

ARGININE METHYLTRANSFERASE INHIBITOR AND USE THEREOF

Technical field

5 The invention relates to the field of pharmaceutical chemistry and medicine, in particular to a class of type I PRMT inhibitor compound, preparation method therefor and its application in the field of disease treatment.

Background

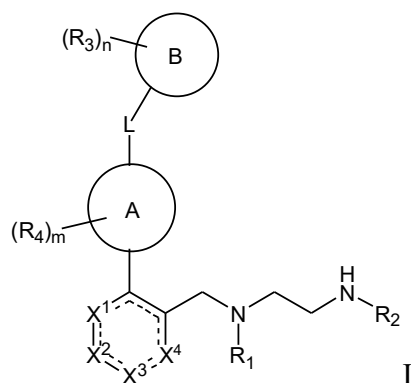
10 Protein arginine methylation is a highly-abundant post-translational modification that exists widely in the cytoplasm and nucleus. The protein arginine methyltransferases (PRMTs) family is involved in the process of protein arginine methylation, which mainly uses S-adenosylmethionine (SAM) as a methyl donor to methylate the nitrogen atom of the protein arginine side chain to generate S-adenosyl-L-homocysteine and methylated arginine. The PRMTs family contains 9 kinds of PRMT isoforms. According to the type of catalytic
15 reaction, PRMTs can be divided into type I (PRMT1\PRMT2\PRMT3\PRMT4\PRMT6\PRMT8), type II (PRMT5\PRMT9) and type III (PRMT7). Type I PRMT is responsible for asymmetric dimethylated arginine (ADMA), type II PRMT is responsible for symmetric dimethylated arginine (SDMA), and type III PRMT is responsible for monomethylated arginine (MMA).

20 At present, many documents have confirmed that the abnormal expression of type I PRMT is closely related to the occurrence and development of various diseases. For example, PRMT1 has been found to play an oncogenic role in leukemia, lung cancer, liver cancer, gastric cancer, colon cancer, breast cancer, pancreatic cancer, head and neck cancer, prostate cancer, bladder cancer, ect. In malignant glioma, PRMT2 was found to be over-expressed, and this was closely related to poor prognosis. In 70% of acute myeloid leukemia (AML)
25 patients, at least a two-fold over-expression of PRMT4 was observed. PRMT6 was found to be over-expressed in 52.6% of gastric cancer cells, and its expression had a significant positive correlation with the modification level of its substrate. Meanwhile, type I PRMT is mainly responsible for catalyzing the asymmetric dimethylation of arginine, and the changed
30 ADMA levels in vivo are closely related to cardiovascular diseases, diabetes, renal failure, asthma and chronic non-obstructive diseases. Therefore, it can be said that the abnormal expression of type I PRMT is related to the occurrence and development of various diseases. In summary, it is of great significance to develop new PRMT inhibitor molecules.

SUMMARY

35 The purpose of the present invention is to provide novel PRMT inhibitor molecules.

The first aspect of the present invention provides a compound represented by the following formula I, or a pharmaceutically acceptable salt or deuterated compound thereof:



X^1 , X^2 , X^3 and X^4 are each independently selected from the group consisting of: CR, NR and N; the dash line is a chemical bond or absent;

ring A is selected from the group consisting of substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 4-8 membered carbocycle, and substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 4-8 membered heterocycle;

ring B is selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted C_6 - C_{10} aryl, substituted or unsubstituted 5-12 membered heteroaromatic ring, substituted or unsubstituted 3-12 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur, and nitrogen, substituted or unsubstituted $-C_1$ - C_6 alkyl-6-10 membered aryl, substituted or unsubstituted C_3 - C_{12} carbocycle, substituted or unsubstituted C_2 - C_{10} acyl, substituted or unsubstituted C_2 - C_{10} ester group, substituted or unsubstituted C_6 - C_{10} aryloxy, substituted or unsubstituted C_1 - C_6 amide, substituted or unsubstituted C_1 - C_4 alkyl-S(O)₂, and substituted or unsubstituted C_1 - C_4 alkyl-SO-;

m and n are each independently selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6;

L is selected from the group consisting of chemical bonds, -O-, -(CHR⁶)_p-, -CHR⁶-O-, -CHR⁶-C(O)-, carbonyl, S, -NH-, -NHC(O)-, -NHS(O)₂-, -NHC(O)NH-, -NHC(S)NH-, -COO-, -O-S(O)₂-, -COO-CH₂-, -C(O)CH₂-, and -S(O)₂-, or L is absent;

p is selected from the group consisting of 1, 2 and 3;

