ Hz, 1H), 7.97 – 7.84 (m, 2H), 7.72 (d, $J = 8.8$ Hz, 1H), 7.40 – 7.32 (m, 1H), 7.16 (d, $J = 1.6$ Hz, 1H), 4.89 (s, 2H), 4.75 (d, $J = 10.0$ Hz, 2H), 4.48 – 4.27 (m, 2H).

Example 74:**Synthesis of Compound 243**

**Step 1:**

At -20 °C and under nitrogen atmosphere, to a solution of **Intermediate 243-1** (10.0 g, 49 mmol) in acetic anhydride (80 mL) was added dropwise nitric acid (3.3 mL, 78.4 mmol). After the addition was completed, the mixture was gradually heated to room temperature and stirred for 2 h. After the reaction was completed, the reaction solution was added dropwise to ice water to quench the reaction. The diluted reaction solution was extracted with ethyl acetate. The organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/3) to obtain **Intermediate 243-2** (5.8 g, 23.29 mmol, 47% yield) as a yellow oil.

Step 2:

At 0 °C, to a solution of **Intermediate 243-2** (5.8 g, 23 mmol) in DMF (50 mL) was added NaH (1.16 g, 46 mmol). The mixture was stirred at 0 °C for 1 hour. The reaction solution was added dropwise with 2-(trimethylsilyl)ethoxymethyl chloride (17.51 g, 34.5 mmol) and stirred at room temperature for 3 hours. The reaction solution was quenched with saturated ammonium chloride solution (200 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/10) to obtain **Intermediate 243-3** (3.2 g, 8.4 mmol, 36% yield) as a yellow solid.

Step 3:

To a solution of **Intermediate 243-3** (1.6 g, 4.2 mmol) in 1,4-dioxane (30 mL) and water

(6 mL) were added **Intermediate 243-4** (2 g, 8.44 mmol), X-phos Pd G3 (0.36 g, 0.42 mmol), X-phos (0.40 g, 0.84 mmol) and potassium phosphate (2.7 g, 12.66 mmol). The mixture was reacted at 95 °C for 2 hours under nitrogen atmosphere. After the reaction was completed, the reaction solution was diluted with water (100 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/3) to obtain **Intermediate 243-5** (423 mg, 1.04 mmol, 24% yield) as a white solid.

Step 4:

To a solution of **Intermediate 243-5** (450 mg, 1.11 mmol) in methanol (10 mL) was added Pd/C (10%, 45 mg). The mixture was stirred at room temperature for 2 hours under hydrogen atmosphere. After the reaction was completed, the reaction solution was filtered, washed with methanol three times, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate = 100%) to obtain **Intermediate 243-6** (43 mg, 0.11 mmol, 10% yield) as a red solid.

Step 5:

To a solution of **Intermediate 243-6** (100 mg, 0.27 mmol) in methanol (5 mL)/water (0.5 mL) was added lithium hydroxide (111 mg, 0.27 mmol). The mixture was stirred at room temperature for 3 hours. After the reaction was completed, the reaction solution was concentrated under reduced pressure to obtain a crude **Intermediate 243-7** (100 mg, 0.13 mmol) as a white solid.

Step 6:

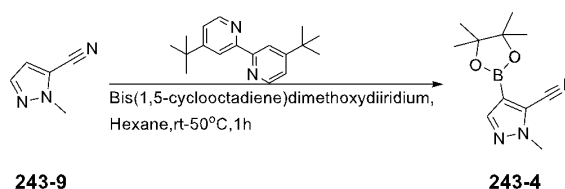
To a solution of **Intermediate 243-7** (100 mg, 0.27 mmol) in DMF (2 mL) were added **Intermediate 134-4** (63 mg, 0.27 mmol), TCFH (116 mg, 0.41 mmol), and N-methylimidazole (57 mg, 0.69 mmol). The mixture was stirred at room temperature for 16 hours. After the reaction was completed, the reaction solution was purified by column chromatography on C18 silica gel (70% acetonitrile in 1% NH₄HCO₃ in H₂O) and lyophilized to obtain **Intermediate 243-8** (20 mg, 0.03 mmol, 12% yield) as a white solid.

Step 7:

To a solution of **Intermediate 243-8** (50 mg, 0.09 mmol) in dichloromethane (4 mL) was

added trifluoroacetic acid (2 mL). The mixture was stirred at room temperature for 2 hours. After the reaction was completed, the reaction solution was concentrated under reduced pressure to obtain the resulting product. The resulting product was added with ammonia in methanol (5 mL), and stirred at room temperature for 2 hours. After the reaction was completed, the crude product was concentrated under reduced pressure, slurried in methanol and then slurried in acetonitrile to obtain **Compound 243** (21 mg, 0.056 mmol, 54% yield) as a white solid. MS *m/z* (ESI): 443.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 12.76 (s, 1H), 8.32 (s, 1H), 8.10 (s, 2H), 7.86 (d, $J = 7.6$ Hz, 1H), 7.34 (d, $J = 7.6$ Hz, 1H), 7.18 (d, $J = 1.6$ Hz, 1H), 6.72 (d, $J = 2.4$ Hz, 1H), 4.93 (d, $J = 4.4$ Hz, 2H), 4.79 (d, $J = 13.6$ Hz, 2H), 4.41 (s, 5H).

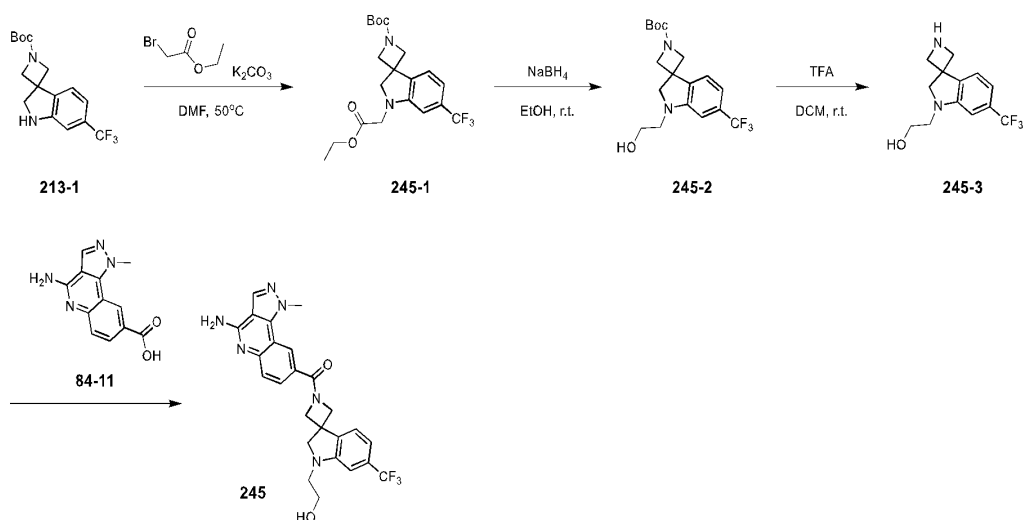
Synthesis of Intermediate 243-4



To a solution of **Intermediate 243-9** (3.0 g, 28 mmol) and bis(boronic acid pinacol) (14.2 g, 56 mmol) in n-hexane (100 mL) were added methoxy(cyclooctadiene)iridium dimer (1.85 g, 2.8 mmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (1.5 g, 2.6 mmol). Under nitrogen atmosphere, the mixture was stirred at 50°C for 1 hour. After the reaction was completed, the reaction solution was diluted with water (100 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5) to obtain **Intermediate 243-4** (6.4 g, 27.46 mmol, 98% yield) as a white solid. MS *m/z* (ESI): 234.0 $[M+H]^+$; 1H NMR (400 MHz, CD $_3$ OD) δ 7.74 (s, 1H), 4.05 (d, $J = 1.6$ Hz, 3H), 1.34 (s, 6H), 1.24 (s, 6H).

Example 75:

Synthesis of Compound 245

**Step 1:**

A solution of **Intermediate 213-1** (200 mg, 0.61 mmol), ethyl bromoacetate (203.45 mg, 1.22 mmol) and potassium carbonate (252.54 mg, 1.83 mmol) in *N,N*-dimethylformamide (1 mL) was stirred at 50 °C for 18 hours. After the reaction was completed, the reaction solution was added with water (10 mL) and extracted with ethyl acetate (10 mL). The combined organic layers were concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate/dichloromethane = 8/1/1) to obtain **Intermediate 245-1** (100 mg, 0.24 mmol, 39.61% yield) as a white solid.

Step 2:

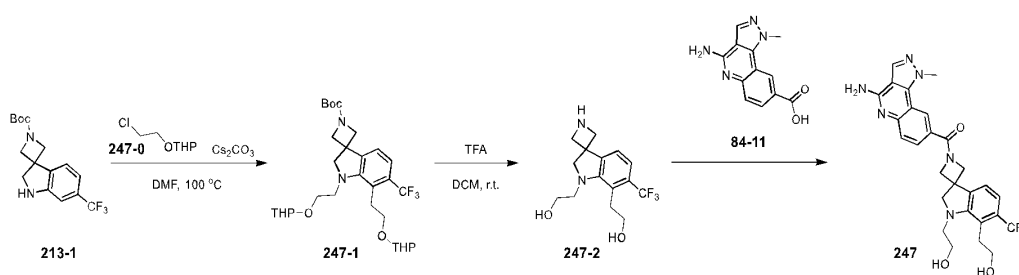
To a solution of **Intermediate 245-1** (90 mg, 0.22 mmol) in ethanol (10 mL) was added sodium borohydride (40 mg, 1.06 mmol). The mixture was stirred at 25 °C for 18 hours. After the reaction was completed, the reaction solution was added with water (2 mL) and extracted with ethyl acetate (2 mL). The organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (DCM /MeOH = 30/1) to obtain **Intermediate 245-2** (80 mg, 0.21 mmol, 98.92% yield) as a white solid.

Step 3:

A solution of **Intermediate 245-2** (90 mg, 0.24 mmol) in dichloromethane (1.5 mL) and trifluoroacetic acid (0.5 mL) was stirred at 25 °C for 2 hours. After the reaction was completed, the reaction solution was concentrated to obtain a crude **Intermediate 245-3** (70 mg, 0.18 mmol, 94.69% yield) as a brown solid, which was directly used in the subsequent step.

Step 4:

A solution of **Intermediate 84-11** (75 mg, 0.31 mmol), chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (110 mg, 0.39 mmol), and *N*-methylimidazole (0.07 mL, 0.84 mmol) in dimethyl sulfoxide (2 mL) was stirred at 25 °C for 10 minutes. The reaction solution was added with **Intermediate 245-3** (76 mg, 0.28 mmol), and then stirred at 25 °C for 2 hours. After the reaction was completed, the reaction solution was filtered and purified by HPLC-MS (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium bicarbonate/water B: acetonitrile; flow rate: 25) to obtain **Compound 245** (5.44 mg, 0.01 mmol, 3.60% yield) as a white solid. MS *m/z* (ESI): 497.2 [M+H]⁺; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.52 (d, *J* = 2.0 Hz, 1H), 8.26 (s, 1H), 7.86 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.59 (t, *J* = 8.5 Hz, 2H), 7.23 (s, 2H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 1.5 Hz, 1H), 4.73 (t, *J* = 5.5 Hz, 1H), 4.64 (s, 2H), 4.42 (s, 3H), 4.26 (d, *J* = 30.0 Hz, 2H), 3.86 (s, 2H), 3.61 (q, *J* = 5.5 Hz, 2H), 3.24 (d, *J* = 7.0 Hz, 2H).

Example 76:**Synthesis of Compound 247****Step 1:**

A solution of **Intermediate 213-1** (150 mg, 0.46 mmol), **Intermediate 247-0** (0.68 mL, 4.57 mmol) and cesium carbonate (1500 mg, 4.60 mmol) in *N,N*-dimethylformamide (10 mL) was stirred at 100°C for 18 hours. After the reaction was completed, the reaction solution was added with water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 247-1** (100 mg, 0.17 mmol, 37.18% yield) as a colorless oil.

Step 2:

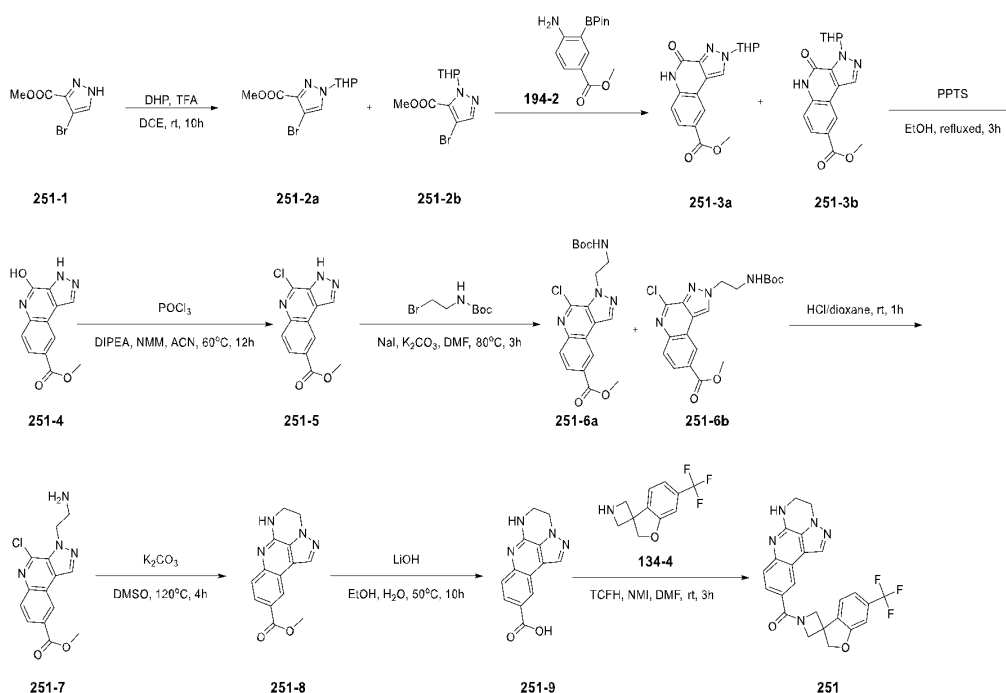
A solution of **Intermediate 247-1** (100 mg, 0.20 mmol) in trifluoroacetic acid (0.5 mL) and dichloromethane (1 mL) was stirred at 25 °C for 2 hours. L After the reaction was completed, the reaction solution was concentrated to obtain a crude **Intermediate 247-2** (50 mg, 0.20 mmol, 83.89% yield) as a yellow solid, which was directly used in the subsequent step.

Step 3:

A solution of **Intermediate 84-11** (80 mg, 0.33 mmol), HATU (188 mg, 0.50 mmol), and *N,N*-diisopropylethylamine (0.29 mL, 1.65 mmol) in dimethyl sulfoxide (2 mL) was stirred at 25 °C for 10 minutes. The reaction solution was added with **Intermediate 247-2** (104 mg, 0.33 mmol) and stirred at 25 °C for 2 hours. After the reaction was completed, the reaction solution was filtered and purified by preparative HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium bicarbonate/water B: acetonitrile; flow rate: 25) to obtain **Compound 247** (10 mg, 0.02 mmol, 5.61% yield) as a white solid. MS m/z (ESI): 541.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.52 (d, *J* = 2.0 Hz, 1H), 8.26 (s, 1H), 7.97 (s, 1H), 7.92 – 7.83 (m, 2H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.25 (s, 2H), 4.93 – 4.61 (m, 4H), 4.42 (brs, 6H), 4.34 – 4.15 (m, 4H), 3.70 – 3.62 (m, 2H).

Example 77:

Synthesis of Compound 251



Step 1:

At room temperature, to a solution of **Intermediate 251-1** (10 g, 48.78 mmol) in 1,2-dichloroethane (100 mL) were added 3,4-dihydro-2H-pyran (8.2 g, 97.56 mmol) and trifluoroacetic acid (0.2 mL). The reaction solution was stirred at room temperature for 10 hours. After the reaction was completed, the reaction solution was diluted with water (300 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4/1) to obtain **Intermediate 251-2a** and **Intermediate 251-2b** (8 g, 27.67 mmol, 56.72% yield) as a colorless solid.

Step 2:

At room temperature, to a solution of **Intermediate 251-2a** and **Intermediate 251-2b** (1.4 g, 4.84 mmol) in 1,4-dioxane (15 mL) were added **Intermediate 194-2** (1.34 g, 4.84 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (0.23 g, 0.48 mmol), methanesulfonic acid (2-dicyclohexylphosphino-2',4',6'-tri-isopropyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium (II) (0.20 g, 0.24 mmol), and potassium phosphate (2.06 g, 9.68 mmol) in sequence under stirring. The mixture was purged with nitrogen three times and

refluxed at 100 °C for 10 hours. After the reaction was completed, the reaction solution was cooled to room temperature and filtered. The filtrate was diluted with water (30 mL), and extracted with ethyl acetate (10 mL). The organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to obtain **Intermediate 251-3a and 251-3b** (800 mg, 2.44 mmol, 50.47% yield) as a white solid.

Step 3:

At room temperature, to a solution of **Intermediate 251-3a and Intermediate 251-3b** (3.80 g, 11.61 mmol) in ethanol (40 mL) was added p-toluenesulfonic acid (0.20 g, 1.16 mmol) under stirring. Under nitrogen atmosphere, the reaction solution was refluxed at 80 °C for 3 hours. The reaction solution was cooled to room temperature and concentrated under reduced pressure. The concentrated solution was slurried in acetonitrile (30 mL) to obtain **Intermediate 251-4** (2.00 g, 8.22 mmol, 70.83% yield) as a gray solid.

Step 4:

At room temperature, to a solution of **Intermediate 251-4** (0.50 mg, 2.06 mmol) in acetonitrile (6 mL) were added *N,N*-diisopropylethylamine (1.59 g, 12.33 mmol) and *N*-methylmorpholine (0.10 g, 1.03 mmol) in sequence under stirring. The mixture was purged with nitrogen three times and added dropwise with phosphorus oxychloride (1.23 g, 8.02 mmol) under ice bath. The reaction solution was stirred at room temperature for 30 minutes, heated to 60 °C and stirred for 12 hours. After the reaction solution was cooled to room temperature, it was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (dichloromethane/methanol = 25/1) to obtain **Intermediate 251-5** (200 mg, 0.76 mmol, 37.18% yield) as a yellow solid.

Step 5:

At room temperature, to a solution of **Intermediate 251-5** (200 mg, 0.76 mmol) in DMF (2 mL) were added potassium carbonate (317 mg, 2.29 mmol), sodium iodide (344 mg, 2.29 mmol) and tert-butyl(2-bromoethyl)carbamate (257 mg, 1.15 mmol) under stirring. The reaction solution was purged with nitrogen three times and stirred at 80 °C for 3 hours. After the reaction was completed, the reaction solution was cooled to room temperature and filtered. The filtrate was diluted with water (10 mL) and extracted with dichloromethane (5 mL). The

organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by C18 column chromatography on silica gel (acetonitrile/water (0.1% FA) = 3/2) to obtain **Intermediate 251-6a** (50 mg, 0.12 mmol, 16.16% yield) and **Intermediate 251-6b** (150 mg, 0.37 mmol, 48.75% yield) as white solids.

Step 6:

At room temperature, a solution of **Intermediate 251-6a** (50 mg, 0.12 mmol) in 1,4-dioxane hydrochloride was stirred for 1 hour. After the reaction was completed, the reaction solution was concentrated under reduced pressure to obtain **Intermediate 251-7** (35 mg, 0.11 mmol, 93.0% yield).

Step 7:

A solution of **Intermediate 251-7** (35 mg, 0.11 mmol) and potassium carbonate (95 mg, 0.69 mmol) in DMSO (0.5 mL) was stirred at 120 °C for 4 hours. The reaction solution was filtered after it was cooled to room temperature. The filtrate was diluted with water (10 mL) and extracted with dichloromethane (5 mL). The organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (dichloromethane/methanol = 10/1) to obtain **Intermediate 251-8** (10 mg, 0.04 mmol, 32.45% yield) as a white solid.

Step 8:

At room temperature, to a mixed solution of methanol (0.5 mL)/water (0.1 mL) were added **Intermediate 251-8** (10 mg, 0.04 mmol) and lithium hydroxide (6.26 mg, 0.15 mmol). The reaction solution was stirred at 50 °C for 10 hours, concentrated under reduced pressure and dried to obtain **Intermediate 251-9** (9 mg, 0.04 mmol, 94.97% yield).

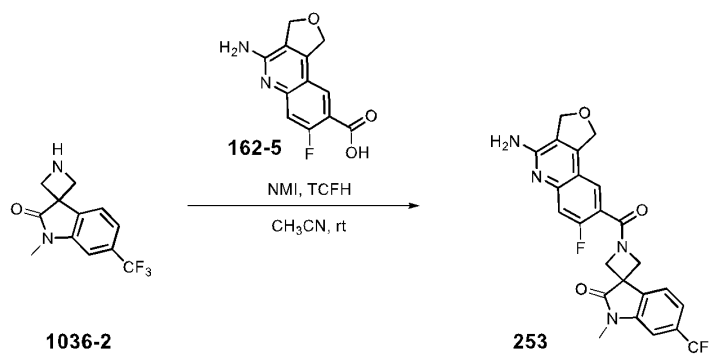
Step 9:

At room temperature, a solution of **Intermediate 251-9** (9 mg, 0.04 mmol) and **Intermediate 134-4** (16 mg, 0.07 mmol) in *N,N*-dimethylformamide (1 mL) were added *N*-methylimidazole (17 mg, 0.21 mmol) and chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (14 mg, 0.05 mmol). The mixture was stirred at room temperature for 3 hours, and then concentrated under reduced pressure. The crude product was purified by

preparative HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10mM NH₄HCO₃; B: ACN, gradient: 30-40%, retention time: 10.5 min) to obtain **Compound 251** (1.0 mg, 6.07% yield). MS m/z (ESI): 465.9 [M+H]⁺; ¹H NMR (400 MHz, MeOD-*d*₄) δ 8.46–8.41 (m, 2H), 7.82–7.74 (m, 3H), 7.32–7.29 (m, 1H), 7.04 (s, 1H), 4.88 (s, 2H), 4.76 (s, 2H), 4.55–4.51 (m, 2H), 4.47 (s, 2H), 3.97 (t, *J* = 5.6 Hz, 2H).

Example 78:

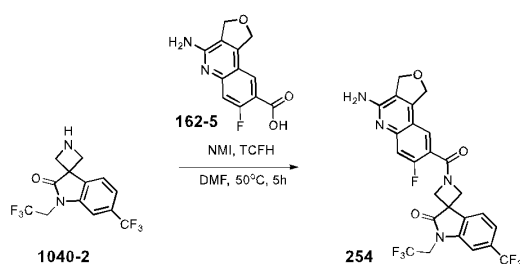
Synthesis of Compound 253



At room temperature, to a solution of **Intermediate 1036-2** (190 mg, 0.74 mmol) in *N,N*-dimethylformamide (4 mL) were added **Intermediate 162-5** (220 mg, 0.89 mmol), *N*-methylimidazole (304 mg, 3.71 mmol) and chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (416 mg, 1.48 mmol). The reaction solution was stirred at 50 °C for 3 hours. The reaction solution was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by C18 column chromatography on silica gel HPLC (column: Welch ultimate XB-NH2 250*50*10 μ m, mobile phase: [Heptane-EtOH(0.1% HCOOH)]; B% 10%-10%, 10min) to obtain **Compound 253** (30 mg, 0.06 mmol, 8.32% yield) as an off-white solid. MS m/z (ESI): 487.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.63 (s, 2H), 8.05 - 8.03 (m, 1H), 7.91 - 7.89 (m, 1H), 7.64 - 7.61 (m, 1H), 7.53 - 7.51 (m, 1H), 7.39 - 7.38 (m, 1H), 5.48 - 5.47 (m, 2H), 5.08 - 5.07 (m, 2H), 4.36 - 4.28 (m, 4H), 3.19 (s, 3H).

Example 79:

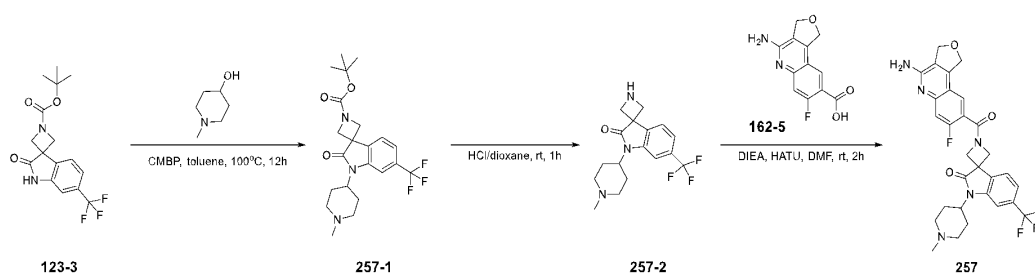
Synthesis of Compound 254



At room temperature, to a solution of **Intermediate 1040-2** (70 mg, 0.22 mmol) in *N,N*-dimethylformamide (4 mL) were added **Intermediate 162-5** (86 mg, 0.35 mmol), *N*-methylimidazole (53 mg, 0.65 mmol) and chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (90 mg, 0.32 mmol). The reaction solution was stirred at 50 °C for 5 hours. The reaction solution was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by C18 column chromatography on silica gel HPLC (column: Welch ultimate XB-NH2 250*50*10um, mobile phase: [heptane-EtOH(0.1% HCOOH)]; B% 10%-10%, 10min) to obtain **Compound 254** (30 mg, 0.05 mmol, 25.06% yield) as an off-white solid. MS *m/z* (ESI): 555.2 [*M*+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.97 - 7.96 (m, 1H), 7.80 - 7.78 (m, 1H), 7.63 - 7.57 (m, 2H), 7.32 - 7.29 (m, 1H), 6.93 (s, 2H), 6.93 (s, 2H), 5.36 (m, 2H), 5.00 - 4.99 (m, 2H), 4.76 - 4.69 (m, 2H), 4.41 - 4.31 (m, 4H).

Example 80:

Synthesis of Compound 257



Step 1:

At room temperature, to a solution of **Intermediate 123-3** (500 mg, 1.46 mmol) in toluene (6 mL) were added *N*-methyl-4-piperidinol (252 mg, 2.19 mmol) and (cyanomethylene)-tri-*n*-butylphosphorane (564 mg, 2.34 mmol) were added under stirring. The reaction solution was purged with nitrogen three times and stirred at 100 °C for 12 hours. After the reaction was

completed, the reaction solution was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (dichloromethane/methanol = 25/1) to obtain **Intermediate 257-1** (350 mg, 0.80 mmol, 54.52% yield) as a yellow oil.

Step 2:

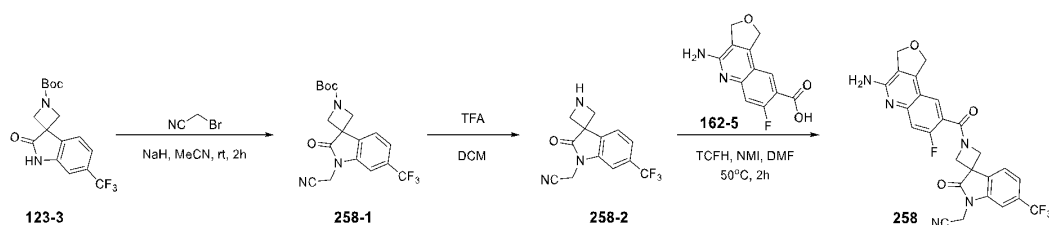
At room temperature, a solution of **Intermediate 257-1** (150 mg, 0.34 mmol) in 1,4-dioxane hydrochloride solution (2 mL) was stirred at room temperature for 1 hour, and then concentrated under reduced pressure to obtain **Intermediate 257-2** (100 mg, 0.29 mmol, 86.34% yield).

Step 3:

At room temperature, to a solution of **Intermediate 257-2** (100 mg, 0.40 mmol) and **Intermediate 162-5** (137 mg, 0.40 mmol) in *N,N*-dimethylformamide (2 mL) were added *N,N*-diisopropylethylamine (156 mg, 1.21 mmol) and HATU (230 mg, 0.60 mmol). The reaction solution was stirred at room temperature for 2 hours, and then concentrated under reduced pressure. The crude product was purified by preparative HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10mM NH₄HCO₃; B: ACN, gradient: 26-56%, retention time: 11 min) to obtain **Compound 257** (13.66 mg, 0.02 mmol, 5.95% yield). MS *m/z* (ESI): 285.6 [1/2M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.94 – 7.87 (m, 1H), 7.81 – 7.75 (m, 1H), 7.53 – 7.47 (m, 1H), 7.43 (s, 1H), 7.34 – 7.27 (m, 1H), 6.92 (s, 2H), 5.41 – 5.30 (m, 2H), 5.03 – 4.91 (m, 2H), 4.38 – 4.23 (m, 4H), 4.17 – 4.07 (m, 1H), 2.95 – 2.84 (m, 2H), 2.38 – 2.31 (m, 2H), 2.23 (s, 3H), 2.14 – 2.04 (m, 2H), 1.66 – 1.56 (m, 2H).

Example 81:

Synthesis of Compound 258



Step 1:

At room temperature, a solution of **Intermediate 123-3** (400 mg, 1.17 mmol) in acetonitrile (5 mL) was stirred until dissolved. Under nitrogen atmosphere the solution was added with sodium hydride (36 mg, 1.17 mmol). The reaction solution was stirred at room temperature for 10 hours, and then added with bromoacetonitrile (144 mg, 1.2 mmol). The reaction solution was stirred at room temperature for 10 hours, added with water (10 mL), and then extracted with ethyl acetate (5 mL). The organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/2) to obtain **Intermediate 258-1** (250 mg, 0.66 mmol, 56.10% yield) as a colorless liquid.

Step 2:

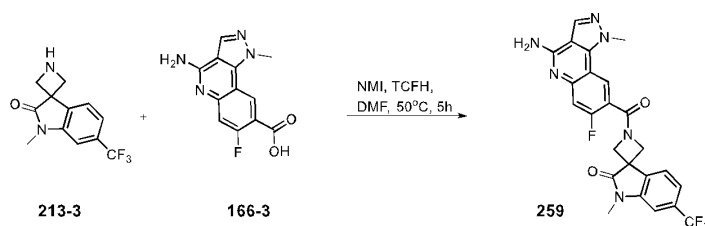
At room temperature, a solution of **Intermediate 258-1** (100 mg, 0.26 mmol) in dichloromethane (1 mL) was prepared. Then the solution was added dropwise with trifluoroacetic acid (0.25 mL) and stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure to obtain **Intermediate 258-2** (80 mg, 0.28 mmol, 108.44% yield) as a colorless liquid.

Step 3:

At room temperature, to a solution of **Intermediate 258-2** (80 mg, 0.28 mmol) and **Compound 162-5** (113 mg, 0.46 mmol) in *N,N*-dimethylformamide (1 mL) were added dropwise *N*-methylimidazole (82 mg, 1.42 mmol) and chloro-*N,N,N',N'*-tetramethylformamidium hexafluorophosphate (280 mg, 0.43 mmol). The reaction solution was stirred at room temperature for 1 hour. The organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10mM NH₄HCO₃; B: ACN, gradient: 5-95%, retention time: 8.3 min) to obtain **Compound 258** (28.45 mg, 0.06 mmol, 19.56% yield). MS *m/z* (ESI): 512.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.40 (d, *J* = 7.59 Hz, 1H), 8.26 (s, 1H), 7.87 (d, *J* = 8.00 Hz, 1H), 7.80 (d, *J* = 7.91 Hz, 1H), 7.75 (s, 1H), 7.36 (s, 2H), 7.31 (d, *J* = 12.54 Hz, 1H), 5.15 (d, *J* = 6.18 Hz, 2H), 4.47 – 4.39 (m, 7H).

Example 82:

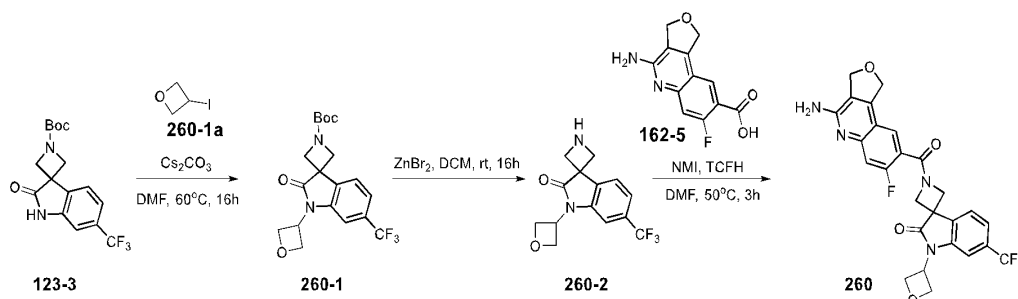
Synthesis of Compound 259



At room temperature, to a solution of **Intermediate 213-3** (126 mg, 0.49 mmol) in *N,N*-dimethylformamide (4 mL) were added **Compound 166-3** (230 mg, 0.89 mmol), *N*-methylimidazole (202 mg, 2.46 mmol) and chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (276 mg, 0.98 mmol). The reaction solution was stirred at 50 °C for 5 hours, cooled to room temperature and concentrated under reduced pressure. The crude product was purified by C18 column chromatography on silica gel HPLC (column: Welch ultimate XB-NH2 250*50*10um, mobile phase: [heptane-EtOH(0.1% HCOOH)]; B% 10%-10%, 10min) to obtain **Compound 259** (60 mg, 0.12 mmol, 24.48% yield) as an off-white solid.

Example 83:

Synthesis of Compound 260



Step 1:

At room temperature and under nitrogen atmosphere, to a solution of **Intermediate 123-3** (700 mg, 2.04 mmol) and **Intermediate 260-1a** (451 mg, 2.45 mmol) in *N,N*-dimethylformamide (5 mL) was added cesium carbonate (1.3 g, 4.09 mmol). The reaction solution was stirred at 60 °C for 16 hours, added with water (2 mL) and extracted with ethyl acetate (5 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4) to obtain

Intermediate 260-1 (400 mg, 1.00 mmol, 49.10% yield) as a white solid.

Step 2:

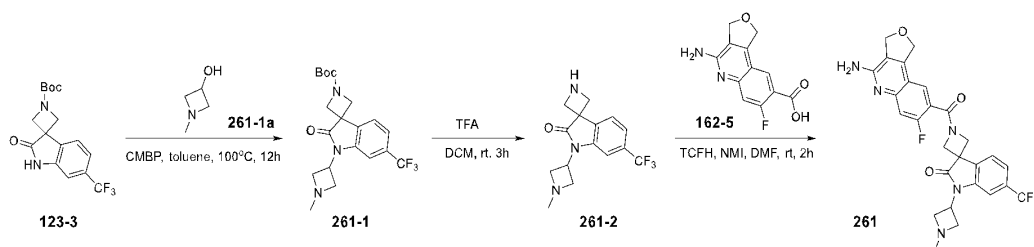
At room temperature, to a solution of **Intermediate 260-1** (560 mg, 1.41 mmol) in dichloromethane (30 mL) was added zinc bromide (1.27 g, 5.62 mmol). The reaction solution was stirred at room temperature under nitrogen atmosphere for 16 hours. After the reaction was completed, the reaction solution was concentrated under reduced pressure. The crude product was purified by C18 column chromatography on silica gel (acetonitrile/water (0.1% FA) = 1/3) to obtain **Intermediate 260-2** (110 mg, 0.34 mmol, 71.98% yield) as a white solid.

Step 3:

At room temperature, to a solution of **Intermediate 260-2** (40 mg, 0.13 mmol) in *N,N*-dimethylformamide (4 mL) were added **Intermediate 162-6** (53 mg, 0.21 mmol), *N*-methylimidazole (55 mg, 0.67 mmol) and chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (75 mg, 0.27 mmol). The reaction solution was stirred at 50 °C for 3 hours, cooled to room temperature and concentrated under reduced pressure. The crude product was purified by C18 column chromatography on silica gel HPLC (column: Welch ultimate XB-NH2 250*50*10um, mobile phase: [Heptane-EtOH(0.1% HCOOH)]; B% 10%-10%, 10min) to obtain **Compound 260** (25 mg, 0.05 mmol, 35.28% yield) as an off-white solid. MS *m/z* (ESI): 529.0 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.97 - 7.95 (m, 1H), 7.80 - 7.78 (m, 1H), 7.64 (s, 1H), 7.58 - 7.56 (m, 1H), 7.32 - 7.29 (m, 1H), 6.93 (s, 2H), 5.48 - 5.44 (m, 3H), 5.02 - 4.99 (m, 4H), 4.93 - 4.89 (m, 2H), 4.35 - 4.25 (m, 4H).

Example 84:

Synthesis of Compound 261



Step 1:

At room temperature and under nitrogen atmosphere, to a solution of **Intermediate 123-3** (300 mg, 0.88 mmol) in toluene (3 mL) were added **Intermediate 261-1a** (76 mg, 0.88 mmol) and cyanomethylenetri-n-butylphosphorane (317 mg, 1.31 mmol). The reaction solution was stirred at 100 °C for 10 hours, added with water (10 mL), and extracted with ethyl acetate (5 mL). The organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/2) to obtain **Intermediate 261-1** (130 mg, 0.32 mmol, 36.05% yield) as a colorless liquid.

Step 2:

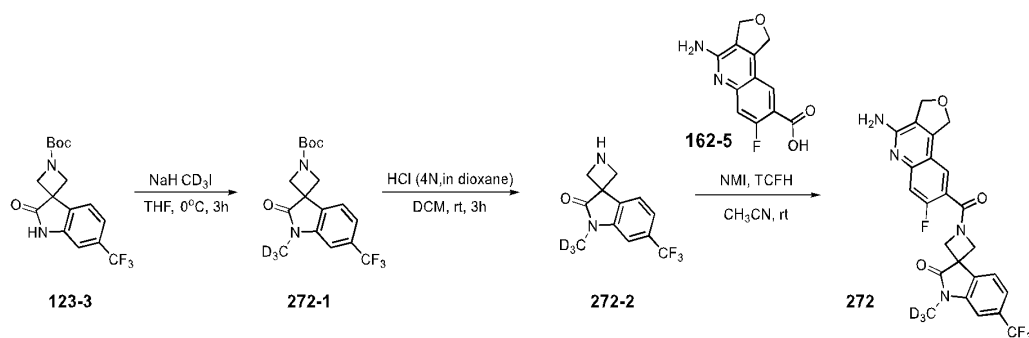
At room temperature, to a solution of **Intermediate 261-1** (130 mg, 0.32 mmol) in dichloromethane (1 mL) was added dropwise trifluoroacetic acid (0.25 mL). The reaction solution was stirred at room temperature for 1 hour, and then concentrated under reduced pressure to obtain **Intermediate 261-2** (98.36 mg, 0.32 mmol, 100% yield) as a colorless liquid.

Step 3:

At room temperature, to a solution of **Intermediate 261-2** (98 mg, 0.32 mmol) and **Intermediate 162-5** (127 mg, 0.51 mmol) in *N,N*-dimethylformamide (1 mL) were added dropwise *N*-methylimidazole (131 mg, 1.60 mmol) and chloro-*N,N,N',N'*-tetramethylformamidium hexafluorophosphate (135 mg, 0.48 mmol). The reaction solution was stirred at room temperature for 1 hour. The organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10mM NH₄HCO₃; B: ACN, gradient: 10-95%, retention time: 9.3 min) to obtain **Compound 261** (12.48 mg, 0.02 mmol, 7.20% yield). MS *m/z* (ESI): 542.4 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.97 (s, 1H), 7.92 (d, *J* = 7.77 Hz, 1H), 7.78 (d, *J* = 7.80 Hz, 1H), 7.53 (d, *J* = 7.93 Hz, 1H), 7.30 (d, *J* = 12.52 Hz, 1H), 6.92 (s, 2H), 5.40 – 5.30 (m, 2H), 5.03 – 4.96 (m, 2H), 4.89 – 4.80 (m, 1H), 4.34 – 4.23 (m, 4H), 3.67 – 3.54 (m, 4H), 2.35 (s, 3H).

Example 85:

Synthesis of Compound 272

**Step 1:**

At 0°C and under nitrogen atmosphere, to a solution of **Intermediate 123-3** (400 mg, 1.17 mmol) in tetrahydrofuran (5 mL) was added sodium hydride (60 mg, 1.52 mmol, 60% purity). The reaction solution was stirred at 0°C for 30 minutes, and then added with deuterated iodomethane (220 mg, 1.52 mmol). The reaction solution was stirred at 0°C for 3 hours, added with water (2 mL) and extracted with ethyl acetate (5 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/3) to obtain **Intermediate 272-1** (80 mg, 0.22 mmol, 19.05% yield) as a white solid.

Step 2:

At room temperature and under nitrogen atmosphere, to a solution of **Intermediate 272-1** (20 mg, 0.06 mmol) in dichloromethane (1 mL) was added 1,4-dioxane hydrochloride (4 N, 1.00 mL, 5.00 mmol). The reaction solution was stirred for 3 hours at room temperature under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure. The crude product was purified by C18 column chromatography on silica gel (acetonitrile/water (0.1% FA) = 2/3) to obtain **Intermediate 272-2** (10 mg, 0.04 mmol, 69.30% yield) as a white solid.

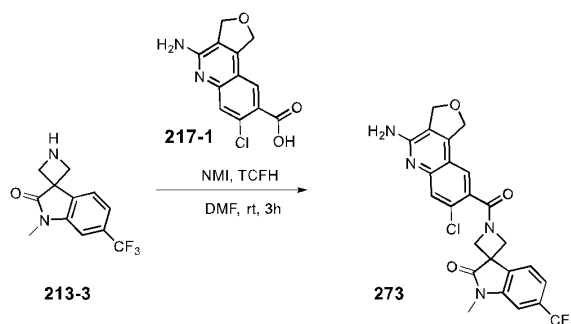
Step 3:

At room temperature, to a solution of **Intermediate 272-2** (67 mg, 0.26 mmol) in *N,N*-dimethylformamide (4 mL) were added **Intermediate 162-5** (96 mg, 0.39 mmol), *N*-methylimidazole (106 mg, 1.29 mmol) and chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (145 mg, 0.52 mmol). The reaction solution was stirred at 50 °C for 3

hours, cooled to room temperature and concentrated under reduced pressure. The crude product was purified by C18 column chromatography on silica gel HPLC (column: Welch ultimate XB-NH2 250*50*10um, mobile phase: [Heptane-EtOH(0.1% HCOOH)]; B% 10%-10%, 10min) to obtain **Compound 272** (20 mg, 0.04 mmol, 15.81% yield) as an off-white solid. MS m/z (ESI): 490.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 7.90 – 7.89 (m, 1H), 7.82 – 7.80 (m, 1H), 7.52 – 7.49 (m, 1H), 7.37 – 7.32 (m, 2H), 7.05 (s, 2H), 5.39 – 5.36 (m, 2H), 5.01 – 4.99 (m, 2H), 4.34 – 4.25 (m, 4H).

Example 86:

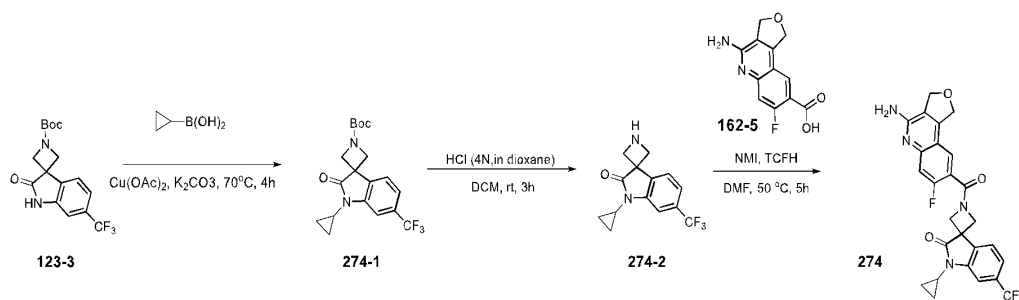
Synthesis of Compound 273



At room temperature, to a solution of **Intermediate 213-3** (40 mg, 0.15 mmol) in *N,N*-dimethylformamide (4 mL) were added **Intermediate 217-1** (38 mg, 0.15 mmol), *N*-methylimidazole (31 mg, 0.38 mmol) and chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (63 mg, 0.23 mmol). The reaction solution was stirred for 3 hours, and then concentrated under reduced pressure. The crude product was purified by C18 column chromatography on silica gel HPLC (column: Welch ultimate XB-NH2 250*50*10um, mobile phase: [heptane-EtOH (0.1% HCOOH)]; B% 10%-10%, 10min) to obtain **Compound 273** (13 mg, 0.03 mmol, 17% yield) as an off-white solid. MS m/z (ESI): 503.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 7.90 – 7.85 (m, 1H), 7.72 (s, 1H), 7.61 (s, 1H), 7.56 – 7.50 (m, 1H), 7.39 – 7.37 (m, 1H), 6.92 (s, 2H), 5.40 – 5.30 (m, 2H), 4.99 (s, 2H), 4.35 – 4.30 (m, 1H), 4.28 – 4.24 (m, 1H), 4.20 – 4.11 (m, 2H), 3.19 (s, 3H).

Example 87:

Synthesis of Compound 274



Step 1:

A solution of **Intermediate 213-3** (400 mg, 1.17 mmol), cyclopropylboronic acid (1.6 g, 18.7 mmol), potassium carbonate (485 mg, 3.51 mmol), and copper acetate (933 mg, 4.67 mmol) in 1,2-dichloroethane (10 mL) was stirred at 70 °C for 4 hours. After the reaction was completed, the reaction solution was concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to obtain **Intermediate 274-1** (360 mg, 0.94 mmol, 80.57% yield) as a white solid.

Step 2:

At room temperature, to a solution of **Intermediate 274-1** (20 mg, 0.05 mmol) in dichloromethane (1 mL) was added 1,4-dioxane hydrochloride (4 N, 1 mL, 4.00 mmol). The reaction solution was stirred at room temperature under nitrogen atmosphere for 3 hours. After the reaction was completed, the reaction solution was concentrated under reduced pressure. The crude product was purified by C18 column chromatography on silica gel (acetonitrile/water (0.1% FA) = 2/3) to obtain **Intermediate 274-2** (2 mg, 0.01 mmol, 13.55% yield) as a white solid.

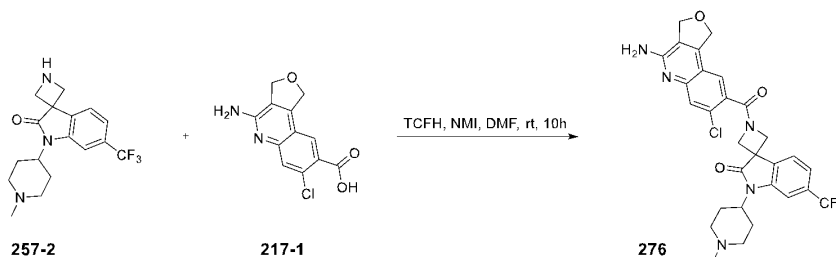
Step 3:

At room temperature, to a solution of **Intermediate 274-2** (100 mg, 0.35 mmol) in *N,N*-dimethylformamide (4 mL) was added **Intermediate 162-5** (132 mg, 0.53 mmol), *N*-methylimidazole (145 mg, 1.77 mmol) and chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (200 mg, 0.71 mmol). The reaction solution was stirred at 50 °C for 5 hours, cooled to room temperature and concentrated under reduced pressure. The crude product was purified by HPLC on a C18 chromatography column (column: Welch ultimate XB-NH2 250*50*10um, mobile phase: [heptane-EtOH (0.1% HCOOH)]; B% 10%-10%, 10min) to obtain **Compound 274** (30 mg, 0.06 mmol, 16.52% yield) as an off-white solid. MS *m/z* (ESI):

513.0 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.90 - 7.88 (m, 1H), 7.84 - 7.82 (m, 1H), 7.53 - 7.51 (m, 1H), 7.38 - 7.35 (m, 1H), 7.29 - 7.28 (m, 1H), 5.40 - 5.37 (m, 2H), 5.02 - 5.00 (m, 2H), 4.31 - 4.23 (m, 4H), 2.72 (m, 1H), 1.03 - 1.01 (m, 2H), 0.82 - 0.81 (m, 2H).

Example 88:

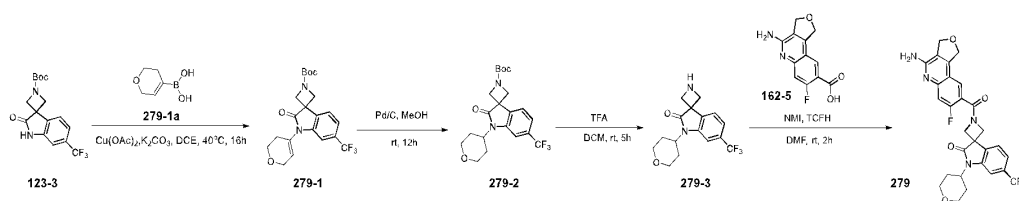
Synthesis of Compound 276



At room temperature, to a solution of **Intermediate 257-2** (200 mg, 0.59 mmol) and **Intermediate 217-1** (156 mg, 0.59 mmol) in *N,N*-dimethylformamide (2 mL) were added chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (165 mg, 0.59 mmol) and *N*-methylimidazole (145 mg, 1.77 mmol). The reaction solution was stirred at room temperature for 10 hours. The reaction solution was added with water (10 mL) and extracted with ethyl acetate (5 mL). The organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by HPLC (Waters-Xbridge-C18-10μm-19*250mm, mobile phase: A: 10mM FA; B: ACN, gradient: 10-95%, retention time: 8.6 min) to obtain **Compound 276** (11.82 mg, 0.02 mmol, 3.42% yield). MS *m/z* (ESI): 586.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.88 (d, *J* = 7.6 Hz, 1H), 7.71 (s, 1H), 7.61 (s, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.43 (s, 1H), 6.90 (s, 2H), 5.40 - 5.30 (m, 2H), 4.99 (d, *J* = 3.6 Hz, 2H), 4.34 - 4.24 (m, 2H), 4.19 - 4.07 (m, 3H), 2.86 (d, *J* = 10.0 Hz, 2H), 2.38 - 2.30 (m, 2H), 2.21 (s, 3H), 2.04 (t, *J* = 11.6 Hz, 2H), 1.61 (d, *J* = 12.0 Hz, 2H).

Example 89:

Synthesis of Compound 279

**Step 1:**

A solution of **Intermediate 123-3** (380 mg, 1.11 mmol), **Intermediate 279-1a** (213 mg, 1.67 mmol), sodium carbonate (307 mg, 2.22 mmol), and copper acetate (443 mg, 2.22 mmol) in 1,2-dichloroethane (5 mL) was stirred at 40 °C for 16 hours. After the reaction was completed, the reaction solution was concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 279-1** (300 mg, 0.71 mmol, 63.68% yield) as a yellow oil.

Step 2:

At room temperature, to a solution of **Intermediate 279-1** (100 mg, 0.2 mmol) in methanol (2 mL) was added Pd/C (251 mg, 2.02 mmol, 60%) and the solution was stirred at room temperature for 12 hours. After the reaction was completed, the reaction solution was concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to obtain **Intermediate 279-2** (20 mg, 0.04 mmol, 19.9% yield) as a white solid.