R^1 and R^2 are each independently selected from the group consisting of H, substituted or unsubstituted C_1 - C_6 alkyl, and substituted or unsubstituted C_3 - C_6 cycloalkyl;

R^3 is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted C_1 - C_6 alkylamino, substituted or unsubstituted C_6 - C_{10} aryl, substituted or unsubstituted 5-12 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted $-C_1$ - C_6 alkyl-phenyl, substituted or unsubstituted C_3 - C_{12} carbocycle, substituted or unsubstituted C_2 - C_{10} acyl, substituted or unsubstituted C_2 - C_{10} ester group, substituted or unsubstituted C_6 - C_{10} aryloxy, substituted or unsubstituted C_1 - C_6 amide, substituted or unsubstituted C_1 - C_4 alkyl-S(O)₂-, and substituted or unsubstituted

C₁-C₄alkyl-SO-;

R is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-12 membered heteroaryl, substituted or unsubstituted 4-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₃-C₁₂carbocycle, substituted or unsubstituted C₂-C₁₀acyl, substituted or unsubstituted C₂-C₁₀ester group, substituted or unsubstituted C₆-C₁₀aryloxy, substituted or unsubstituted C₁-C₆amide, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-;

or two R located on adjacent ring atoms together with the ring atoms to which they are attached form a substituted or unsubstituted 5-11 membered carbocycle or heterocycle, and the ring is partially unsaturated or saturated; preferably, the carbocycle or heterocycle is a 5-9 membered carbocycle or heterocycle, more preferably a 5-7 membered carbocycle or heterocycle (the carbocycle or heterocycle is saturated, partially unsaturated or aromatic);

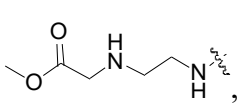
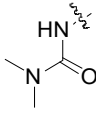
R⁴ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-12 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₃-C₁₂carbocycle, substituted or unsubstituted C₂-C₁₀acyl, substituted or unsubstituted C₂-C₁₀ester group, substituted or unsubstituted C₆-C₁₀aryloxy, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-;

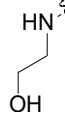
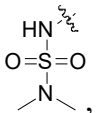
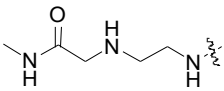
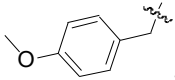
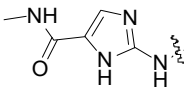
or two R⁴ on the same or adjacent ring atoms together with the ring atoms to which they attached form a substituted or unsubstituted 3-11 membered carbocycle or heterocycle, and the ring is a partially unsaturated ring, saturated ring or aromatic ring;

R⁶ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, acyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, and substituted or unsubstituted C₁-C₆alkylamino;

unless otherwise specified, in the above formulas, the “substituted” means that the hydrogen atom on the corresponding group is substituted by one or more substituents selected from the group consisting of: deuterium, tritium, halogen, hydroxyl, carboxyl, thiol, benzyl, oxo (=O), C₁-C₁₂alkoxycarbonyl, C₁-C₆aldehyde group, amino, C₁-C₆ amide, nitro, cyano, unsubstituted or halogenated C₁-C₆alkyl, C₂-C₁₀alkenyl, C₁-C₆alkoxy, C₁-C₆alkyl-amino, C₁-C₆alkyl-sulfonamide, C₁-C₆alkyl-ureido, C₁-C₆alkyl-S-, C₆-C₁₀aryl, five- or six-membered heteroaryl, five- or six-membered non-aromatic heterocyclyl, five- or six-membered non-aromatic heterocyclyl-(CH₂)-, -O-(C₆-C₁₀aryl), -O-(five or six membered heteroaryl),

-NH-(C₆-C₁₀aryl), -NH-(five-membered or six-membered heteroaryl),
C₁-C₁₂alkylaminocarbonyl, unsubstituted or halogenated C₂-C₁₀acyl, sulfonyl (-SO₂-OH),
sulfonamide (-SO₂-NH₂), phosphoryl (-PO₃-OH), unsubstituted or halogenated

C₁-C₄alkyl-S(O)₂-, unsubstituted or halogenated C₁-C₄alkyl-SO-, , ,

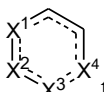
5 , , , , and ; in each formula, the heterocycle or heteroaromatic ring has 1-3 heteroatoms selected from the group consisting of N, S and O; each aryl, heteroaryl, and heterocyclyl can be independently substituted by 1-3 substituents selected from the group consisting of deuterium, tritium, halogen, hydroxyl, carboxyl, thiol, C₁-C₆alkyl, and C₁-C₆alkoxy.