Step 3:

A solution of **Intermediate 279-2** (30 mg, 0.07 mmol) in trifluoroacetic acid (1 mL)/dichloromethane (1 mL) was stirred at 25 °C for 5 hours. After the reaction was completed, the reaction solution was quenched with saturated aqueous sodium bicarbonate solution (3 mL), extracted with ethyl acetate (2 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to obtain a crude **Intermediate 279-3** (10 mg, 0.03 mmol, 43.56% yield) as a brown solid.

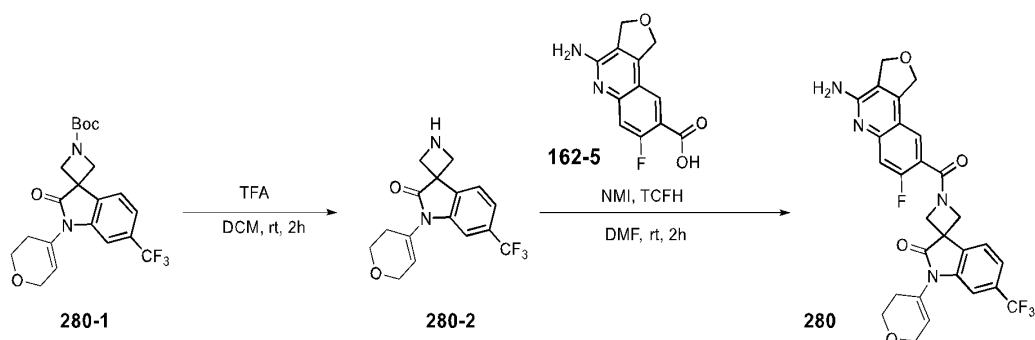
Step 4:

A solution of **Intermediate 162-5** (22.8 mg, 0.09 mmol), chloro-*N,N,N',N'*-tetramethylformamidium hexafluorophosphate (34 mg, 0.12 mmol), and *N*-methylimidazole (25 mg, 0.31 mmol) in *N,N*-dimethylformamide (3 mL) was stirred at 25 °C for 30 minutes,

and then added with **Intermediate 279-3** (20 mg, 0.06 mmol). The reaction was stirred at 25 °C for 2 hours. After the reaction was completed, the reaction solution was concentrated and then added with dimethyl sulfoxide (3 mL). The crude product was purified by preparative HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium bicarbonate/water B: acetonitrile; flow rate: 25) to obtain **Compound 279** (10 mg, 0.02 mmol, 29.32% yield) as a white solid. MS m/z (ESI): 557.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.92 - 7.90 (m, 1H), 7.80 - 7.78 (m, 1H), 7.51 - 7.50(m, 2H), 7.32 - 7.29 (m, 1H), 6.94 (s, 2H), 5.38 - 5.35 (m, 2H), 5.01 - 4.99 (m, 2H), 4.37 - 4.25 (m, 5H), 3.96 - 3.94 (m, 2H), 3.49 - 3.43 (m, 2H), 2.39 - 2.36 (m, 2H), 1.62 - 1.61 (m, 2H).

Example 90:

Synthesis of Compound 280



Step 1:

A solution of **Intermediate 280-1** (20 mg, 0.04 mmol) in trifluoroacetic acid (1 mL)/dichloromethane (1 mL) was stirred at 25 °C for 2 hours. After the reaction was completed, the reaction solution was quenched with saturated aqueous sodium bicarbonate solution (3 mL) and extracted with ethyl acetate (2 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to obtain a crude **Intermediate 280-2** (4 mg, 0.01 mmol, 26.18% yield) as a brown solid.

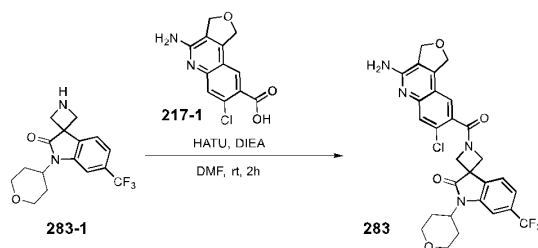
Step 2:

A solution of **Intermediate 162-5** (23 mg, 0.09 mmol), chloro-*N,N,N',N'*-tetramethylformamidium hexafluorophosphate (35 mg, 0.12 mmol), and *N*-methylimidazole

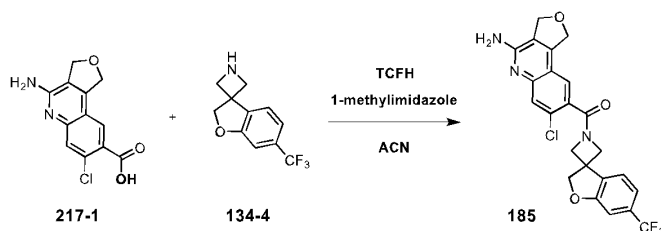
(25 mg, 0.31 mmol) in *N,N*-dimethylformamide (5 mL) was stirred at 25°C for 30 minutes, and then added with **Intermediate 280-2** (20 mg, 0.06 mmol). The reaction solution was stirred at 25 °C for 2 hours. After the reaction was completed, the reaction solution was concentrated and dissolved in dimethyl sulfoxide (3 mL). The crude product was purified by preparative HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium bicarbonate/water B: acetonitrile; flow rate: 25) to obtain **Compound 280** (5 mg, 0.01 mmol, 14.62% yield) as a white solid. MS *m/z* (ESI): 555.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.96 - 7.94 (m, 1H), 7.80 - 7.78 (m, 1H), 7.55 - 7.53 (m, 1H), 7.32 - 7.29 (m, 1H), 7.14 - 7.13(m, 1H), 6.93 (s, 2H), 6.04 -6.02 (m, 1H), 5.37 - 5.36 (m, 2H), 5.01 - 4.99 (m, 2H), 4.37 – 4.27 (m, 6H), 3.88 - 3.85 (m, 2H), 2.34 (s, 2H).

Example 91:

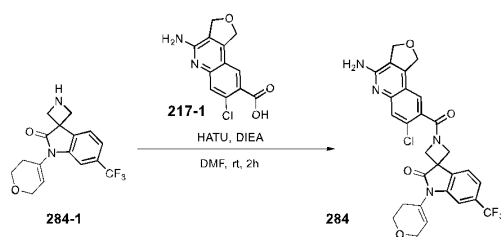
Synthesis of Compound 283



A solution of **Intermediate 217-1** (12 mg, 0.05 mmol), *N,N,N',N'*-tetramethylurea hexafluorophosphate (14 mg, 0.04 mmol), and *N,N*-diisopropylethylamine (6.0 mg, 0.05 mmol) in *N,N*-dimethylformamide (2 mL) was stirred at 25 °C for 30 minutes, and then added with **Intermediate 283-1** (10 mg, 0.03 mmol). The reaction solution was stirred at 25 °C for 2 hours. After the reaction was completed, the reaction solution was concentrated and dissolved in dimethyl sulfoxide (3 mL). The crude product was purified by preparative HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium bicarbonate/water B: acetonitrile; flow rate: 25) to obtain **Compound 283** (2 mg, 3.49 μ mol, 11.39% yield) as a white solid. MS *m/z* (ESI): 573.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.89 - 7.88(m, 1H), 7.72 (s, 1H), 7.62 (s, 1H), 7.53 - 7.51 (m, 2H), 6.91 (s, 2H), 5.37 - 5.34 (m, 2H), 5.00 - 4.98 (m, 2H), 4.37 – 4.25 (m, 3H), 4.19 – 4.12 (m, 2H), 3.96 - 3.94 (m, 2H), 3.49 - 3.43 (m, 2H), 2.39 – 2.35 (m, 2H), 1.61 - 1.60 (m, 2H).

Example 92:**Synthesis of Compound 185**

To a solution of **Intermediate 217-1** (158 mg, 0.30 mmol) in dimethyl sulfoxide (3 mL) were added **Intermediate 134-4** (130 mg, 0.57 mmol), 1-methylimidazole (190 μ L, 2.39 mmol) and TCFH (167 mg, 0.60 mmol). The mixture was stirred at 20 °C for 2 hours. After the reaction was completed, the crude product was purified by preparative HPLC (SunFire-C18-10 μ m-19*250mm, flow rate: 25 mL/min, mobile phase: A: 10 mM NH_4HCO_3 / H_2O B: ACN) to obtain **Compound 185** (16.86 mg, 0.04 mmol, 11.87% yield) as a white solid. MS m/z (ESI): 476.3 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.78 (d, J = 7.6 Hz, 1H), 7.68 (s, 1H), 7.61 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 1.6 Hz, 1H), 6.89 (s, 2H), 5.34 (s, 2H), 5.00 (t, J = 3.2 Hz, 2H), 4.94 – 4.77 (m, 2H), 4.39 (d, J = 10.4 Hz, 1H), 4.31 – 4.19 (m, 2H), 4.14 (d, J = 9.2 Hz, 1H).

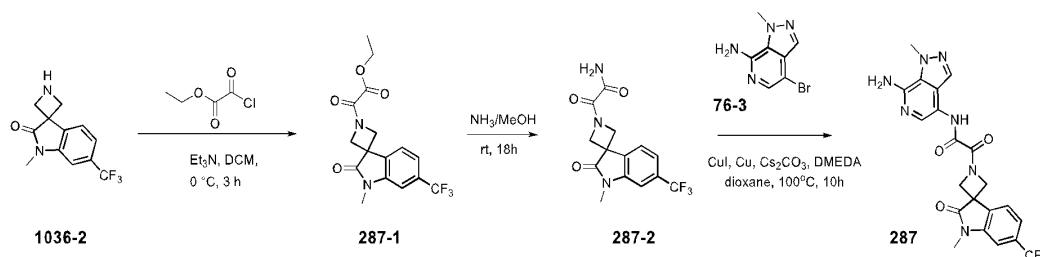
Example 93:**Synthesis of Compound 284**

A solution of **Intermediate 217-1** (12 mg, 0.05 mmol), *N,N,N',N'*-tetramethylurea hexafluorophosphate (14 mg, 0.04 mmol), and *N,N*-diisopropylethylamine (6.0 mg, 0.05 mmol) in *N,N*-dimethylformamide (2 mL) was stirred at 25 °C for 30 minutes, and then added with **Intermediate 284-1** (10 mg, 0.03 mmol). The reaction solution was stirred at 25 °C for 2

hours. After the reaction was completed, the reaction solution was concentrated and dissolved in dimethyl sulfoxide (3 mL). The crude product was purified by preparative HPLC (Waters-Xbridge-C18-10 μ m-19*250mm; mobile phase: A: 10mM ammonium bicarbonate/water B: acetonitrile; flow rate: 25) to obtain **Compound 284** (2 mg, 3.52 μ mol, 11.69% yield) as a white solid. MS m/z (ESI): 571.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.93 – 7.91 (m, 1H), 7.72 (s, 1H), 7.62 (s, 1H), 7.57 – 7.55 (m, 1H), 7.14 – 7.13 (m, 1H), 6.90 (s, 2H), 6.04 – 6.03 (m, 1H), 5.36 – 5.35 (m, 2H), 5.00 – 4.98 (m, 2H), 4.38 – 4.15 (m, 6H), 3.87 – 3.85 (m, 2H), 2.34 (s, 2H).

Example 94:

Synthesis of Compound 287



Step 1:

At 0 °C, to a solution of **Intermediate 1036-2** (210 mg, 1.00 mmol) in dichloromethane (6 mL) were added triethylamine (124 mg, 1.23 mmol) and ethyl oxalyl chloride (123 mg, 0.9 mmol). The reaction solution was stirred at 0 °C for 3 hours and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to obtain **Intermediate 287-1** (200 mg, 0.56 mmol, 68% yield) as a yellow solid.

Step 2:

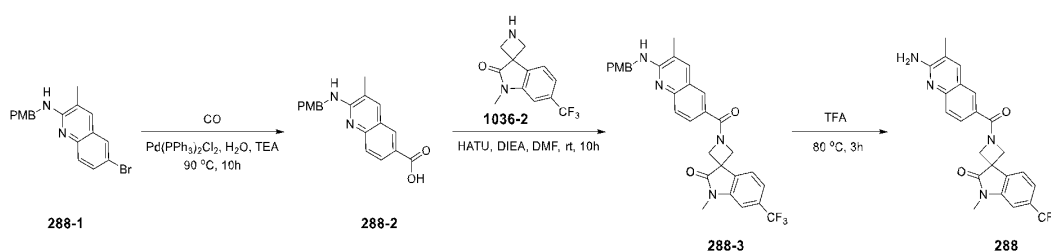
A solution of **Intermediate 287-1** (200 mg, 0.9 mmol) in ammonia (5 mL, 7 M in methanol) was stirred at room temperature for 18 hours. The reaction solution was concentrated under reduced pressure to obtain **Intermediate 287-2** (170 mg, 0.52 mmol, 92% yield) as a yellow solid.

Step 3:

To a solution of **Intermediate 76-3** (34 mg, 0.15 mmol) and **Compound 6** (50 mg, 0.15 mmol) in 1,4-dioxane (2 mL) were added copper powder (11 mg, 0.18 mmol), cuprous iodide (34 mg, 0.18 mmol), cesium carbonate (99 mg, 0.31 mmol) and *N,N'*-dimethylethylenediamine (20 mg, 0.23 mmol). The reaction solution was stirred at 100 °C under nitrogen atmosphere for 10 hours. The reaction solution was quenched with water (20 mL), and then extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative HPLC (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10mM NH₄HCO₃; B: ACN, gradient: 5-61%, retention time: 9.5 min) to obtain white **Compound 287** (6 mg, 0.01 mmol, 8.3% yield). MS *m/z* (ESI): 474.2 [M+H]⁺; ¹H NMR (400 MHz, CH₃OD) δ 7.97 (s, 1H), 7.91 – 7.86 (m, 1H), 7.81 (s, 1H), 7.51 – 7.48 (m, 1H), 7.30 – 7.27 (m, 1H), 5.00 – 4.96 (m, 1H), 4.92 – 4.88 (m, 1H), 4.50 – 4.45 (m, 1H), 4.40 – 4.36 (m, 1H), 4.34 (s, 3H), 3.28 (s, 3H).

Example 95:

Synthesis of Compound 288



Step 1:

At room temperature, to a solution of **Intermediate 288-1** (500 mg, 1.40 mmol) in triethylamine (5 mL)/water (1 mL) were added bistriphenylphosphine palladium dichloride (98 mg, 0.14 mmol) and triphenylphosphine (73 mg, 0.28 mmol). The system was subject to replacement of carbon monoxide three times, and the reaction solution was refluxed for 10 hours. The reaction solution was filtered. The filtrate was added with water (20 mL) and extracted with ethyl acetate (10 mL). The organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (methanol/dichloromethane = 1/10) to obtain **Intermediate 288-2** (100 mg, 0.31 mmol, 22.16% yield) as a white solid.

Step 2:

At room temperature, to a solution of **Intermediate 288-2** (100 mg, 0.31 mmol) and **Intermediate 1036-2** (79 mg, 0.31 mmol) in *N,N*-dimethylformamide (1 mL) were added 2-(7-azobenzotriazole)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (118 mg, 0.31 mmol) and *N,N*-diisopropylethylamine (10 mg, 0.31 mmol). The reaction solution was stirred at room temperature for 10 hours, added with water (10 mL), and extracted with ethyl acetate (5 mL). The organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate) to obtain **Intermediate 288-3** (70 mg, 0.12 mmol, 40.25% yield) as a white solid.

Step 3:

At room temperature, a solution of **Intermediate 288-3** (70 mg, 0.12 mmol) in trifluoroacetic acid (1 mL) was stirred at 80 °C for 3 hours, and then concentrated under reduced pressure. The crude product was purified by high performance liquid chromatography (Waters-Xbridge-C18-10 μ m-19*250mm, mobile phase: A: 10mM FA; B: ACN, gradient: 0-66%, retention time: 13.2 min) to obtain **Intermediate 288** (3.20 mg, 0.01 mmol, 5.82% yield). MS *m/z* (ESI): 441.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.02 (s, 1H), 7.96 (d, *J* = 7.72 Hz, 1H), 7.84 (s, 1H), 7.75 (dd, *J* = 8.8, 2.00 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.38 (s, 1H), 6.59 (s, 2H), 4.79 – 4.49 (m, 2H), 4.43 – 4.19 (m, 2H), 3.20 (s, 3H), 2.21 (s, 3H).

Example 96

Other specific compounds of Formula (I) were synthesized by procedures similar to those described in Example 1 to 95 above.

Biological examples:**Example A. PRMT5 inhibition based on TR-FRET assay**

Biological examples:

Example A. PRMT5 inhibition based on TR-FRET assay

Example compounds were prepared in the form of stock solutions in DMSO at 10mM and 20mM. The stock solutions were further formulated to serial diluted solutions for test; 4 μ L of each sample of the test compounds was introduced into a 384-well microplate. Then, 5 μ L of a mixture solution of PRMT5 enzyme and MTA was added to each well of such microplate, and the test samples were incubated for 30 minutes at room temperature.

Histone H4 peptide and S-adenosylmethionine were mixed to produce a PRMT5 substrate solution and each well of the microplate was added with 8 μ L of the PRMT5 substrate solution to initiate the reaction. The reaction samples were incubated for 90 minutes at room temperature and then each well was added with a mixed solution of Protin-A-Eu, anti-Histone H4 (symmetric dimethyl R3) antibody and streptavidin-d2 to terminate the reaction. The microplate was placed on a BMG reader for reading at wavelengths of 615 nm and 665 nm in accordance with TR-FRET protocol. The relation diagram of percentage inhibition and concentration of the test compounds were plotted using GraphPad Prism to calculate the IC₅₀.

Table 1: TR-FRET MTA+ activity data

Compound No.	TR-FRET MTA+ IC ₅₀ (nM)
084	1.29
112	0.48
134	0.57
135	2.52
139	0.82
140	0.71
146	0.49
166	0.59
902	0.59
1045	0.58
234	0.86
237	0.55
253	0.49

Example B. Cell proliferation assay in MTAPdel HCT116 and Wild Type HCT116 cell lines

On day 0, HCT116 MTAPdel cell and HCT116 wild type cell lines were seeded in 384-well microplate supplemented with McCOYS 5A containing 10% fetal bovine serum and pen/strep and incubated overnight in an incubator under the condition of 37°C, 5% CO₂. On the following day, 40µL of DMSO vehicle, as a control, and different concentrations of Example compounds were added to independent wells of the microplate. Such microplate was placed in the incubator under the condition of 37°C, 5% CO₂ for incubation for ten days.

On Day 10, each well of the microplate was added with 40µL CTG solution (Promega, Cat No. G7573) and then the microplate was placed in the incubator under the condition of 37°C, 5% CO₂ for incubation for 30 minutes. The inhibitory effect was evaluated using a CTG assay kit (CellTiterGlo; Promega cat.no G7573) in accordance with the manufacturer's instructions. The IC₅₀ values for each compound after 10 days of treatment were calculated using GraphPad PRISM software.

Calculation of IC₅₀:

$$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogIC}_{50} - X) * \text{HillSlope})})$$

X: log of inhibitor concentration

Y: % Inhibition.

Table 2 shows the cell amplification activity data in MTAPdel HCT116 and Wild Type HCT116 cell lines (10 days):

EXAMPLE	HCT-116 MTAPdel IC ₅₀ (nM)	HCT-116 WT IC ₅₀ (nM)
084	12	1863
112	956	21220
122	13	2327
123	15	5469
131	9	2246
133	40	961
134	6	1247
135	2369	42920
136	134	10270

EXAMPLE	HCT-116 MTAPdel IC ₅₀ (nM)	HCT-116 WT IC ₅₀ (nM)
137	34	7898
139	351	7320
140	366	14340
146	23	3515
149	1	129
155	17	3503
160	71	9320
162	11	2059
163	28	2758
164	25	1762
165	3	234
166	2	478
167	151	15080
901	2	266
178	46	4648
1036	3	502
1040	3	652
902	11	2799
185	14	1297
1039	3	425
1038	3	434
189	139	1888
1102	10150	>50000
1090	9	915
194	261	3401
195	10	2257
196	11	2289
1100	1356	17590
1045	3	322
1093	104	6890

EXAMPLE	HCT-116 MTAPdel IC ₅₀ (nM)	HCT-116 WT IC ₅₀ (nM)
202	11	1427
203	17	328
204	49	329
205	4020	3438
1088	620	14410
208	4758	13430
209	810	23950
210	163	8476
211	6845	27340
919	283	12670
213	4	1448
1041	4	802
215	15	2321
216	32	3147
217	4	711
218	13	1340
219	4	233
220	4	551
221	8	531
222	5027	9886
223	8	897
224	3	315
225	2	343
228	6	1268
229	38	3303
230	32	4618
1042	13	1316
232	16	1932
233	28	9066
234	0.2	175

EXAMPLE	HCT-116 MTAPdel IC ₅₀ (nM)	HCT-116 WT IC ₅₀ (nM)
237	0.1	59
238	31	19100
239	28	1319
1044	17	2363
242	200	4910
243	1375	16810
245	15	2091
247	80	5328
251	8191	8473
253	6	984
254	5	974
257	18	2540
258	16	3664
259	3.4	431
260	10.8	3289
261	70	10300
272	8	2280
273	5	1739
274	4	1229
276	7	1071
279	11.3	832
280	11.2	1450
283	6	438
284	9	1061
287	3832	>50000
288	1837	10300

Example C: In vivo pharmacokinetics studies

Formulation preparation:

Compounds to be tested were formulated into solutions for intravenous (IV)

administration or suspensions for oral (PO) administration, at different concentrations. The IV formulations were prepared with 20% SBE- β -CD in 50 mM citric acid, pH 5 solution and the PO formulations were prepared with water containing 0.5% methylcellulose (viscosity 4,000 cP) and 0.2% Tween 80 (polyoxyetbylenesorbitan monooleate).

Dosage administration and sample collection:

The formulations were administered intravenously via tail vein at dose of 3 mg/Kg or orally via oral gavage at dose of 10 mg/Kg to male CD-I mice, 6-8 weeks. Blood was collected via facial vein bleeding. Blood samples were put on ice and centrifuged to obtain plasma sample (2000g, 5 min under 4°C) within 15 minutes of collection. The concentration of tested compounds in mouse plasma was determined by LC/MS/MS.

The pharmacokinetic parameters were calculated using Phoenix WinNonlin V 8.2 statistics software with a non-compartmental model. Key parameters such as half-life ($T_{1/2}$) from IV dosing and maximum concentration (C_{max}), AUC_{0-t} , oral bioavailability (F%) from PO dosing were obtained and summarized in Table 3.

Table 3: Pharmacokinetic (PK) Parameters of Exemplary Compounds

Compound	Half-life (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)	F%
084	11	2813	40272	41
134	16	2373	39639	63
146	5.8	3427	37818	42
166	12	3407	46846	82
183	2.8	8013	40006	55
196	2.9	9413	41950	55
200	5.3	1633	19628	45
221	2.9	5900	17419	73
234	3.3	3297	18901	88
253	4.1	23967	134926	58
272	3.5	7300	94305	57

The result of pharmacokinetic studies showed desired PK parameters that provide drug exposure and flexibility for the treatment in cancers.

Example D: In vivo pharmacodynamic evaluation of human lung cancer LU99 cell subcutaneous xenograft tumor BALB/c nude mouse model

The BALB/c nude mouse model of human lung cancer LU99 xenograft tumors with

homozygous MTAP gene deletion was used to determine the inhibitory effect of compounds in MTAP gene deleted cancer.

Cell culture: LU99 cells were maintained in vitro as monolayer culture in RPMI-1640 Medium supplemented with 10% fetal bovine serum at 37°C in an atmosphere of 5% CO₂ in air. The tumor cells were routinely subcultured weekly by trypsin-EDTA treatment, not to exceed 4-5 passages. The cells growing in an exponential growth phase were harvested and counted for tumor inoculation.

Method for Tumor Inoculation and Randomization: 0.1 mL of LU99 tumor cells (1×10^7) was subcutaneously inoculated on the right flank of each mouse. When the average tumor volume reached 150 mm³, they were divided into groups by randomization to minimize group to group variation in tumor volume.

Compounds were suspended in an aqueous solution containing 0.5% (w/v) methyl cellulose (MC) and 0.2% (v/v) Tween 80, and administered at 10 mL/kg Volumetric gavage was given to mice once a day (QD).

The measurement of tumor size was conducted twice per week with a caliper and the tumor volume (mm³) was estimated using the formula: $TV = a \times b^2/2$, where “a” and “b” are the long and short diameters of a tumor, respectively. The TVs are used for calculation of the tumor growth inhibition rate (TGI (%), an indicator of antitumor effectiveness) using the formula: $TGI (\%) = (1-T/C) \times 100\%$, where “T” and “C” are the mean relative volumes (% tumor growth) of the tumors in the treated and the control groups, respectively.

sDMA levels in tumor from treated and control groups were also determined to evaluate the PRMT5 inhibition in tumors. Tumors from each mouse were weighted and homogenized in RIPA buffer supplemented with protease inhibitor (Halt Protease & Phosphatase inhibitor cocktail, EDTA-free (100x), ThermoFisher Scientific, Catalog #: 78445). Lysate were centrifuged at 12,000 rpm for 15 min at 4°C. to remove debris. Total protein concentrations of lysate were determined by BCA assay (ThermoFisher Scientific, Catalog #: 23227). Equal amount of total proteins from each tumor were separated on SDS-PAGE gel, and sDMA levels were determined by Western Blotting.

Western Blotting: Total 20 µg protein from each sample were loaded for electrophoresis and the gels run at constant voltage of 120 min in MOPS running buffer. After transferring to a nitrocellulose membrane using Transblot (0.3A,1.5h), the membrane was blocked with blocking buffer for 1 hour at room temperature. The membrane was then incubated overnight at 4°C with primary antibody (SYM11, Sigma, Catalog #: 07-413). The membrane was washed

6 times with 1 x 0.5%TBST and incubated with secondary antibody (anti-rabbit or anti-mouse IgG, Li-Cor 926-32211 or 926-68070) for 1 hour at room temperature. The membrane was washed 6 times again with 1 x 0.5%TBST and the result was detected with Odyssey CLx imager. The scale of the target band was analyzed using Image studio. Normalization with control was applied to calculate the related expression of groups following the equations as below: $\text{Related expression} = \text{Density}_{\text{target}} / \text{Density}_{\text{control}}$

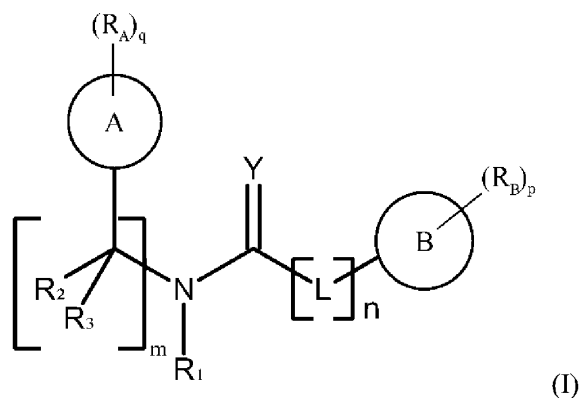
The result showed that Compound 134, Compound 166 and Compound 253, administered QD at doses of 25 mg/kg, demonstrated significant anti-tumor effect. After 21 days of administration, the tumor growth inhibition rate (TGI%) was 90.3%, 95.8%, and 92.2%, respectively. The sDMA level was measured from tumor samples collected at the time around C_{max} (T_{max}) after final dosing. Comparing to control, significant sDMA level reductions (>90%) were observed for Compound 134, Compound 166 and Compound 253.

While the invention has been described and illustrated with reference to specific embodiments thereof, these descriptions and illustrations are not limiting. It will be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention as defined by the appended claims. Illustrations may not necessarily be drawn to scale. Differences may exist between the process reproductions in this disclosure and actual equipment due to manufacturing processes and tolerances. There may be other embodiments of the invention not specifically illustrated. The specification and drawings are to be regarded as illustrative rather than restrictive. Modifications may be made to adapt a particular situation, material, composition of matter, method or process to the object, spirit and scope of the invention. All such modifications are intended to be within the scope of the appended claims. Although the methods disclosed herein have been described with reference to specific operations performed in a specific order, it should be understood that these operations may be combined, subdivided, or reordered to form equivalent methods without departing from the teachings of the invention. Accordingly, the order and grouping of operations are not limitations of the invention unless specifically indicated herein.

Claims

We claim:

1. A compound of formula (I) or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled:



wherein ring A, ring B, Y, L, R₁, R₂, R₃, R_A, R_B, m, n, p and q are defined as follows:

Ring A is selected from 5-11 membered monocyclic or fused bicyclic aryl, 5-11 membered monocyclic or fused bicyclic heteroaryl;

Ring B is selected from 6 membered monocyclic heteroaryl, 8-11 membered fused bicyclic heteroaryl, 8-11 membered fused bicyclic heterocyclyl, 10-15 membered fused tricyclic heteroaryl and 10-15 membered fused tricyclic heterocyclyl,;

Y is O or S;

L is $\#-C(=O)-NH-\$$, wherein # is connected to  and \$ is connected to ring B;

R₁ is C₁-C₅ alkyl or C₁-C₅ alkoxy; wherein the C₁-C₅ alkyl or C₁-C₅ alkoxy is optionally substituted by 1-3 groups selected from the following: deuterium, halogen, oxo, -CN, -OH, -NH₂, C₁-C₆ alkyl optionally substituted by 1-3 R_z, C₁-C₆ alkoxy optionally substituted by 1-3 R_z, C₁-C₆ haloalkyl optionally substituted by 1-3 R_z, C₁-C₆ haloalkoxy optionally substituted by 1-3 R_z, C₃-C₆ cycloalkyl optionally substituted by 1-3 R_z, -NH(C₁-C₆ alkyl) optionally substituted by 1-3 R_z, -N(C₁-C₆ alkyl)(C₁-C₆ alkyl) optionally substituted by 1-3 R_z, C₃-C₆ cycloalkyl optionally substituted by 1-3 R_z, 5-15 membered monocyclic or fused bicyclic or fused tricyclic heterocyclic group optionally substituted by 1-3 R_z, 5-15 membered monocyclic or fused bicyclic or fused tricyclic aryl optionally substituted by 1-3 R_z, or 5-15 membered monocyclic or fused bicyclic or fused tricyclic heteroaryl;

R₂ and R₃ are independently hydrogen, deuterium, halogen, C₁-C₆ alkyl or C₁-C₆ alkoxy;

wherein R₁, the nitrogen atom to which R₁ is connected, the carbon atom to which R₂ and R₃ are connected, and one atom of the ring A form a ring group, wherein the ring group and the ring A are connected in the form of sharing the one atom to form a spiro ring structure;

R_A is deuterium, halogen, hydroxyl, oxo, cyano, nitro, amine, C₁-C₆ alkyl, cyano C₁-C₆ alkyl, C₁-C₆ alkoxy, -C₁-C₆ alkyl-C₁-C₆ alkoxy, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)(C₁-C₆ alkyl), C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, -O-(C₁-C₆ haloalkyl), -NH-(C₁-C₆ haloalkyl), -N(C₁-C₆ haloalkyl)(C₁-C₆ haloalkyl), pentafluorosulfur (-SF₅), C₁-C₆ haloalkoxy or halocycloalkyl, -S(O)₂-(C₁-C₆ alkyl), -S(=O)(C₁-C₆ alkyl)NR_z, -S(=O)(=NR_z)(C₁-C₆ alkyl), -P(=O)(C₁-C₆ alkyl)₂, a 4-8 membered heterocyclyl optionally substituted by 1-3 R_z, a 5-8 membered heteroaryl optionally substituted by 1-3 R_z, a 6-10 membered aryl optionally substituted by 1-3 R_z, a C₃-C₆ cycloalkyl optionally substituted by 1-3 R_z, or

two R_A connected to the same carbon atom form an oxo group, or

two R_A connected to the same carbon atom together with the carbon atom to which they are connected form a C₃-C₈ cycloalkyl;

R_B is deuterium, halogen, hydroxyl, oxo, thioketone, cyano, nitro, amine, C₁-C₆ alkyl, C₁-C₆ alkoxy, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-OH, C₃-C₈ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy or C₃-C₈ halocycloalkyl, or

two R_B connected to the same carbon atom together with the carbon atom to which they are connected form a C₃-C₈ cycloalkyl or 6-7 membered heterocyclyl, or

two R_B connected to different carbon atoms are connected to form a 6-7 membered ring;

R_z is independently selected from deuterium, halogen, C₁-C₆ alkyl, -CN, -OH, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₃-C₆ cycloalkyl, -NH₂, -NH(C₁-C₆ alkyl) or -N(C₁-C₆ alkyl)(C₁-C₆ alkyl), (C₁-C₆ alkyl)C(O)NH-, (C₁-C₆ alkyl)C(O)-, phenyl, pentafluorosulfur, 5-6 membered heteroaryl or 4-6 membered heterocyclyl, or

two R_z connected to the same carbon atom form an oxo group, or

two R_z connected to the same carbon atom together with the carbon atom to which they are connected form a C₃-C₈ cycloalkyl group;

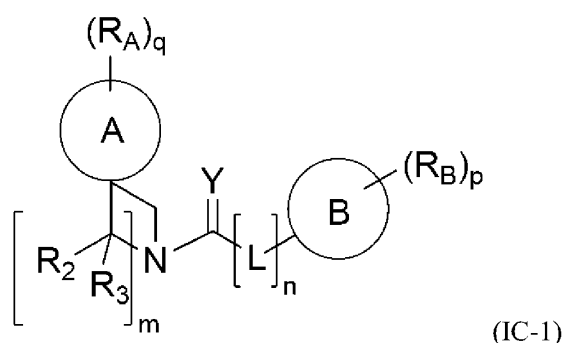
m is 1 or 2;

n is 0 or 1;

p is 0, 1, 2, 3 or 4; and

q is 0, 1, 2, 3, 4 or 5.

2. The compound of formula (I) according to Claim 1, or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, wherein the compound has Formula (IC-1):



wherein ring A, ring B, Y, L, R₂, R₃, R_A, R_B, m, n, p and q are defined as follows:

Ring A is selected from 8-11 membered fused bicyclic aryl and 8-11 membered fused bicyclic heteroaryl;

m is 1 or 2;

Ring B is selected from 6-membered monocyclic heteroaryl, 8-11-membered fused bicyclic heteroaryl, 8-11-membered fused bicyclic heterocyclyl, 10-15-membered fused tricyclic heteroaryl and 10-15-membered fused tricyclic heterocyclyl;

Y is O or S;

L is #-C(=O)-NH-\$, wherein # is connected to  and \$ is connected to ring B;
n is 0 or 1;

each R₂ and each R₃ are independently hydrogen, deuterium, halogen, C₁-C₆ alkyl or C₁-C₆ alkoxy;

R_A is deuterium, halogen, hydroxyl, oxo, cyano, nitro, amine, C₁-C₆ alkyl, cyano C₁-C₆ alkyl, C₁-C₆ alkoxy, -C₁-C₆ alkyl-C₁-C₆ alkoxy, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)(C₁-C₆ alkyl), C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, -O-(C₁-C₆ haloalkyl), -NH-(C₁-C₆ haloalkyl), -N(C₁-C₆ haloalkyl)(C₁-C₆ haloalkyl), pentafluorosulfur, C₁-C₆ haloalkoxy or C₃-C₆ halocycloalkyl, -S(O)₂-(C₁-C₆ alkyl), -S(=O)(=NR₂)(C₁-C₆ alkyl), -P(=O)(C₁-C₆ alkyl)₂, 4-8 membered heterocyclic group optionally substituted by 1-3 R_z, 5-8 membered heteroaryl group optionally substituted by 1-3 R_z, 6-10 membered aryl group optionally substituted by 1-3 R_z, C₃-C₆ cycloalkyl group optionally substituted by 1-3 R_z, or,

two R_A attached to the same carbon atom form an oxo group, or,

two R_A connected to the same carbon atom and the carbon atom to which they are connected form a C₃-C₈ cycloalkyl group;

R_B is deuterium, halogen, hydroxyl, oxo, thioketone, cyano, nitro, amine, C₁-C₆ alkyl, C₁-C₆ alkoxy, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-OH, C₃-C₈ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy or C₃-C₈ halocycloalkyl, or,

two R_B connected to the same carbon atom and the carbon atom to which they are connected form a C₃-C₈ cycloalkyl group or 6-7 membered heterocyclyl, or,

two R_B connected to different carbon atoms are connected to form a 6-7 membered ring;
 R_Z is independently selected from deuterium, halogen, C_1 - C_6 alkyl, $-CN$, $-OH$, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_3 - C_6 cycloalkyl, $-NH_2$, $-NH(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl)(C_1 - C_6 alkyl), $(C_1$ - C_6 alkyl) $C(O)NH$ -, $(C_1$ - C_6 alkyl) $C(O)$ -, phenyl, pentafluorosulfur, 5-6 membered heteroaryl or 4-6 membered heterocyclic group, or

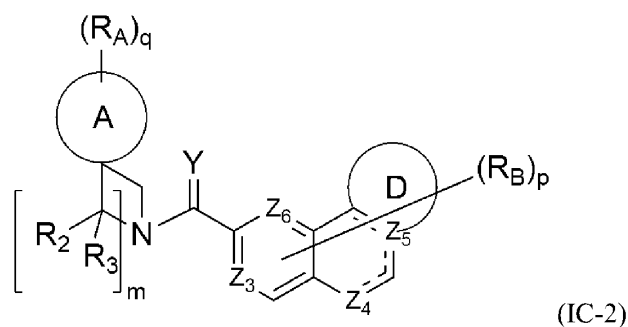
two R_Z connected to the same carbon atom form an oxo group, or

two R_Z connected to the same carbon atom and the carbon atom to which they are connected form a C_3 - C_8 cycloalkyl group;

p is 0, 1, 2, 3 or 4; and

q is 0, 1, 2, 3, 4 or 5.

3. The compound of formula (I) according to Claim 1, or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, wherein the compound has Formula (IC-2):



wherein ring A, ring D, Y, Z_3 , Z_4 , Z_5 , Z_6 , R_2 , R_3 , R_A , R_B , m , p and q are defined as follows:
 Z_3 and Z_6 are N or CR_e ; Z_4 and Z_5 are N, NH, NR_e or CR_e , and at least one of Z_4 and Z_5 is N or NH; wherein  is a single bond or a double bond, and the position of the double bond changes when Z_4 or Z_5 is N or NH;

R_e is hydrogen, deuterium, halogen, hydroxyl, cyano, $-NH_2$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-NH(C_1$ - C_6 alkyl) or $-N(C_1$ - C_6 alkyl)(C_1 - C_6 alkyl);

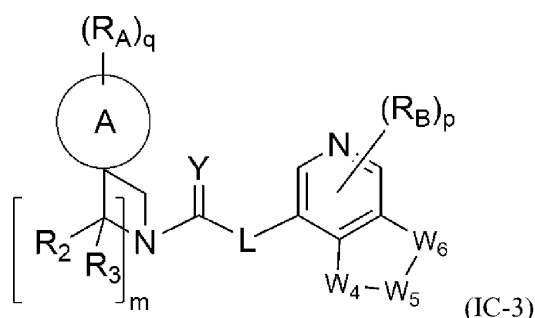
Ring D is a 5-6 membered cycloalkyl, a 5-6 membered heterocyclyl, a 5-6 membered aryl, or a 5-6 membered heteroaryl which is fused to a 10 membered ring, or is absent;

m is 1 or 2;

Ring A is defined as in Claim 1; and

Y, R_2 , R_3 , R_A , R_B , p , q are as defined in Claim 1.

4. The compound of formula (I) according to Claim 1, or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, wherein the compound has Formula (IC-3):



wherein ring A, W₄, W₅, W₆, Y, L, R₂, R₃, R_A, R_B, m, p and q are defined as follows:

-W₄-W₅-W₆- is any one of (1)-CR_f=N-NR_f, (2) -NR_f-N=CR_f, (3)-CR_fR_g-O-CR_fR_g, (4)-S-N=NR_f, (5)-CR_f=N-S-, (6)-CR_fR_g-CR_fR_g-NR_f, and (7) non-existence;

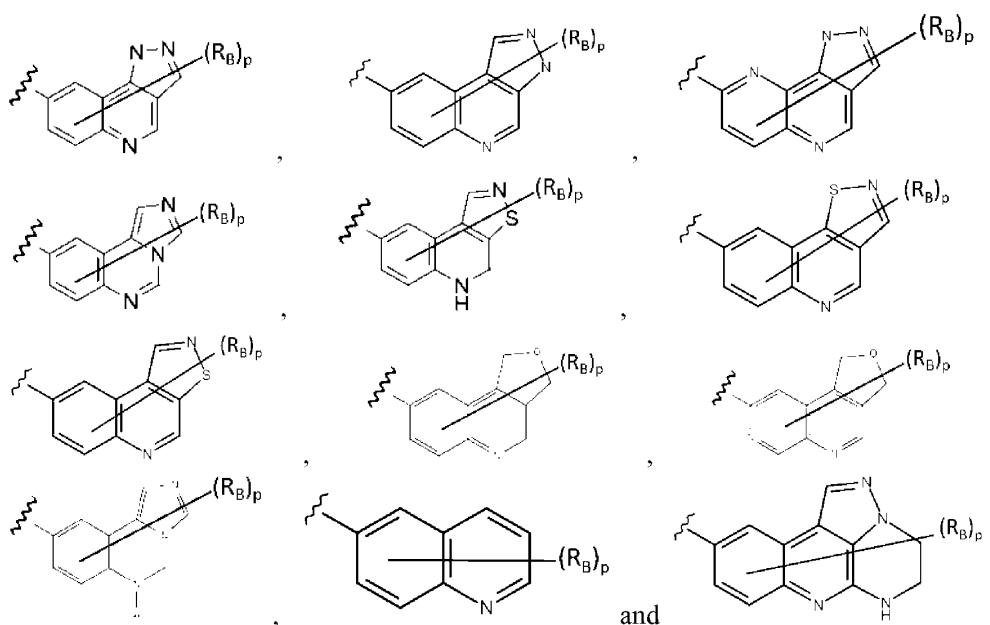
R_f and R_g are independently hydrogen, deuterium, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or two R_f and R_g connected to the same carbon atom form an oxo group, or two R_f and R_g connected to the same carbon atom and the carbon atom to which they are connected together form a C₃-C₈ cycloalkyl group, or R_f and R_B are connected to form a 6-7 membered ring;

m is 1 or 2;

Ring A is as defined in Claim 1; and

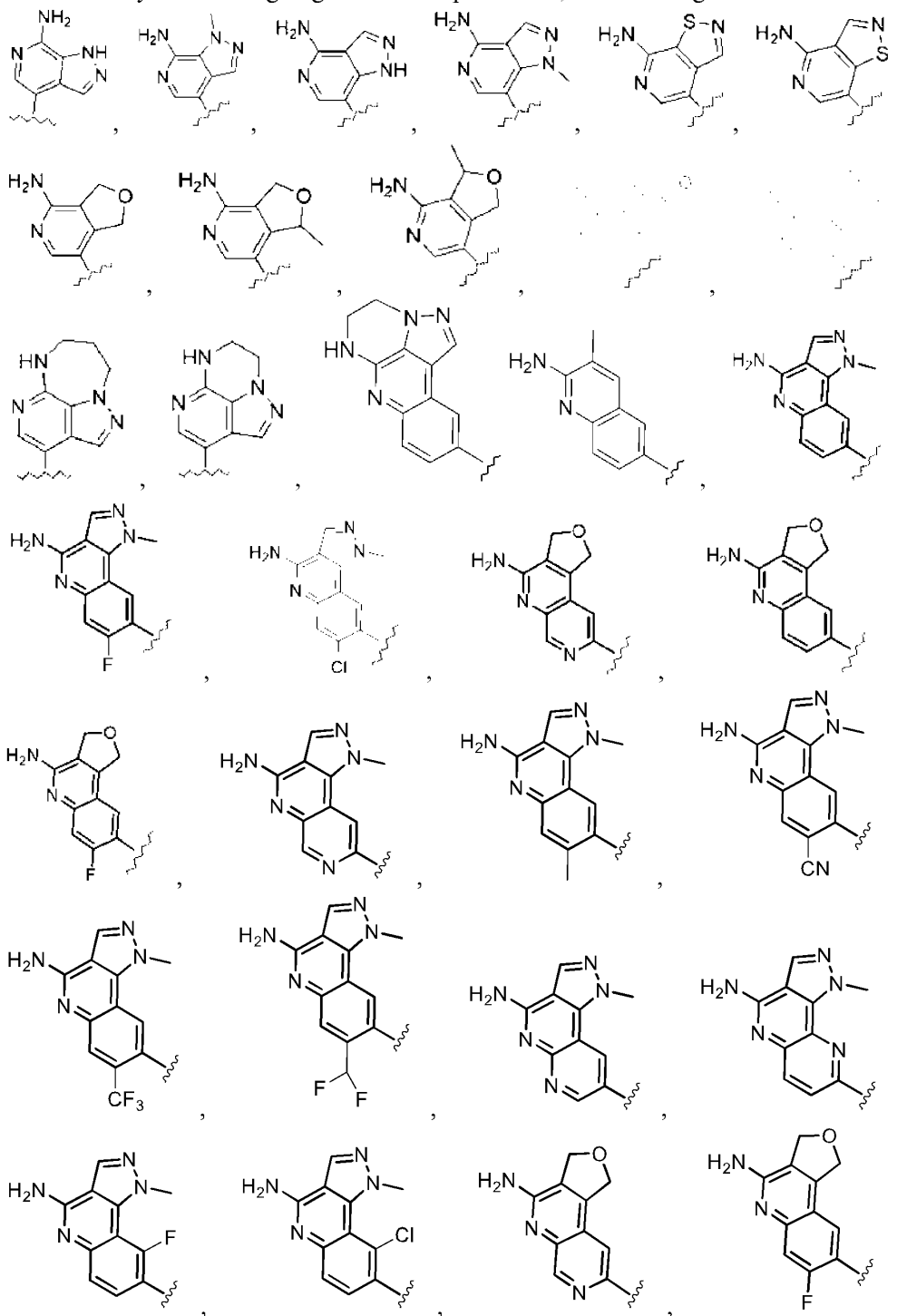
Y, L, R₂, R₃, R_A, R_B, p, q are as defined in Claim 1.

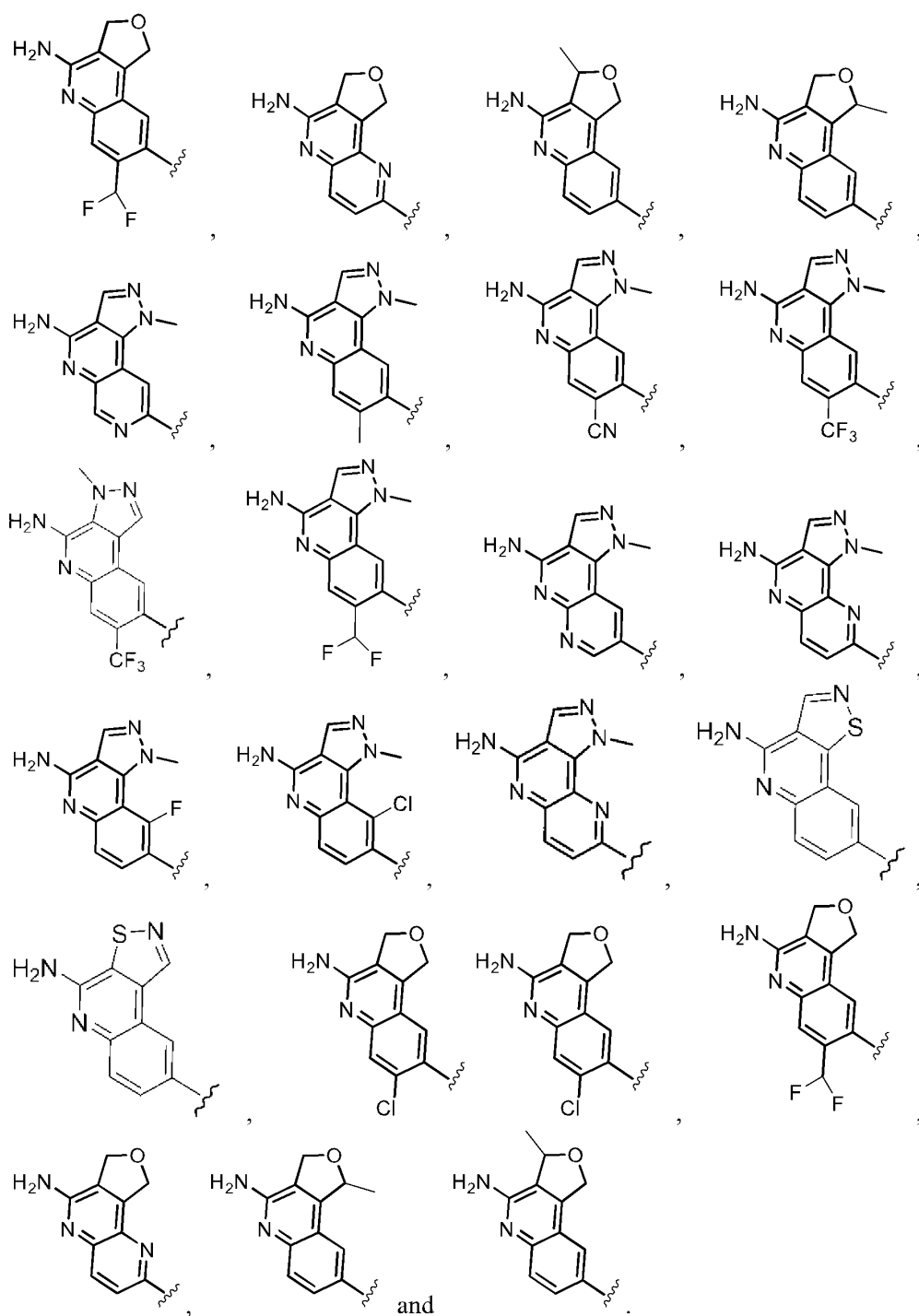
5. The compound of formula (I) according to Claim 1, or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, wherein ring B is selected from



wherein the wavy line represents the connecting point, and R_B and p are as defined in Claim 1.