10 In another preferred embodiment, the aromatic ring, aromatic-ring or aromatic system includes conventional tautomers of aromatic rings, such as pyridone, benzimidazole, benzopyrazole and the like.

In another preferred embodiment, at least one of X¹, X², X³ and X⁴ is N.

In another preferred embodiment, the ring  is an aromatic ring.

15 In another preferred embodiment, two R located on adjacent ring atoms together with the ring atoms to which they are attached form a substituted or unsubstituted 5-11 membered

carbocycle or heterocycle, this ring and the ring  together form an aromatic ring system.

20 In another preferred embodiment, when ring B is H, said m is 2, 3, 4, 5 or 6; and at least two R⁴ on the same or adjacent ring atoms together with the ring atoms to which they are attached form a substituted or unsubstituted 5-11 membered carbocycle or heterocycle (the ring is a partially unsaturated ring, saturated ring or aromatic ring).

25 In another preferred embodiment, L is selected from the group consisting of: chemical bond, -O-, -(CHR⁶)_p-, -CHR⁶-O-, -CHR⁶-C(O)-, carbonyl, S, -NH-, -NHC(O)-, -COO-, -COO-CH₂-, -C(O)CH₂-, and -S(O)₂-, or L is absent.

30 In another preferred embodiment, R³ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted C₃-C₈carbocycle, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₆-C₁₀aryloxy, substituted or unsubstituted C₁-C₆amide, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-; and/or

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R is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₃-C₈carbocycle, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₆-C₁₀aryloxy, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-; or two R located on adjacent ring atoms together with the carbon atoms to which they attached form a substituted or unsubstituted 5-9 membered carbocycle or heterocycle, and the ring is partially unsaturated, saturated or aromatic; and/or

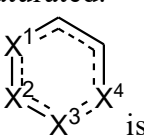
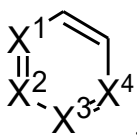
In another preferred embodiment, R⁴ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-7 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₃-C₈carbocycle, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₁₀ester group, substituted or unsubstituted C₆-C₁₀aryloxy, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-; or two R⁴ located on adjacent ring atoms together with the carbon atoms to which they are attached form a substituted or unsubstituted 5-9 membered carbocycle or heterocycle, and the ring is partially unsaturated or saturated.

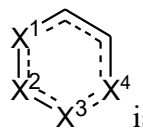
In another preferred embodiment, ring B is selected from the group consisting of: H, or substituted or unsubstituted phenyl, substituted or unsubstituted 5-10 membered heteroaromatic ring, substituted or unsubstituted 3-12 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, and substituted or unsubstituted C₃-C₁₂carbocycle.

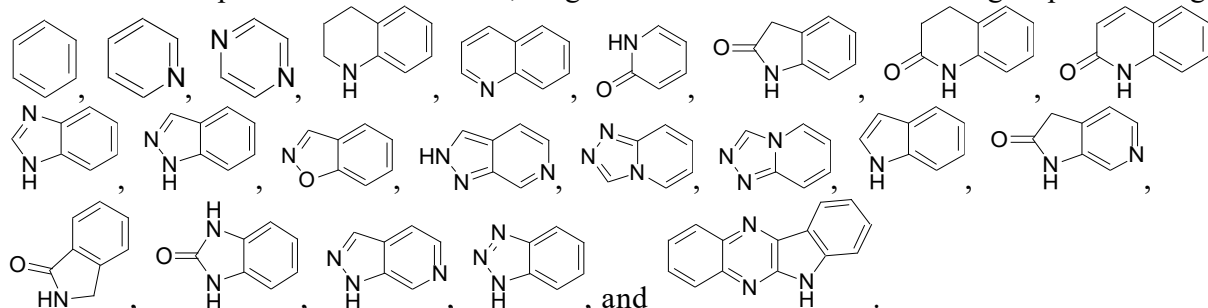
In another preferred embodiment, R³ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-; and/or

R is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-; or two R located on adjacent ring atoms together with the ring atoms to which they are attached form a substituted or unsubstituted 5-7 membered carbocycle or heterocycle; and/or

R⁴ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₃-C₈carbocycle, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₁₀ester group, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-; or two R⁴ on adjacent ring atoms together with the carbon atoms to which they are attached form a substituted or unsubstituted 5-9 membered carbocycle or heterocycle, and the ring is partially unsaturated or saturated.

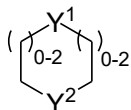
In another preferred example, ring  is .

In another preferred embodiment, ring  is selected from the group consisting of:



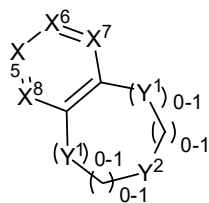
In another preferred embodiment, ring B is selected from the group consisting of substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-12 membered heteroaryl, substituted or unsubstituted 4-12 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, and substituted or unsubstituted C₃-C₁₂carbocycle.