6. The compound of formula (I) according to Claim 1 or 2, or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, wherein ring B is selected from

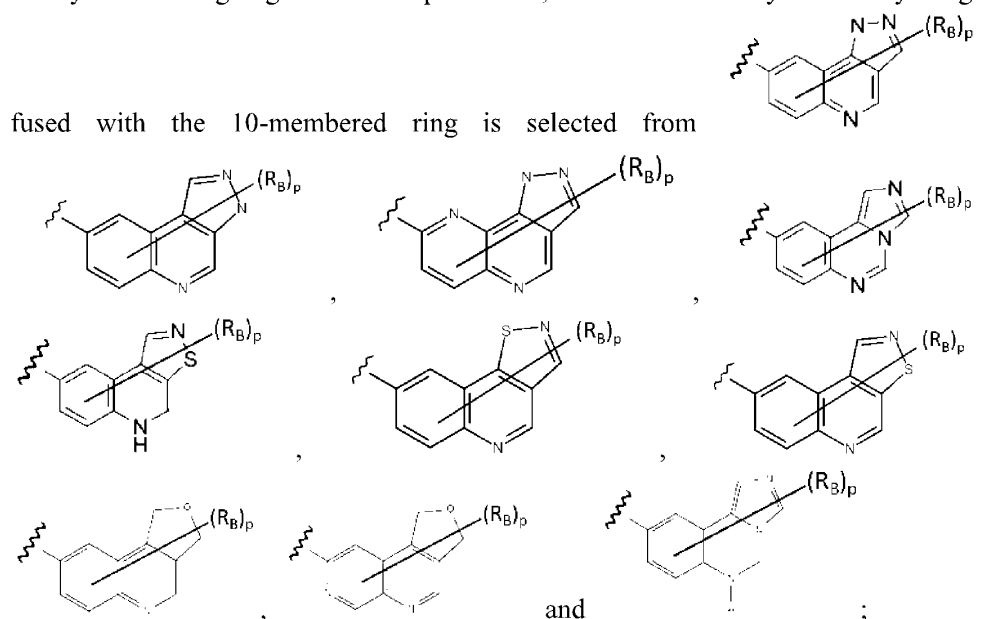




7. The compound of formula (I) according to Claim 3, or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, wherein one of Z_3 and Z_6 is N and the other is CR_e ; and Z_4 is N, NH or NR_e and Z_5 is CR_e .
8. The compound of formula (I) according to Claim 3, or a pharmaceutically acceptable salt,

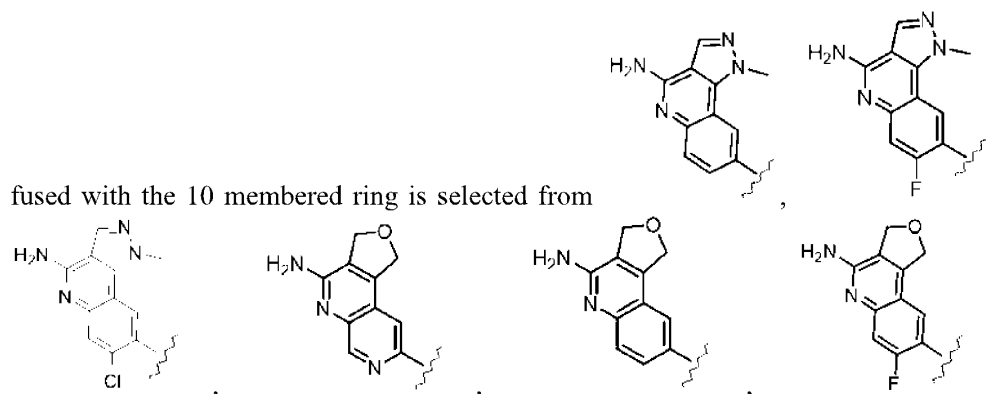
geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, wherein Z_3 and Z_6 are each independently CR_c ; and wherein Z_4 is N, NH or NR_c and Z_5 is CR_c .

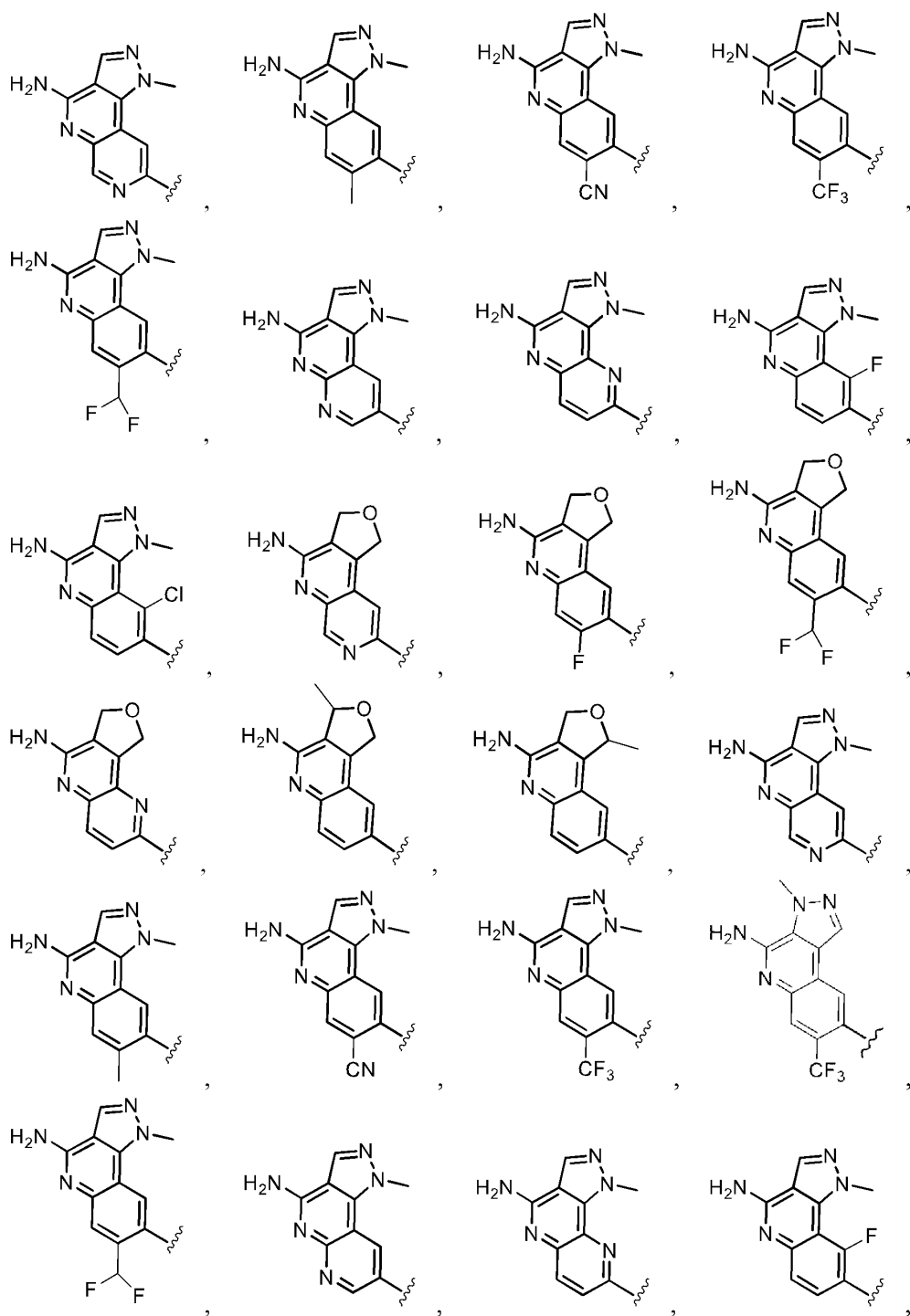
9. The compound of formula (I) according to Claim 3, or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, wherein the moiety formed by Ring D

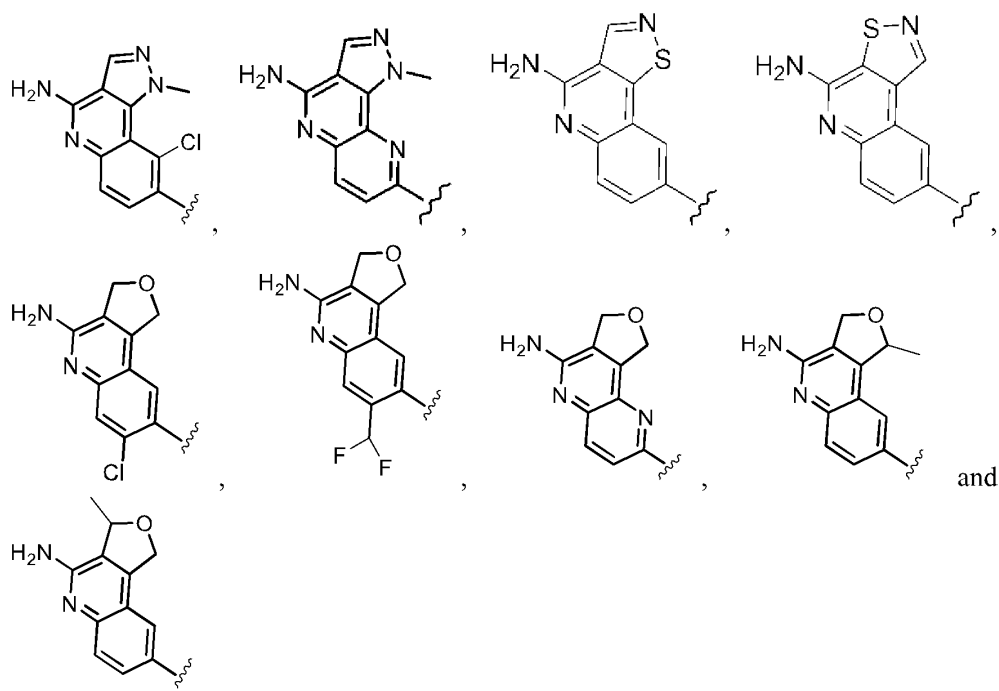


R_B and p are as defined in Claim 3.

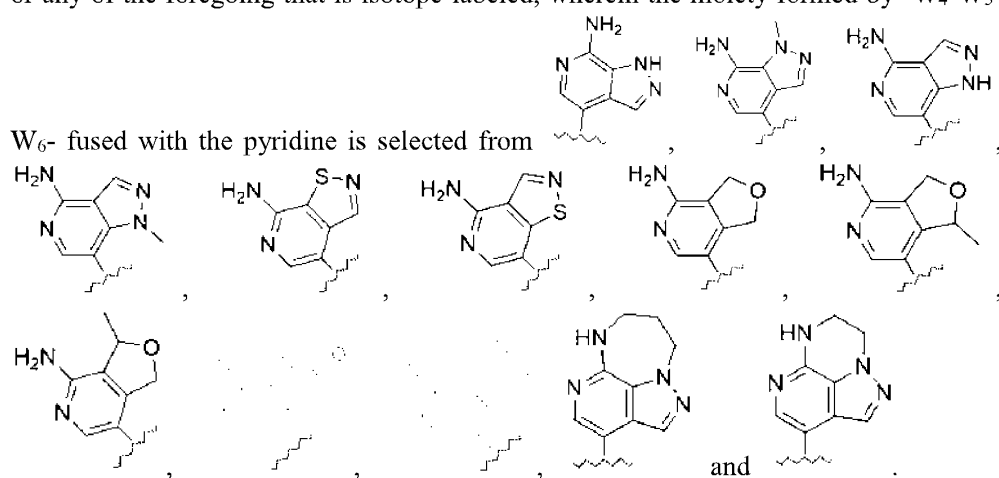
10. The compound of formula (I) according to Claim 3, or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, wherein ring D is absent.
11. The compound of formula (I) according to Claim 3, or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, wherein the moiety formed by ring D



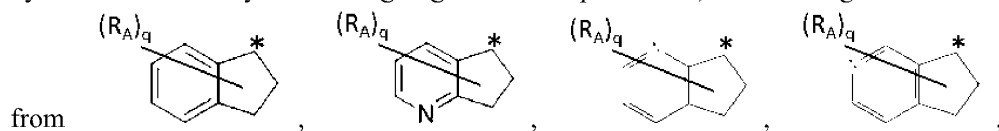


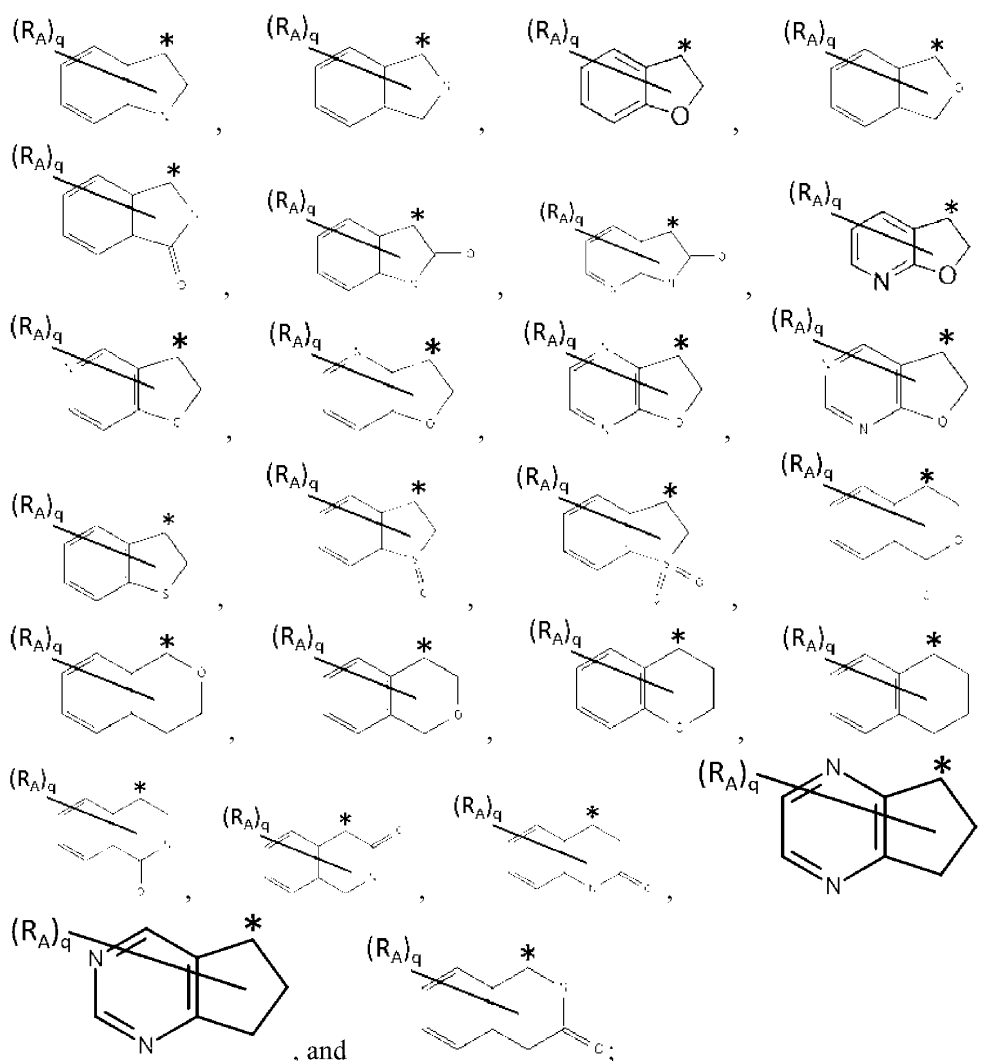


12. The compound of formula (I) according to Claim 4, or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, wherein the moiety formed by $-\text{W}_4-\text{W}_5-$



13. The compound of formula (I) according to any one of Claims 1-12, or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, wherein ring A is selected



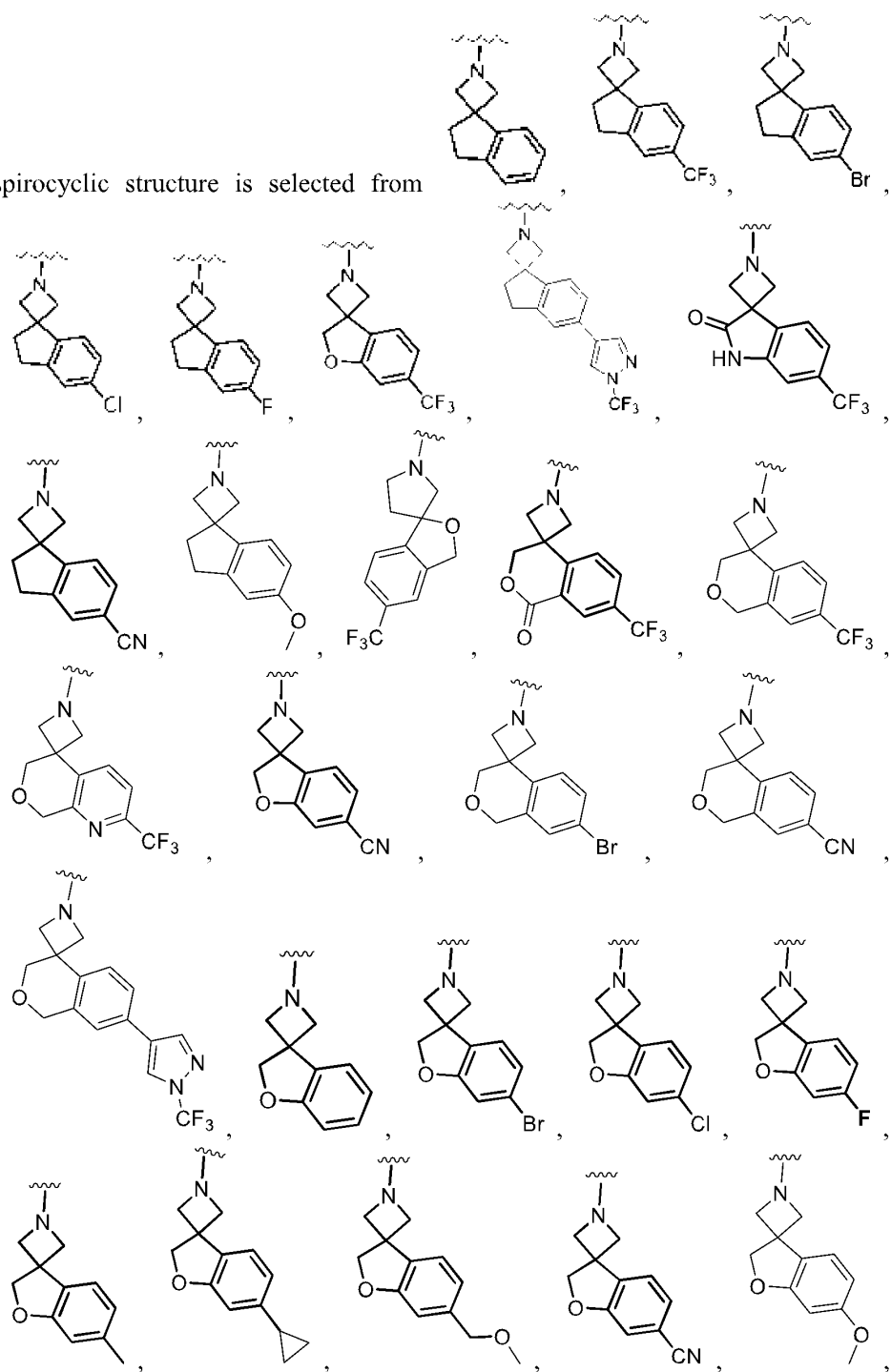


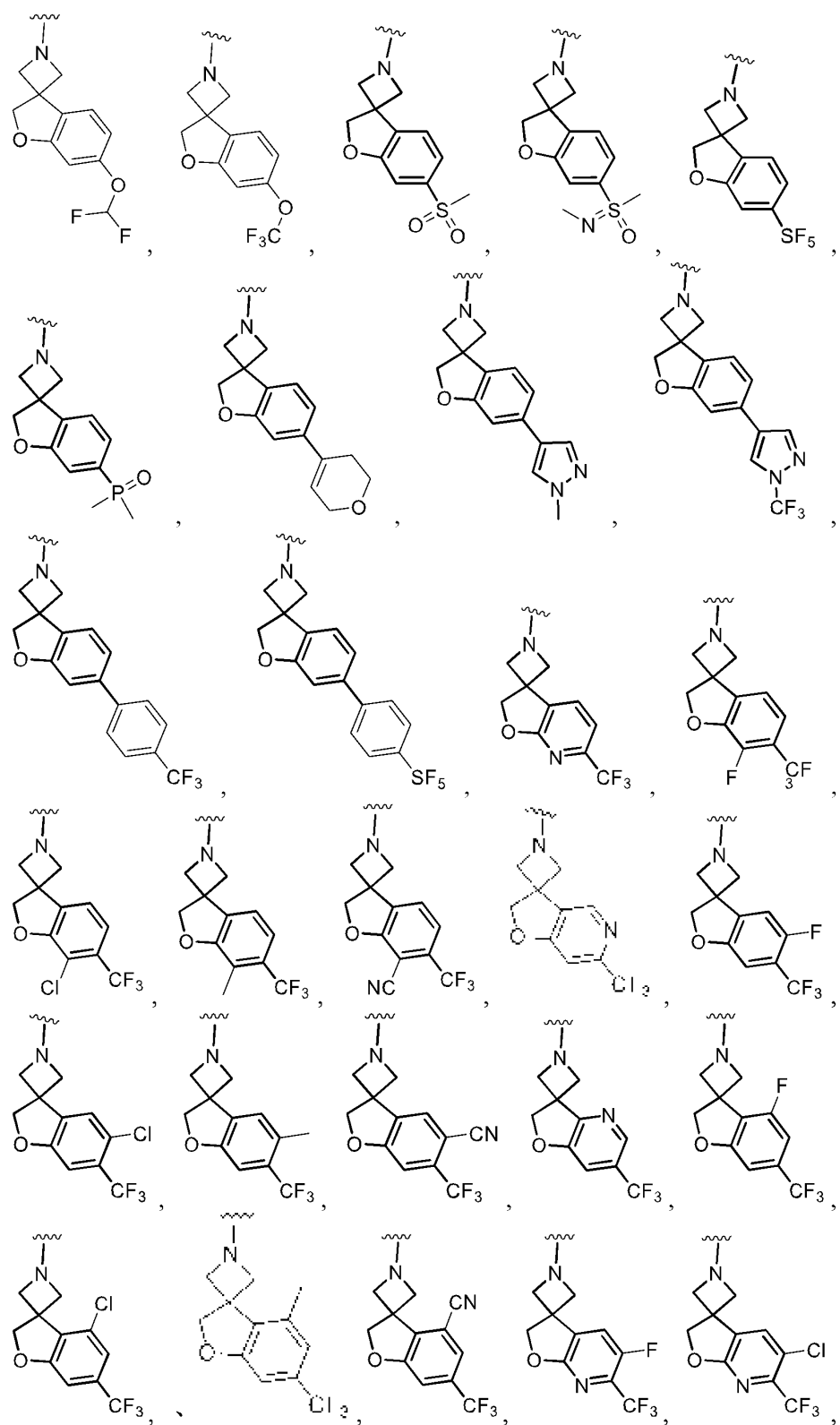
wherein * indicates the connecting point of spiral ring; and

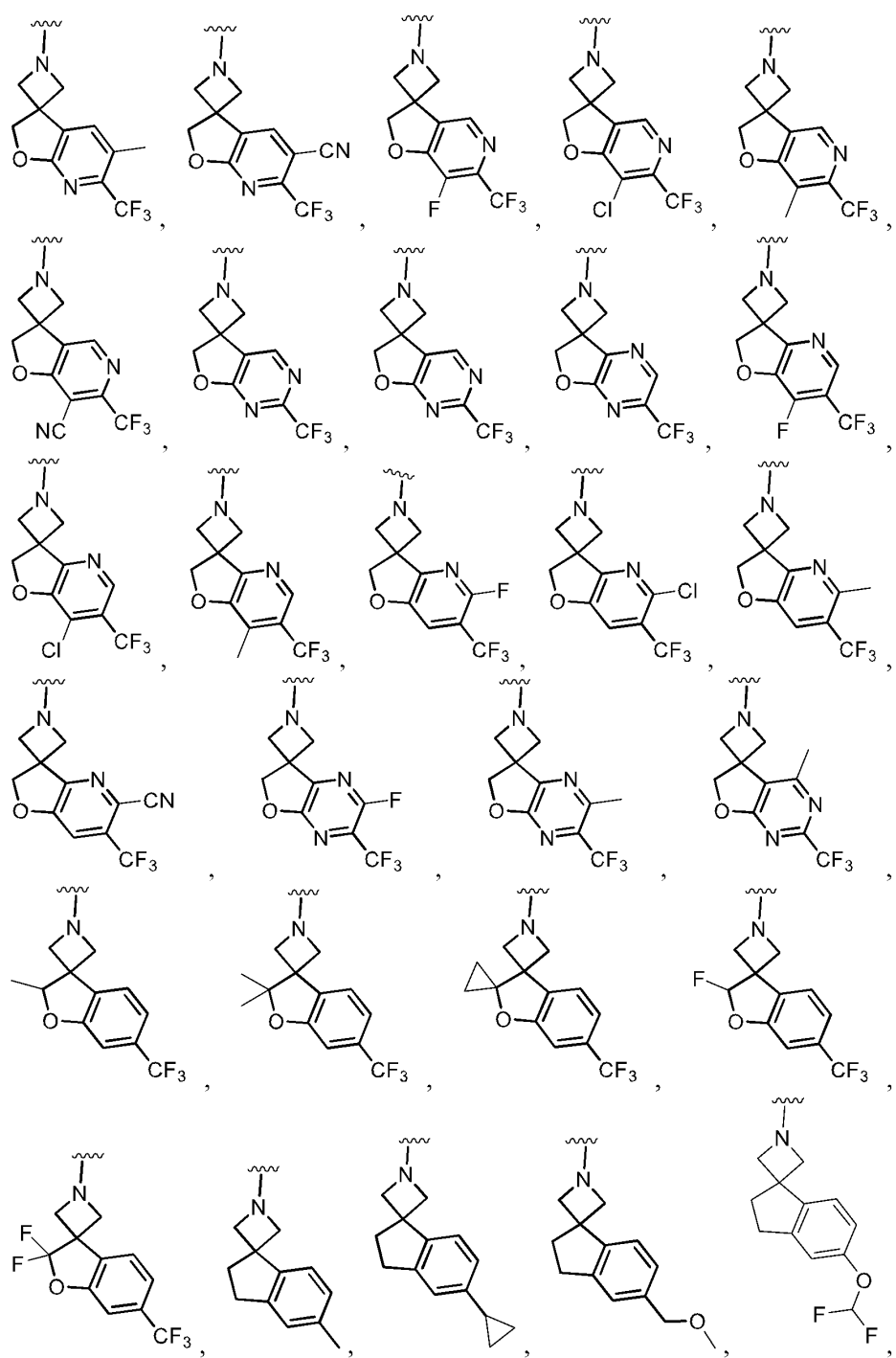
R_A and q are as defined in Claim 1.

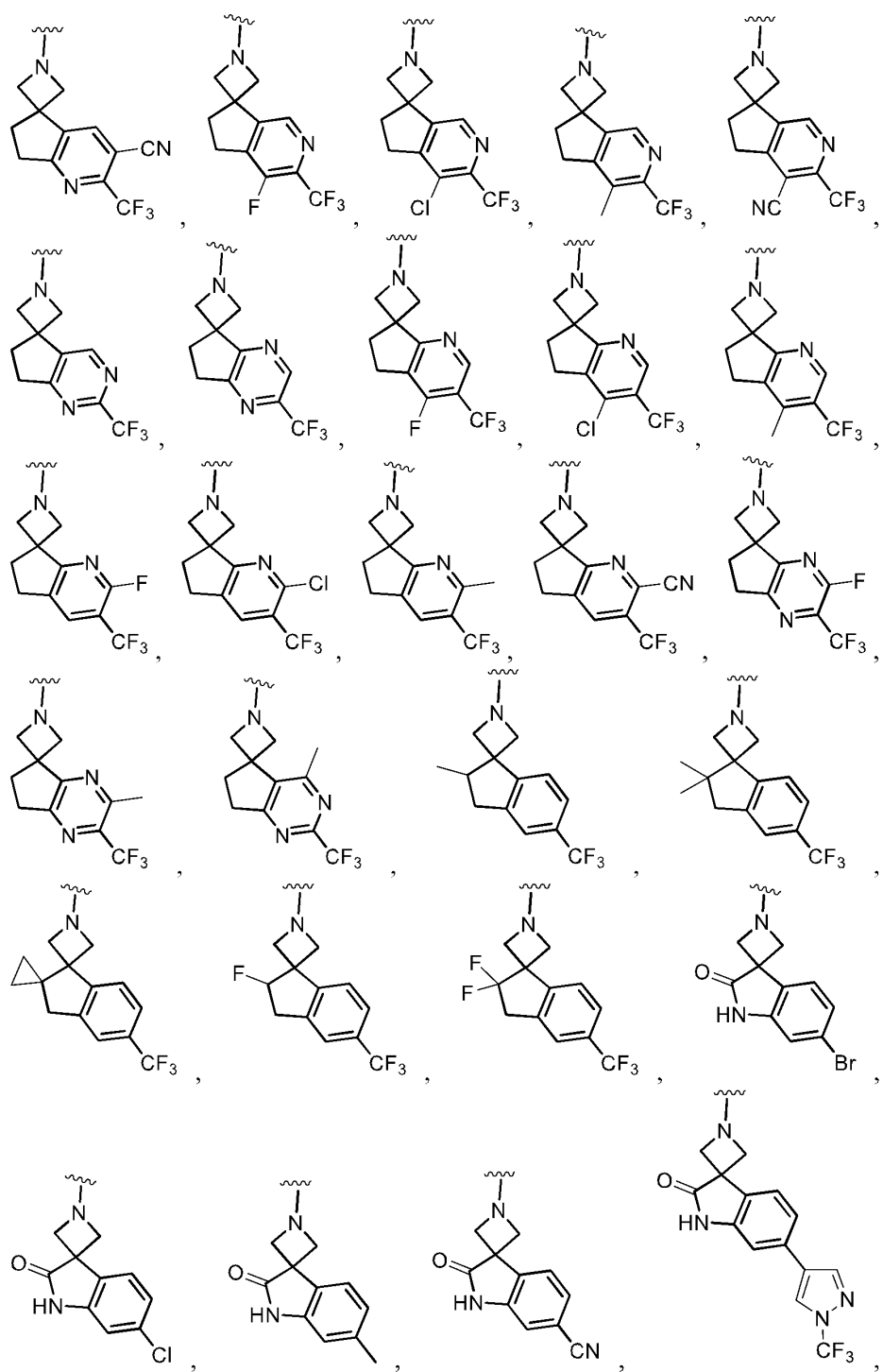
14. The compound of formula (I) according to any one of Claims 1-12, or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, wherein:
- (1) R_1 , the nitrogen atom to which R_1 is connected, the carbon atom to which R_2 and R_3 are connected, and one atom of the ring A form a cyclic group, and this cyclic group and the ring A are connected in the form of sharing such atom to form a spirocyclic structure, or
 - (2) the carbon atom to which R_2 and R_3 are connected, the adjacent nitrogen atom, the adjacent methylene group, and one atom of the ring A form a cyclic moiety, wherein this cyclic moiety and the ring A are connected in the form of sharing such one atom to form a spirocyclic structure,

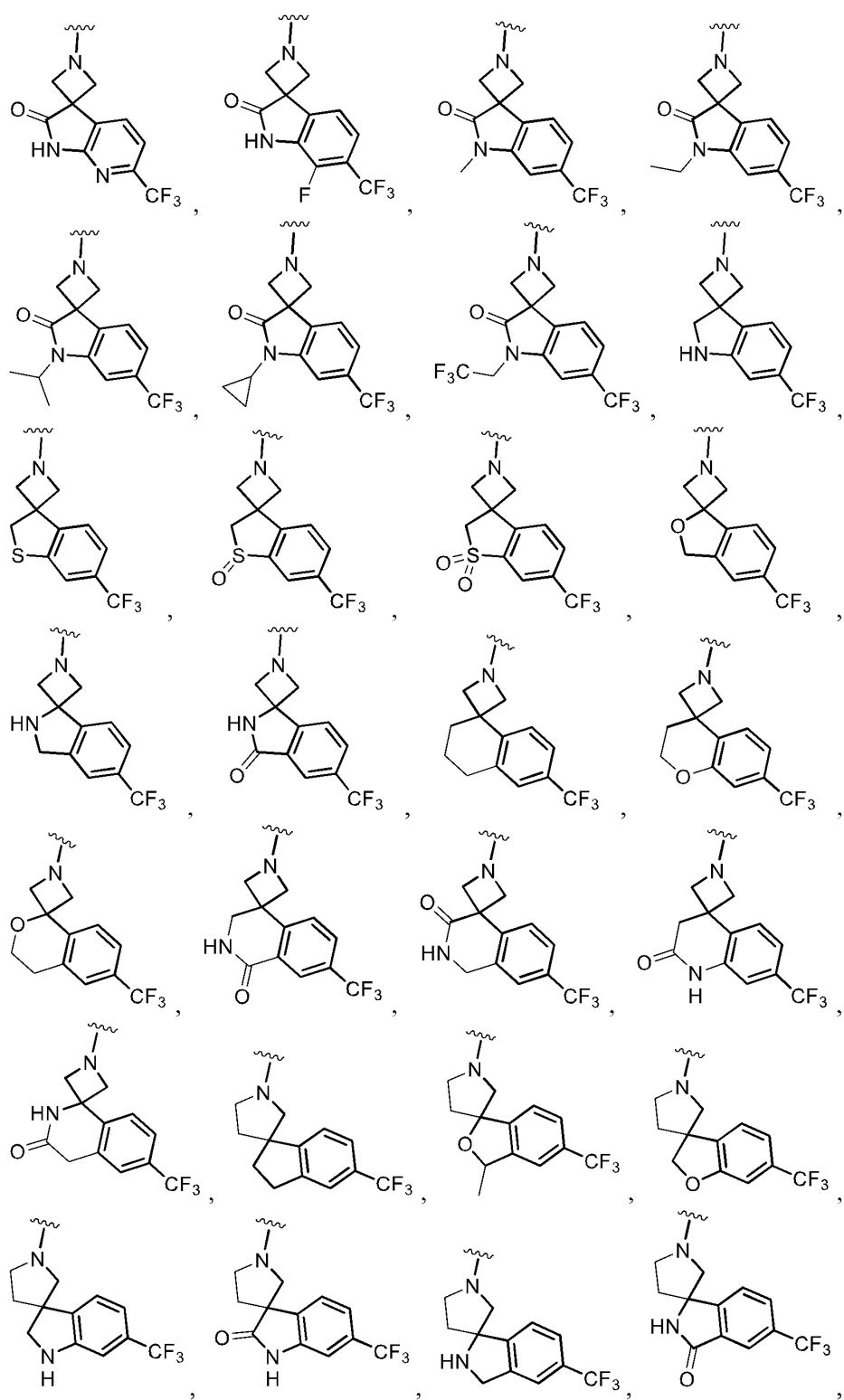
the spirocyclic structure is selected from

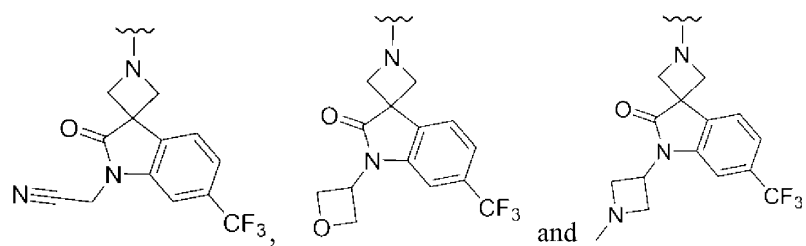




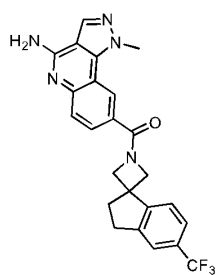




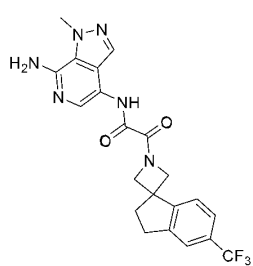




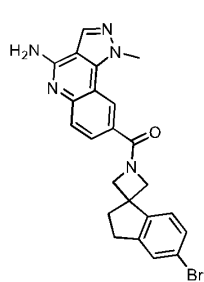
15. The compound of formula (I) according to Claim 1, or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, which is selected from:



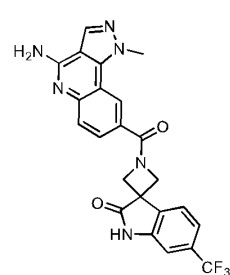
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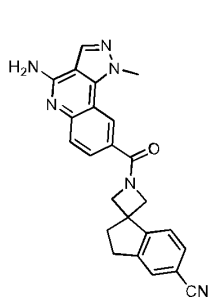
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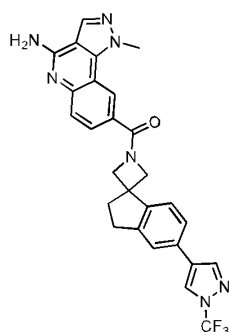
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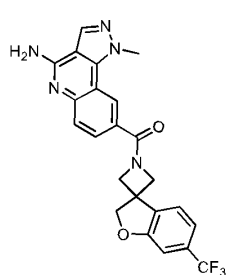
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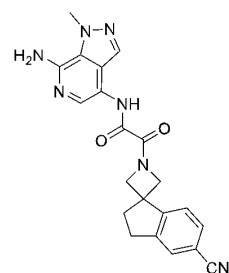
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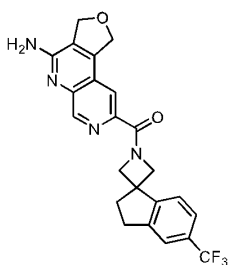
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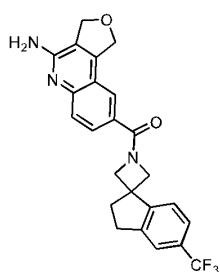
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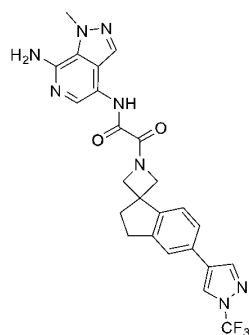
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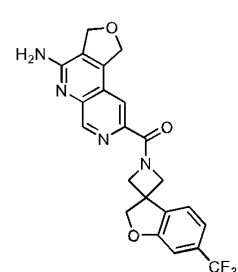
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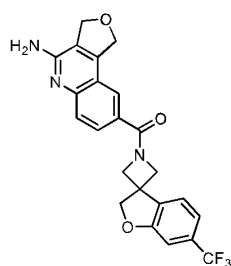
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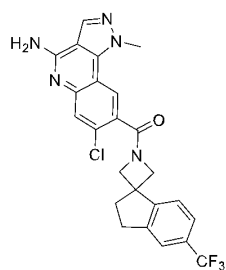
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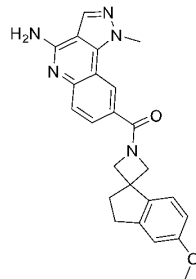
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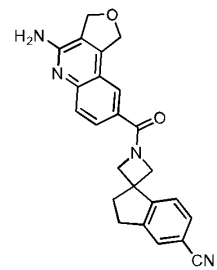
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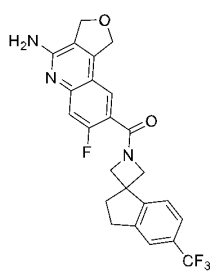
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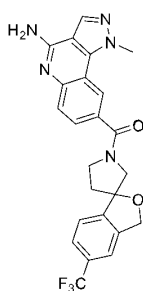
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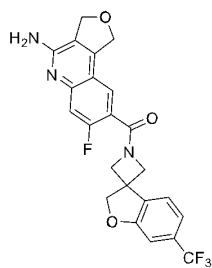
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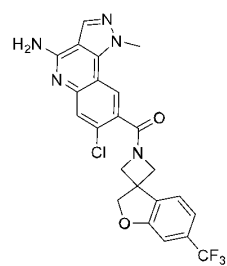
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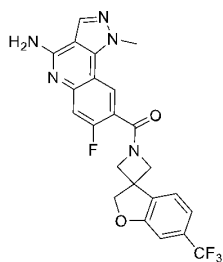
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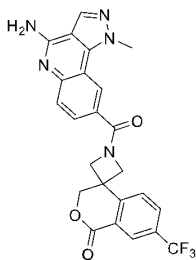
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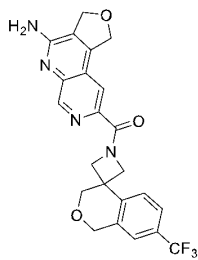
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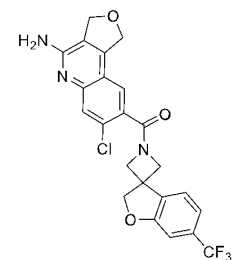
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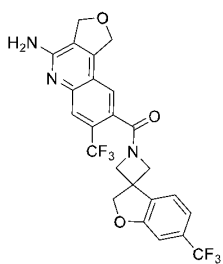
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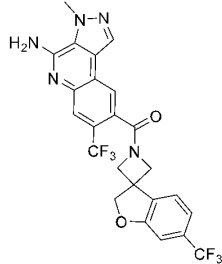
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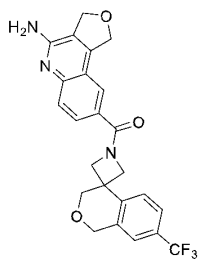
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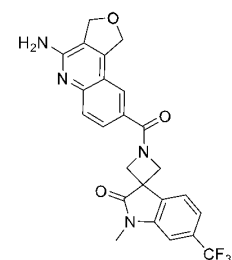
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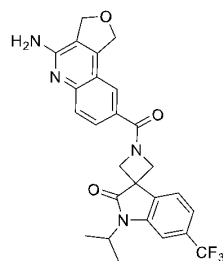
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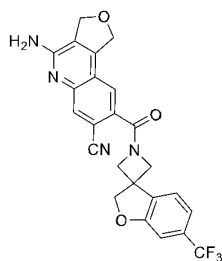
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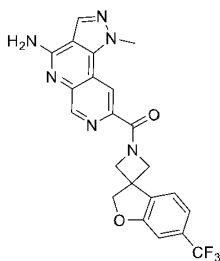
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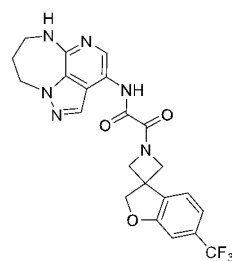
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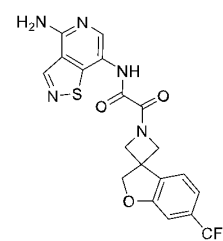
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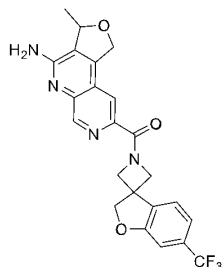
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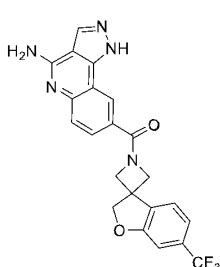
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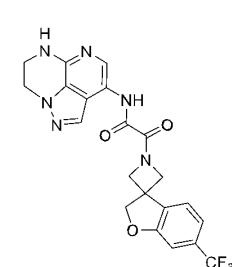
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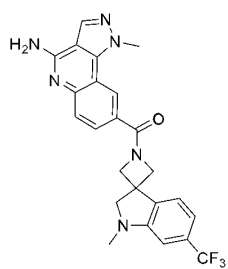
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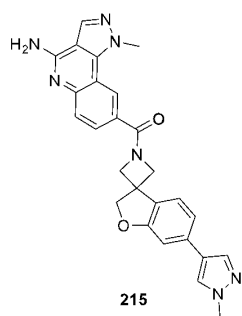
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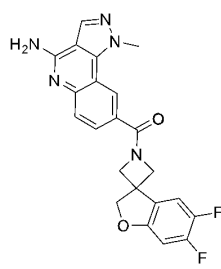
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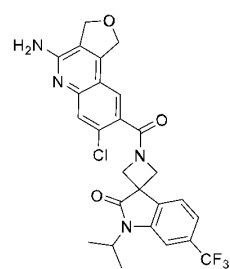
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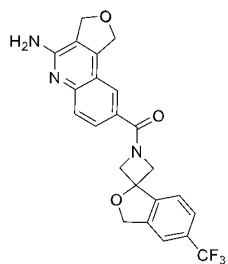
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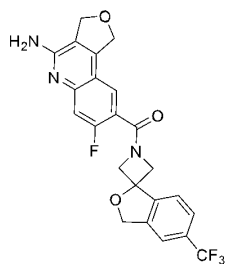
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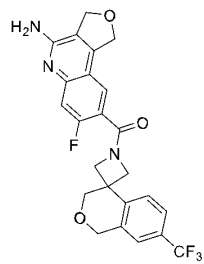
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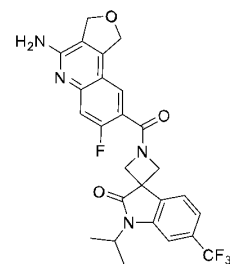
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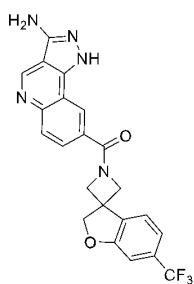
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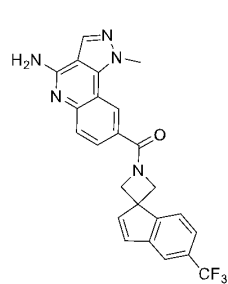
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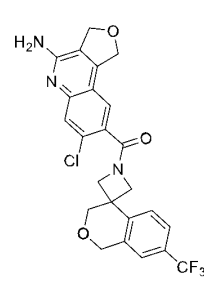
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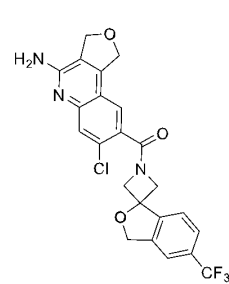
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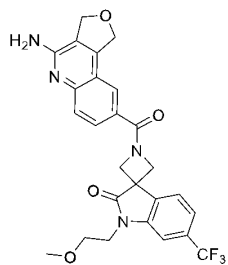
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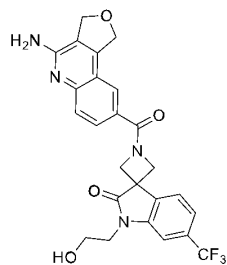
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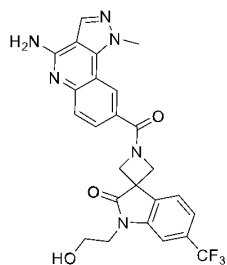
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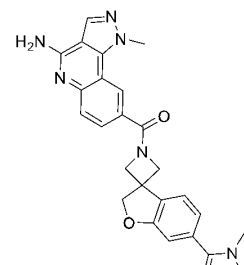
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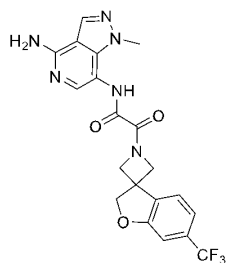
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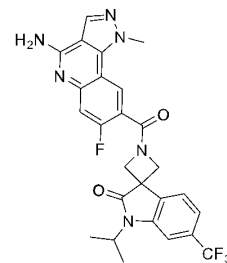
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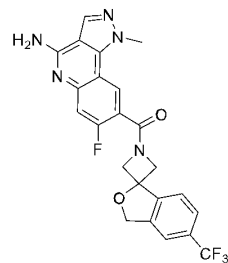
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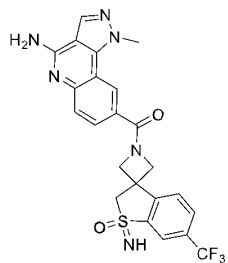
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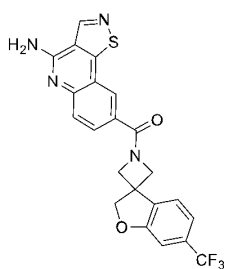
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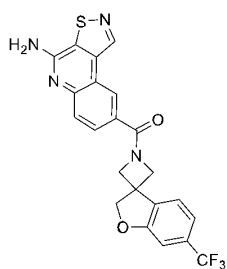
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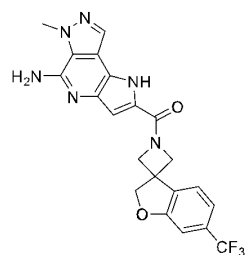
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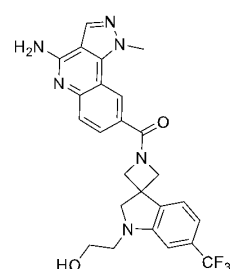
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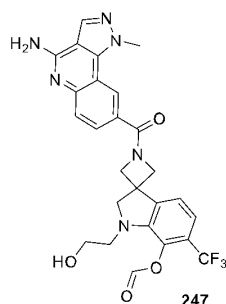
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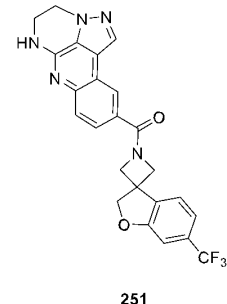
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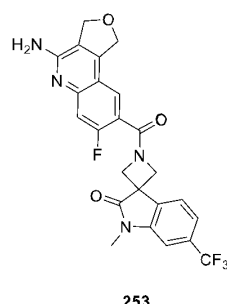
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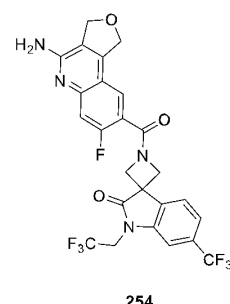
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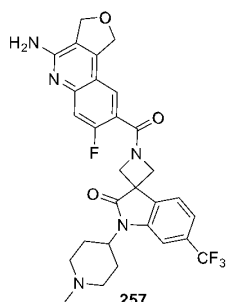
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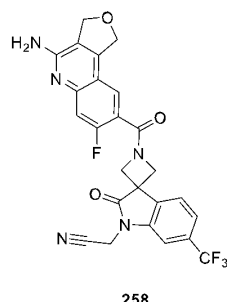
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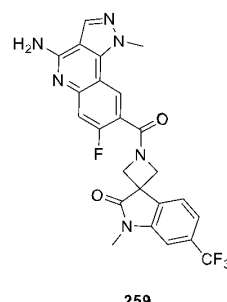
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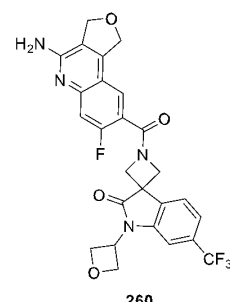
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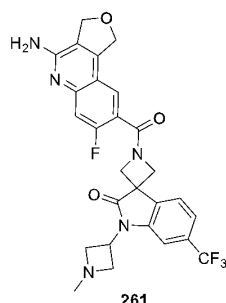
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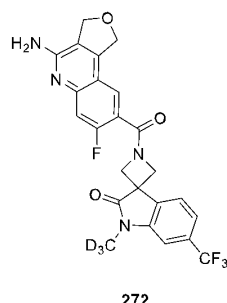
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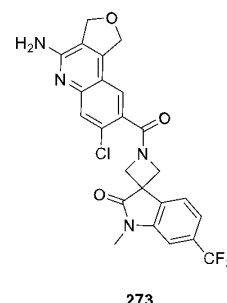
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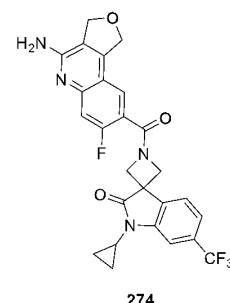
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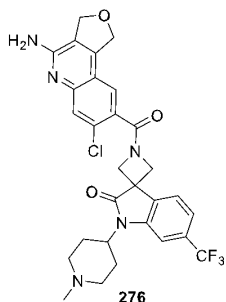
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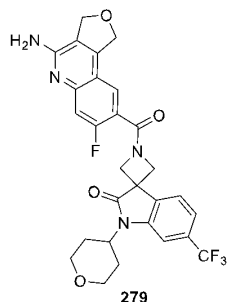
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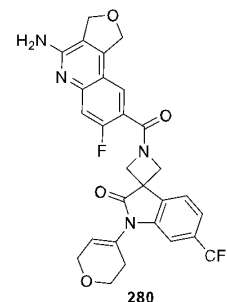
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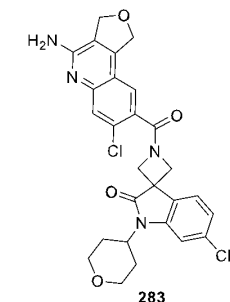
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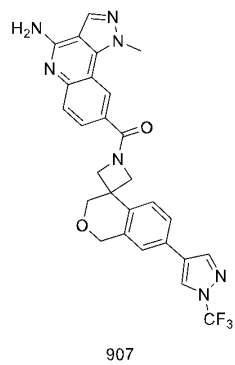
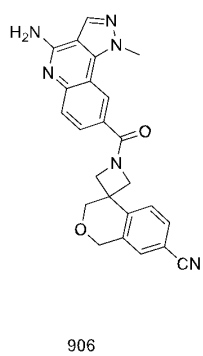
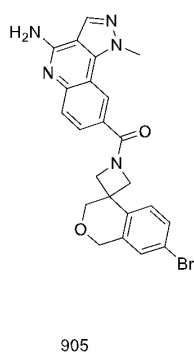
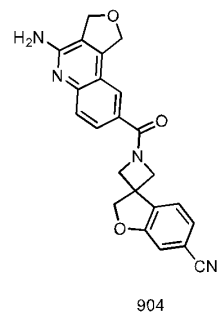
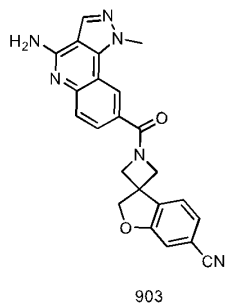
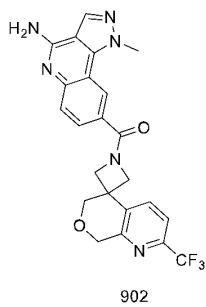
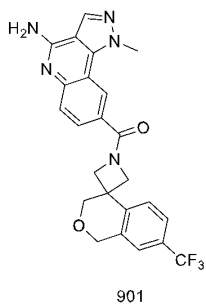
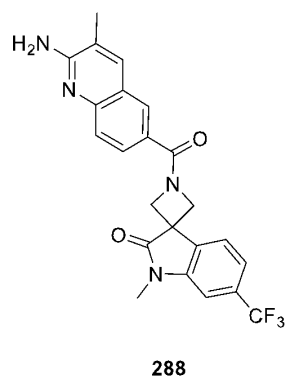
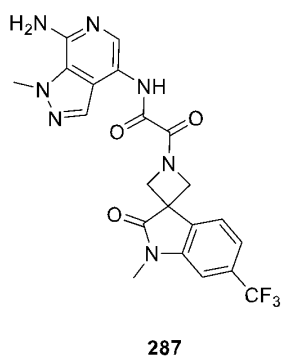
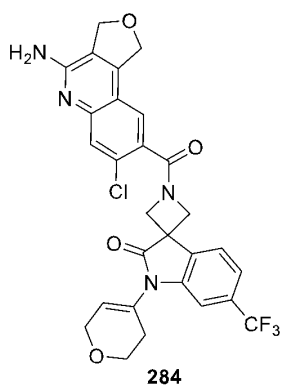
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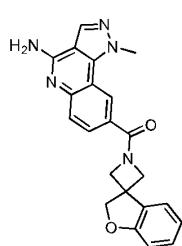


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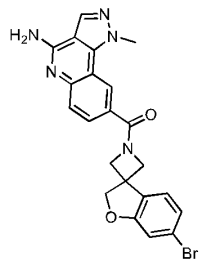


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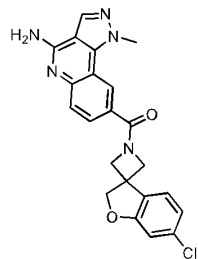




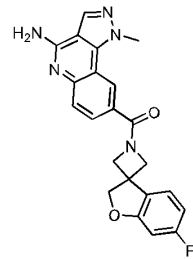
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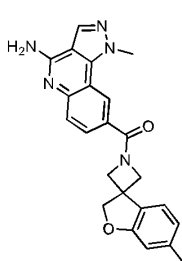
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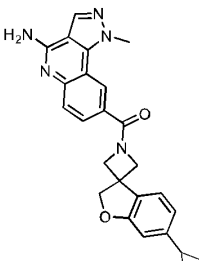
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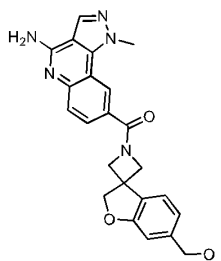
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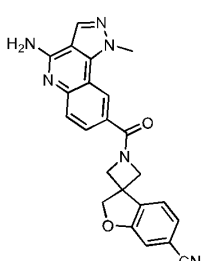
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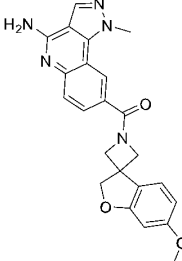
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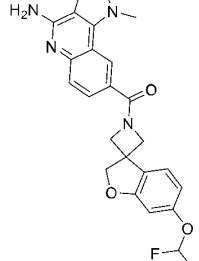
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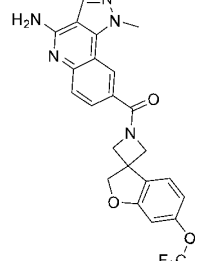
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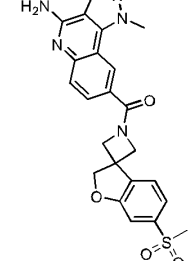
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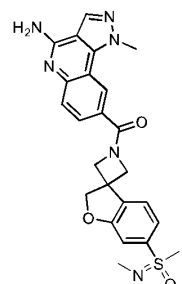
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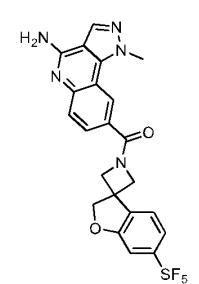
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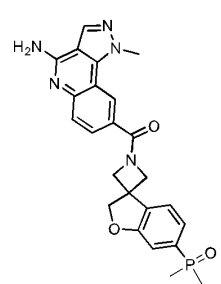
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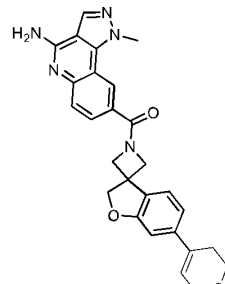
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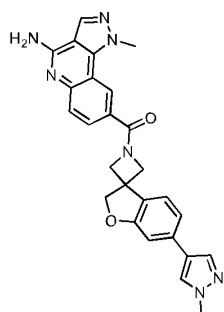
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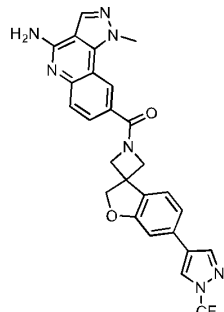
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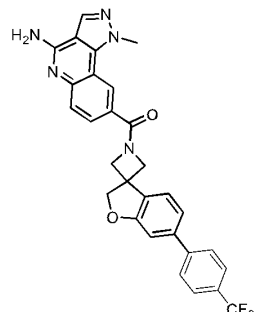
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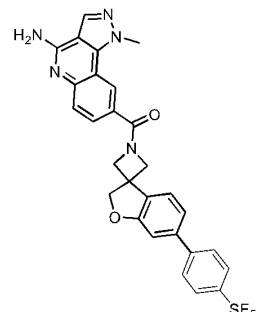
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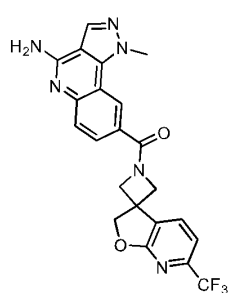
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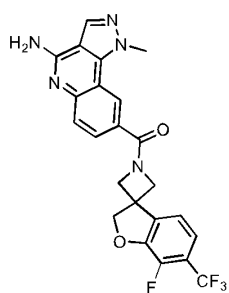
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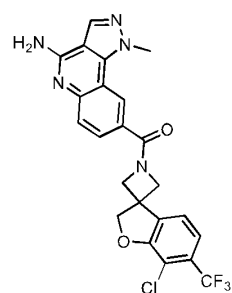
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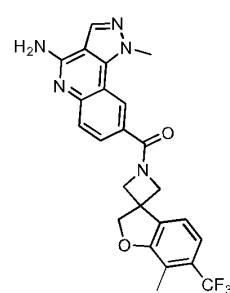
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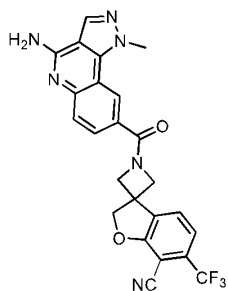
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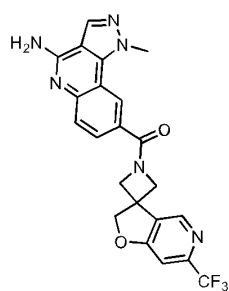
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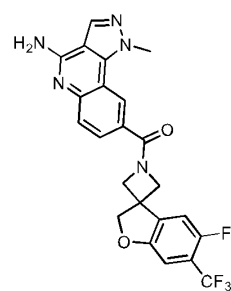
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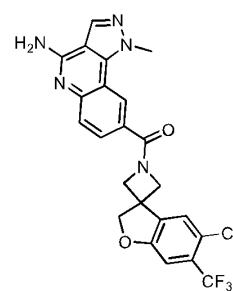
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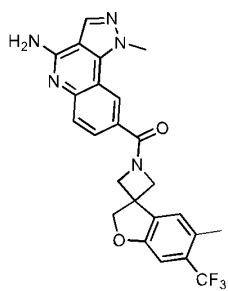
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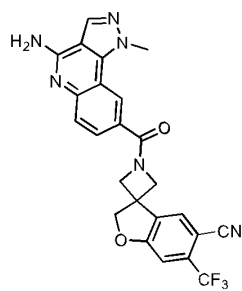
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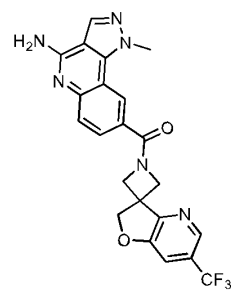
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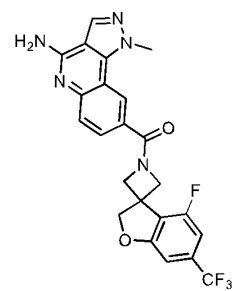
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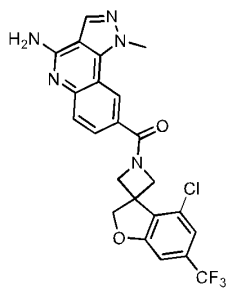
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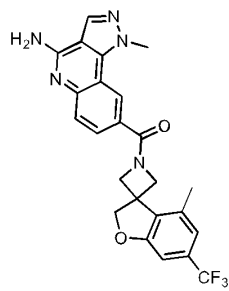
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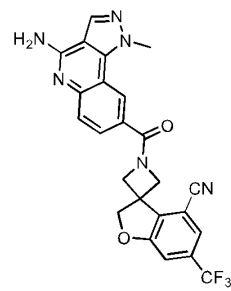
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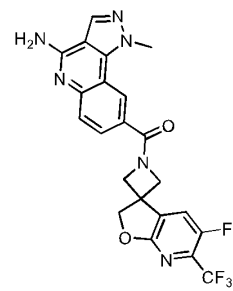
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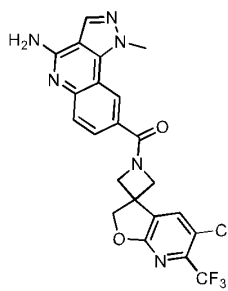
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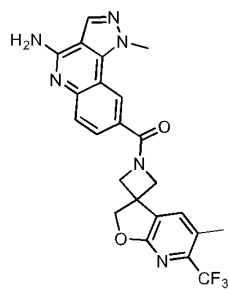
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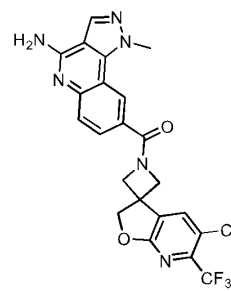
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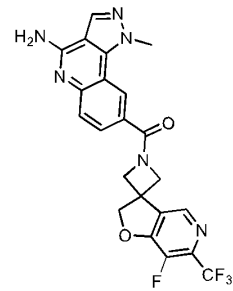
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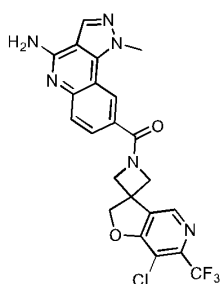
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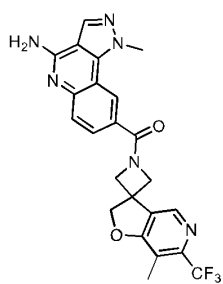
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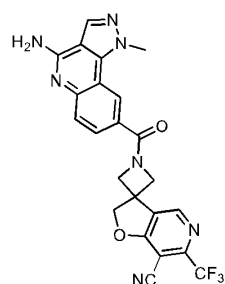
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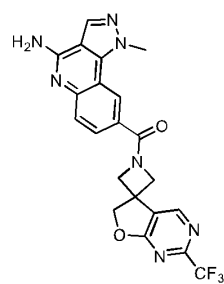
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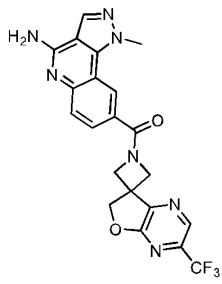
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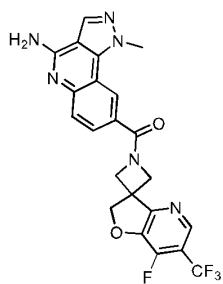
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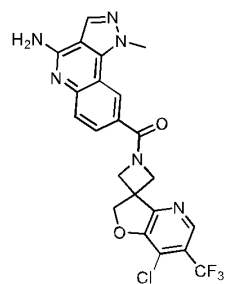
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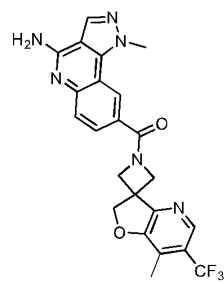
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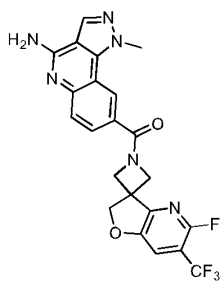
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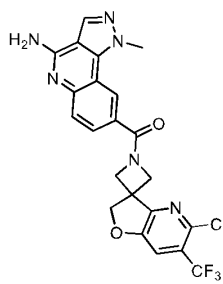
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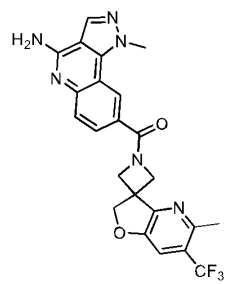
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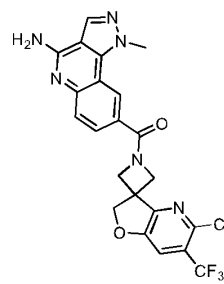
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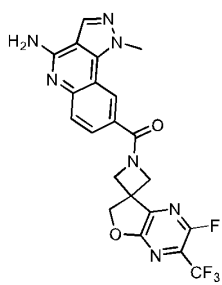
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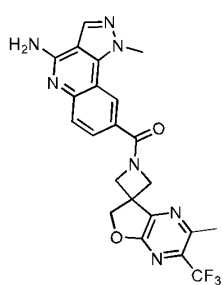
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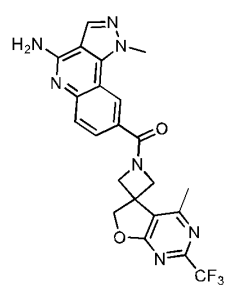
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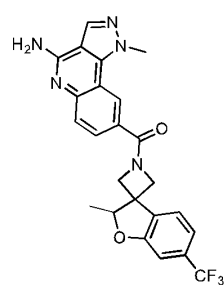
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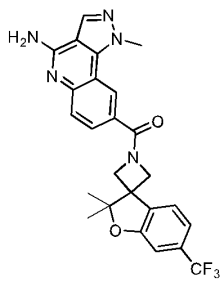
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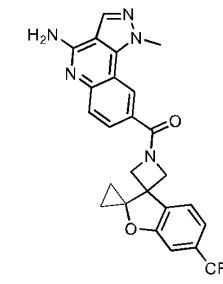
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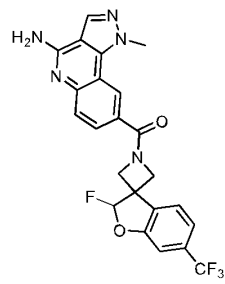
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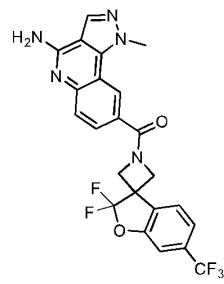
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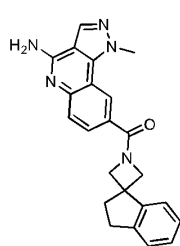
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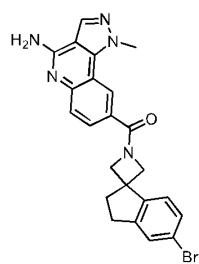
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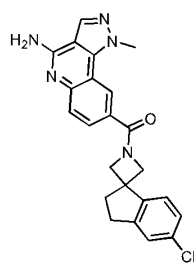
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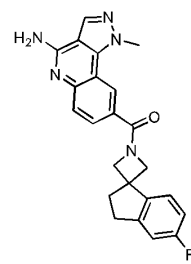
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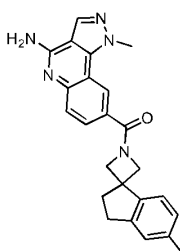
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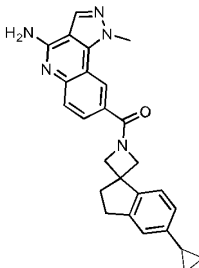
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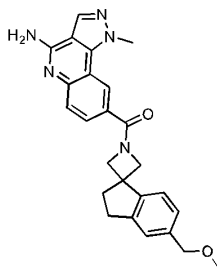
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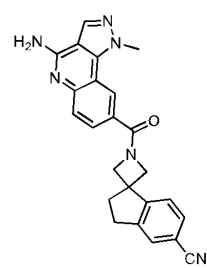
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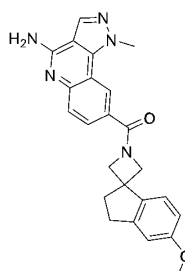
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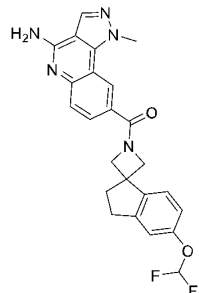
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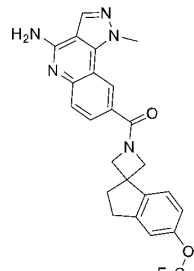
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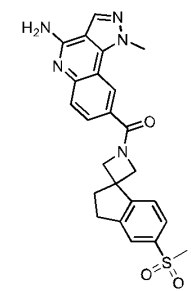
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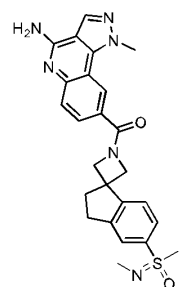
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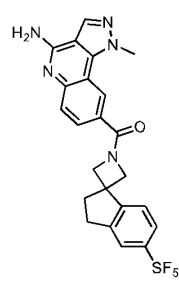
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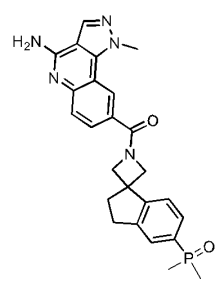
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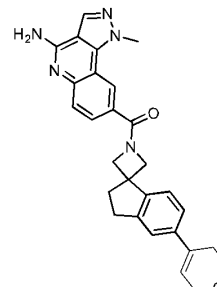
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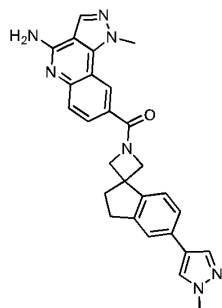
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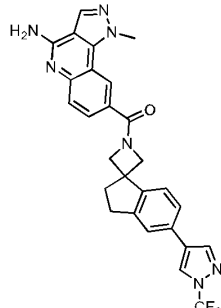
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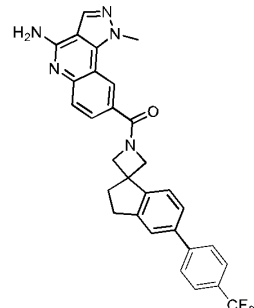
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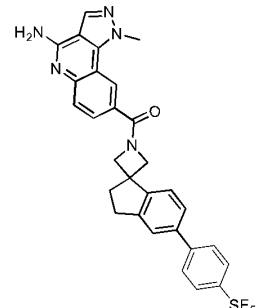
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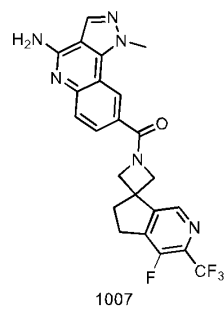
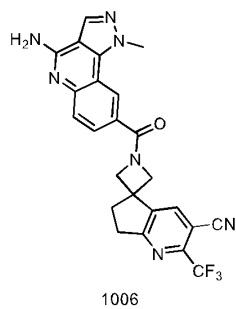
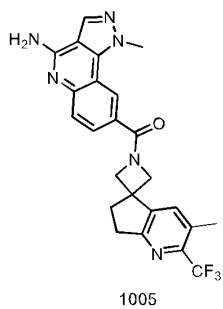
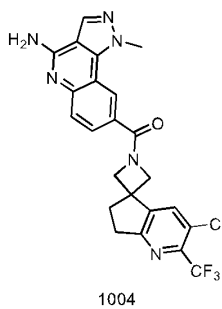
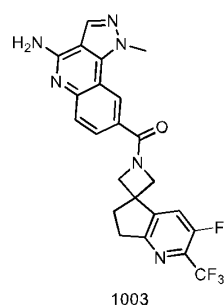
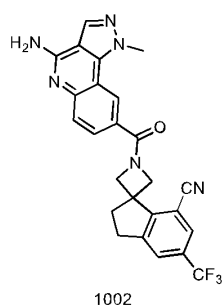
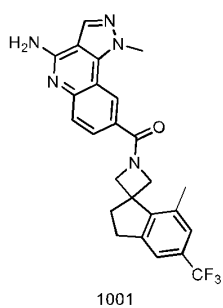
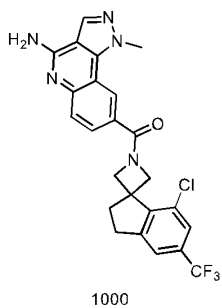
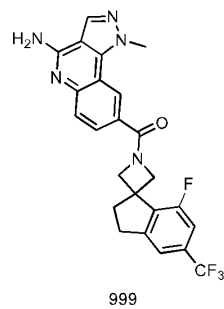
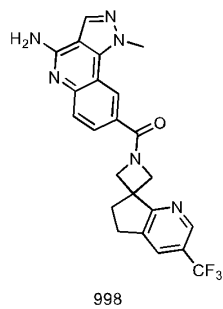
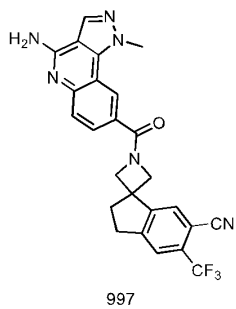
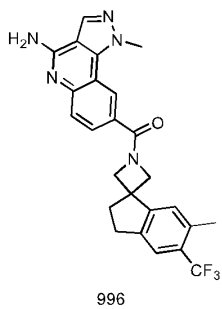
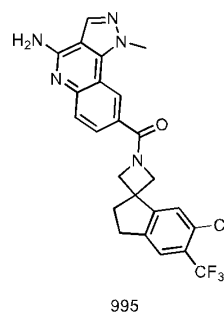
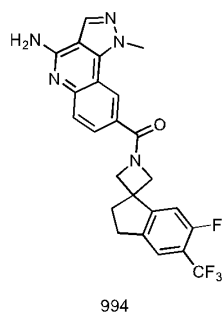
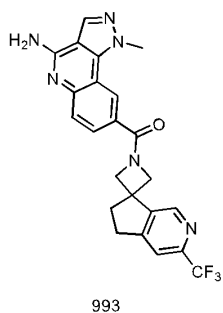
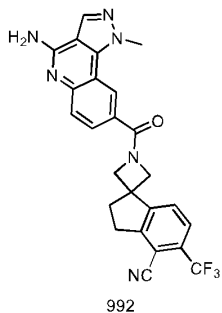
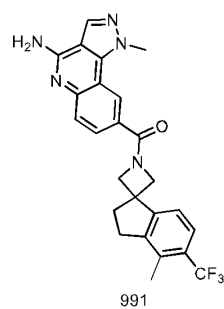
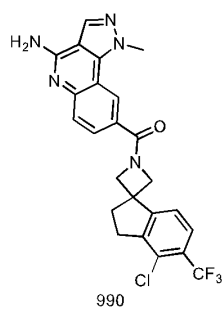
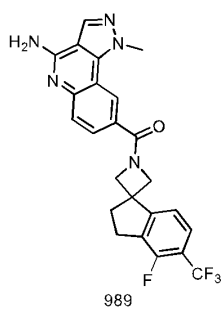
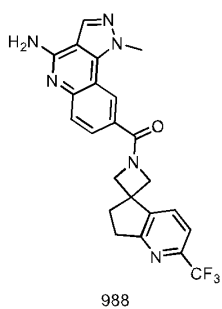
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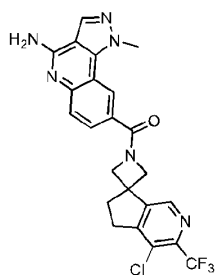


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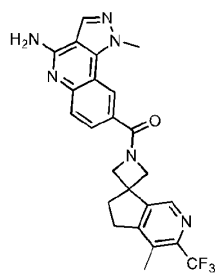


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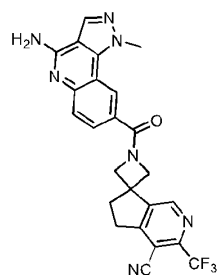




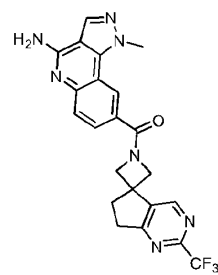
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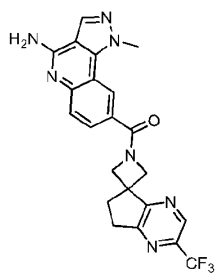
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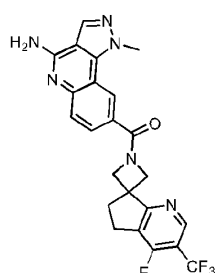
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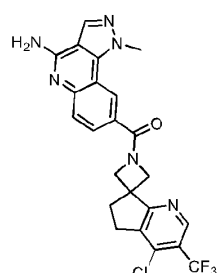
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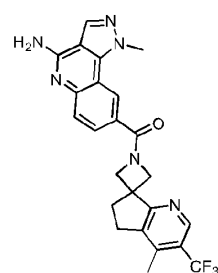
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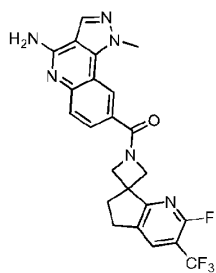
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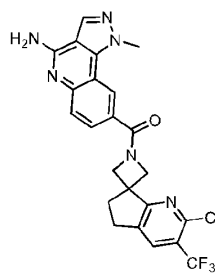
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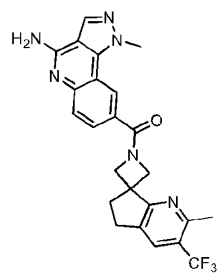
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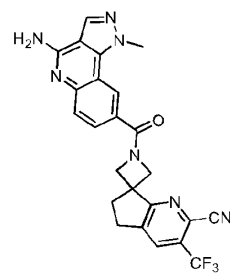
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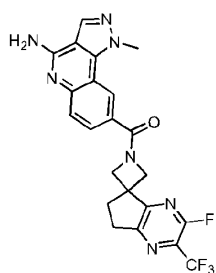
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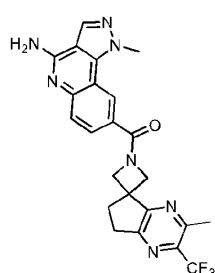
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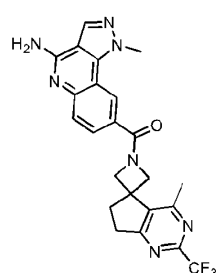
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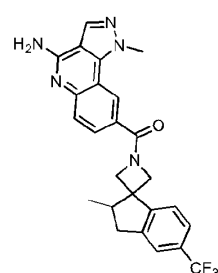
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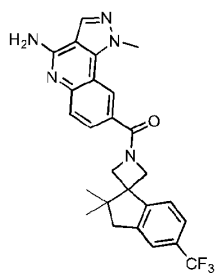
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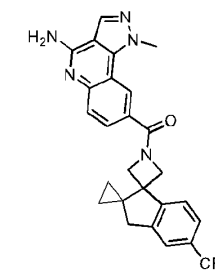
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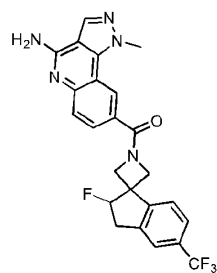
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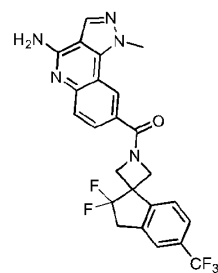
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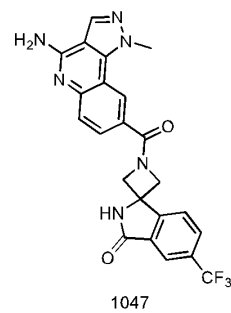
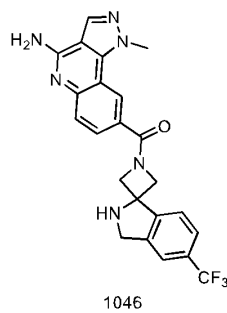
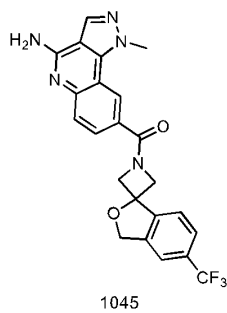
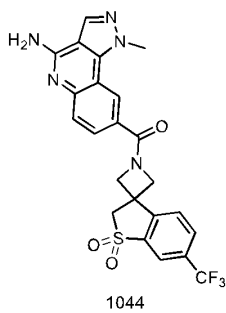
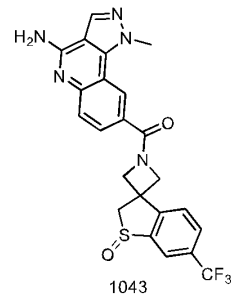
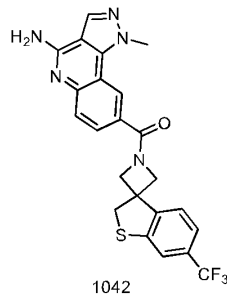
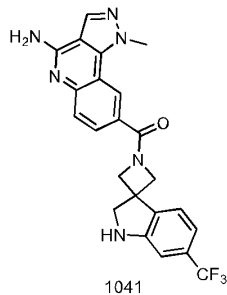
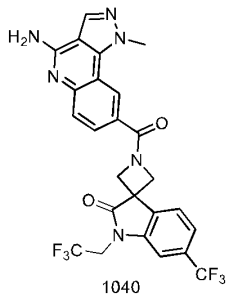
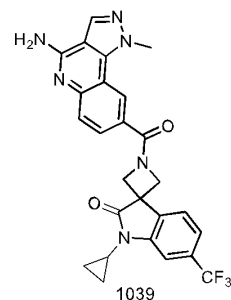
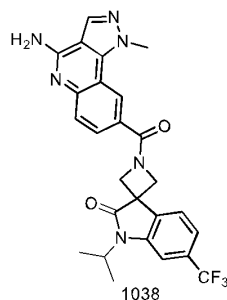
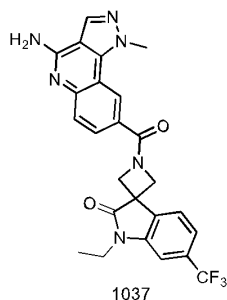
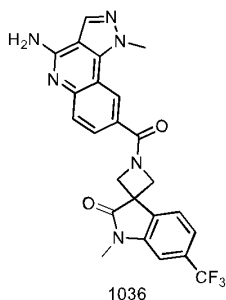
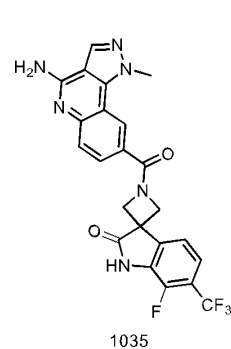
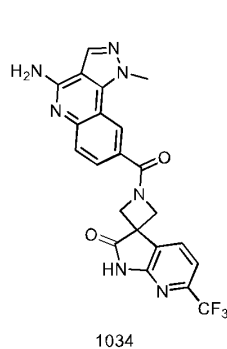
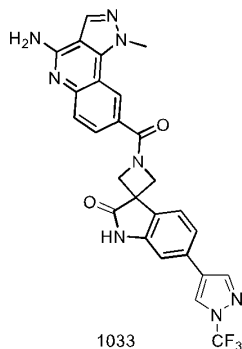
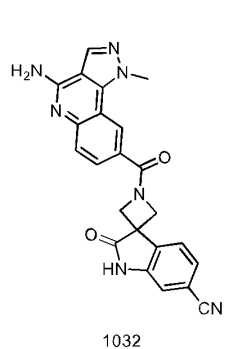
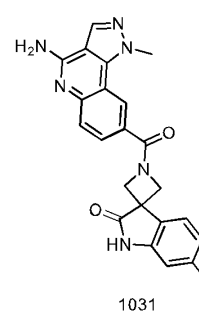
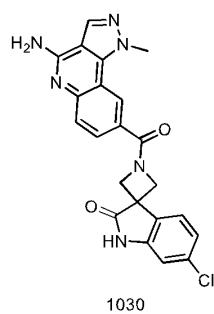
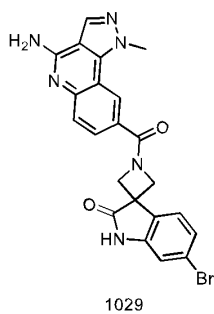
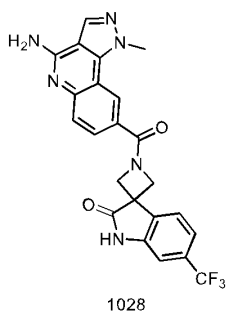
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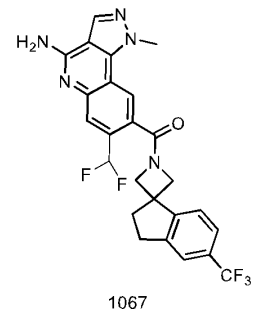
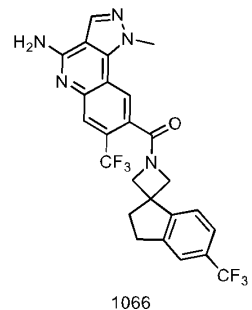
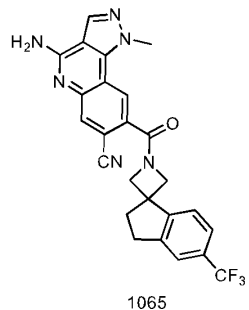
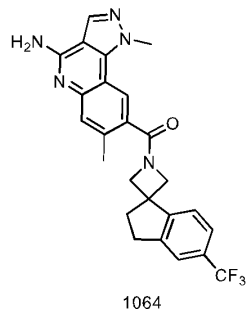
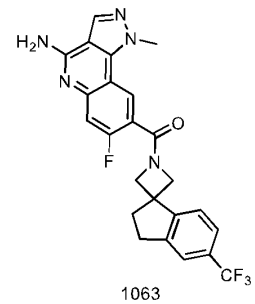
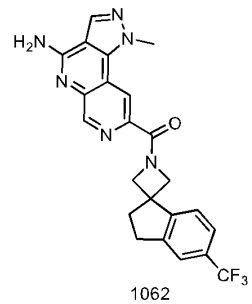
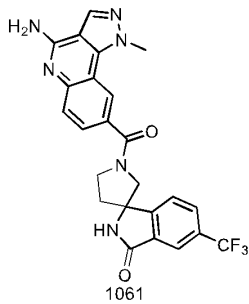
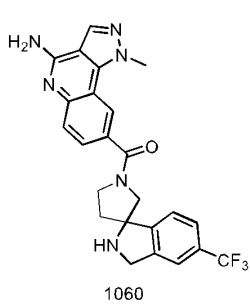
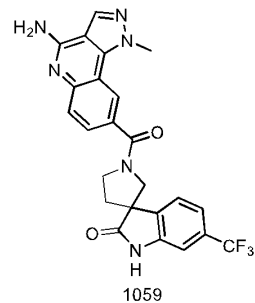
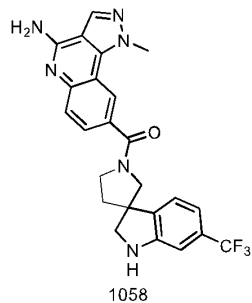
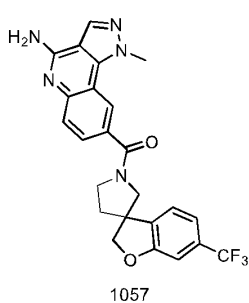
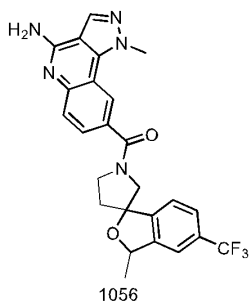
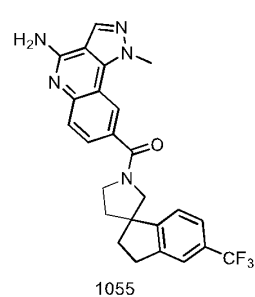
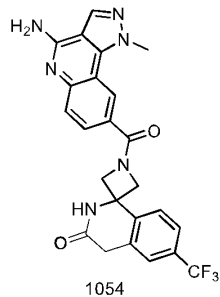
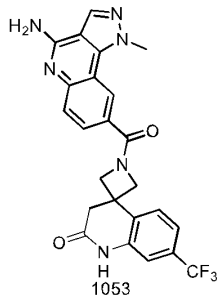
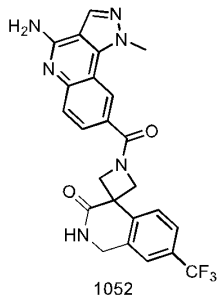
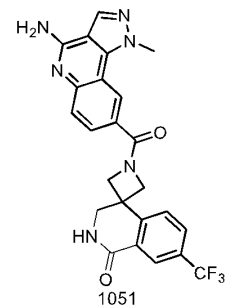
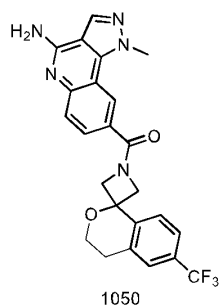
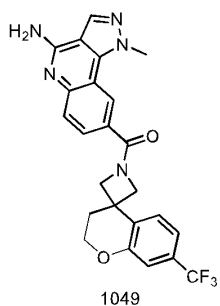
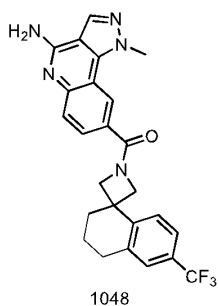


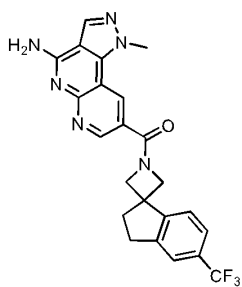
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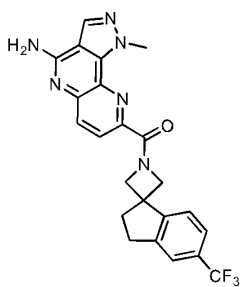
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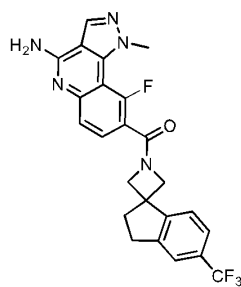




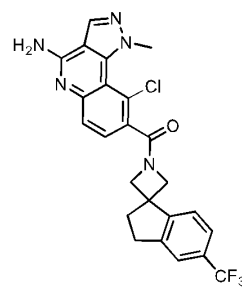
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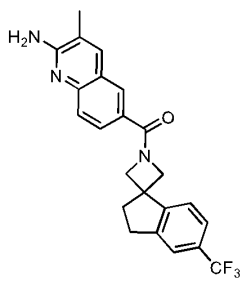
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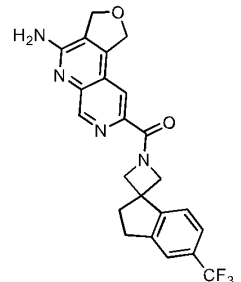
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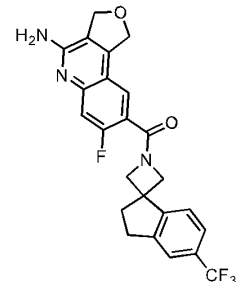
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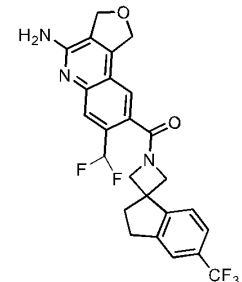
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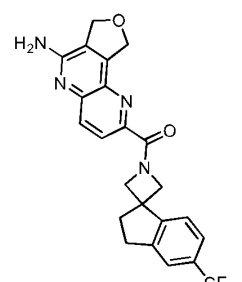
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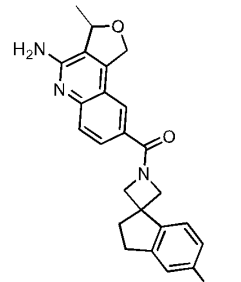
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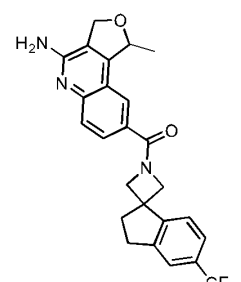
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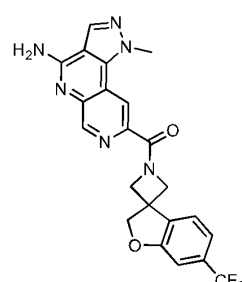
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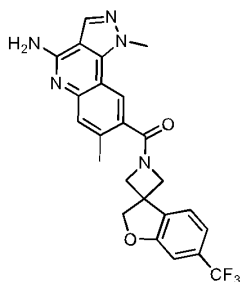
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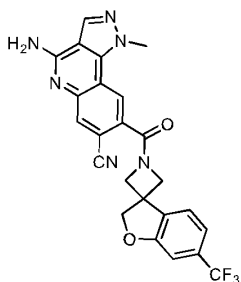
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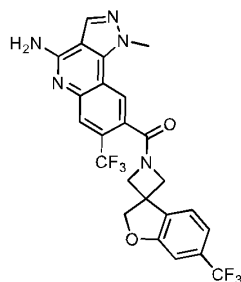
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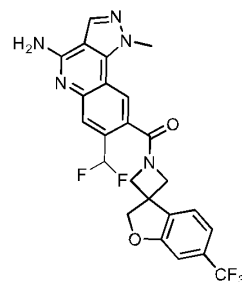
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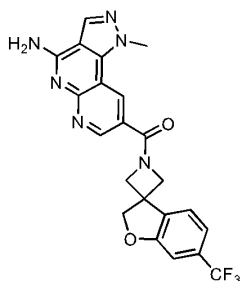
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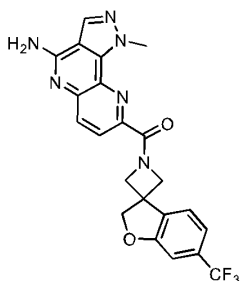
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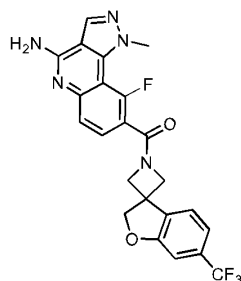
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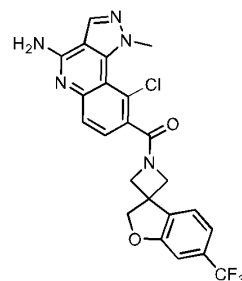
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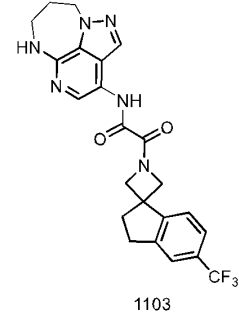
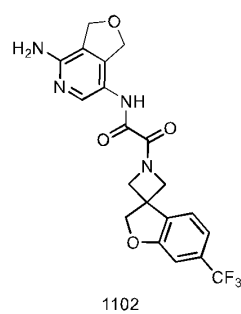
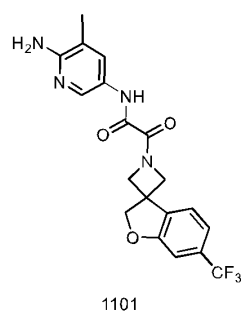
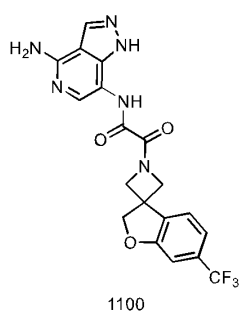
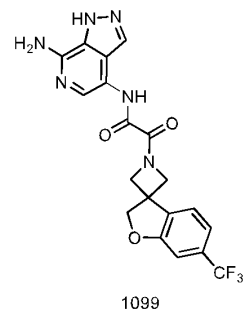
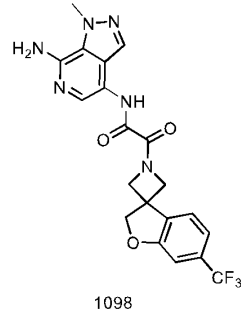
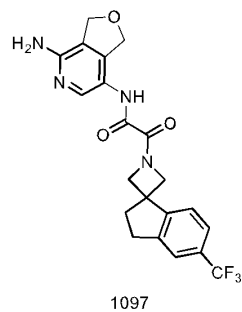
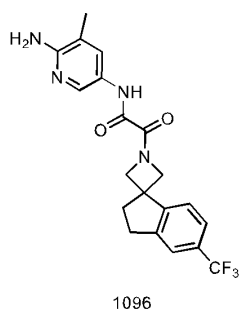
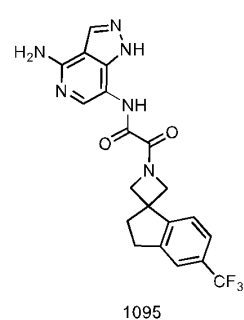
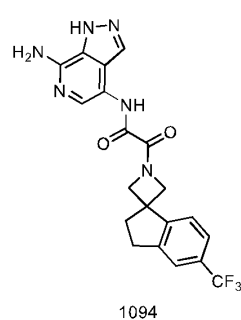
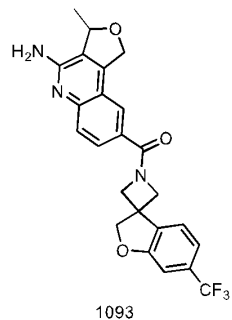
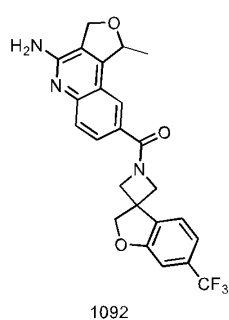
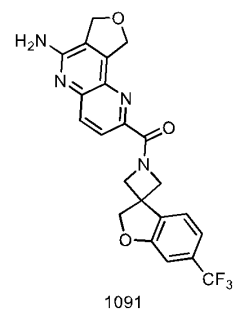
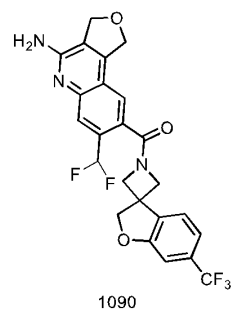
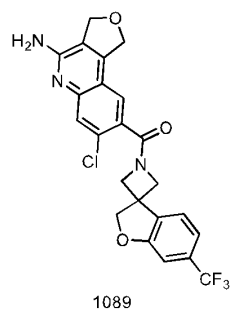
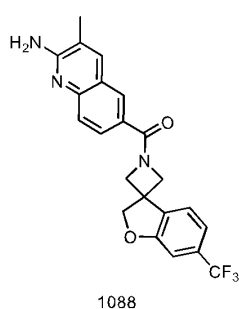
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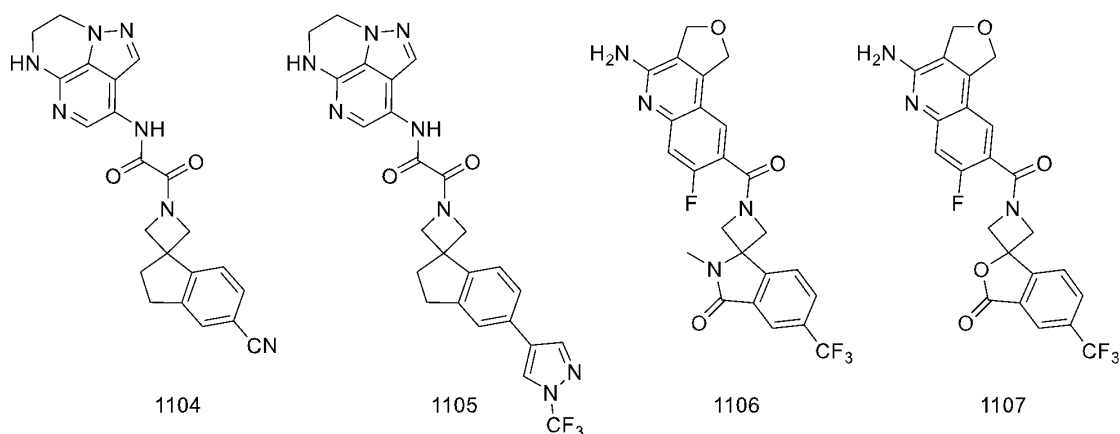


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- , or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled.
16. A pharmaceutical composition, comprising a compound according to any one of Claims 1-15 or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled, and one or more pharmaceutically acceptable carriers or excipients.
 17. Use of a compound according to any one of Claims 1-15 or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled or a pharmaceutical composition, comprising a compound according to Claim 16 in the manufacture of a medicament for treating cancer.
 18. Use of a compound according to any one of Claims 1-15 or a pharmaceutically acceptable salt, geometric isomer, enantiomer, diastereomer, racemate, prodrug, solvate, hydrate thereof or any of the foregoing that is isotope-labeled or a pharmaceutical composition, comprising a compound according to Claim 16 in the manufacture of an MTA-cooperative PRMT5 inhibitor.