In another preferred embodiment, ring A is selected from the group consisting of:



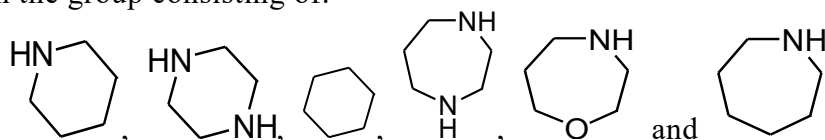
30 , wherein, Y¹ and Y² are each independently selected from the group consisting of: CHR⁶ and NR⁶; 0-2 means that the number of carbon atoms can be 0, 1 or 2; and the L-B structure can be located at Y¹, Y² or other ring atoms (preferably at Y¹, Y²);

or ring A together with two R⁴ form a group selected from the group consisting of:



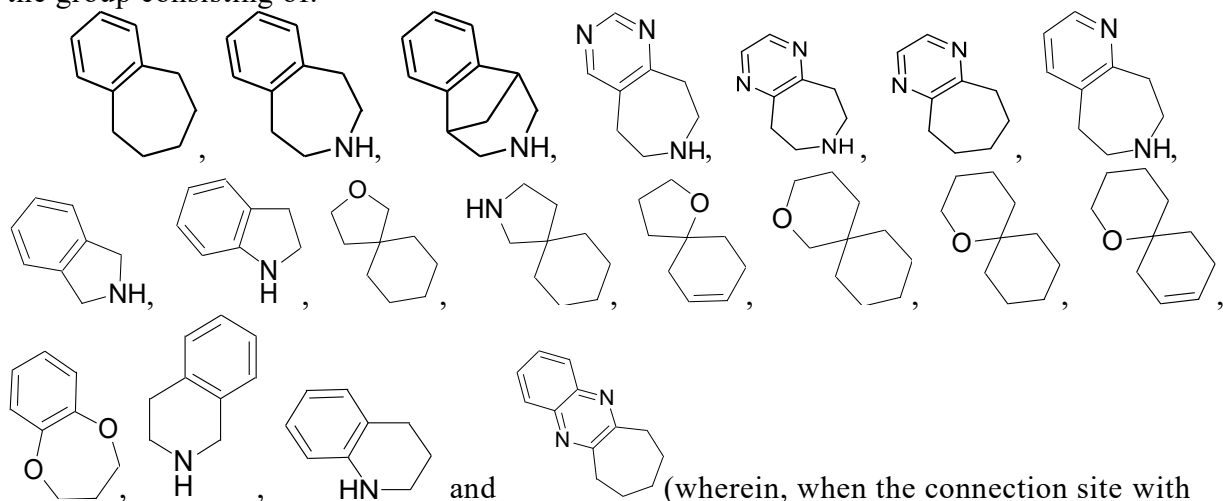
, wherein, Y¹ and Y² are each independently selected from the group consisting of: CHR⁶, O and NR⁶; X⁵, X⁶, X⁷ and X⁸ are each independently selected from the group consisting of: CR⁶ and N.

In another preferred embodiment, ring A is a substituted or unsubstituted group selected from the group consisting of:



(wherein, when the connection site connected to other structural fragments or substituents is NH, the hydrogen atom on NH is lost to form the connection site);

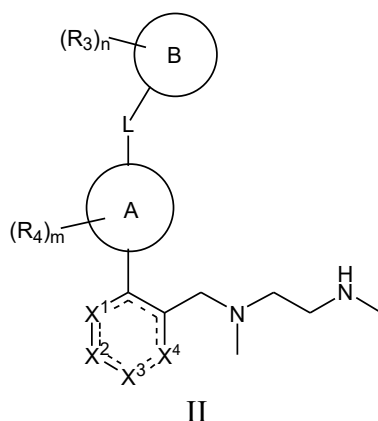
or ring A together with two R⁴ form a substituted or unsubstituted group selected from the group consisting of:



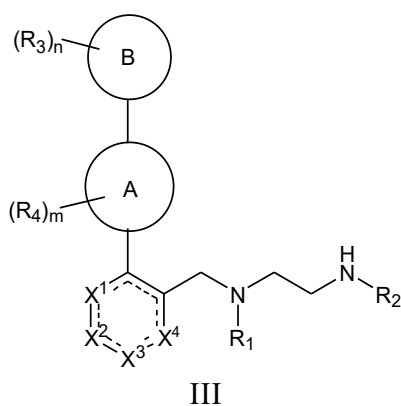
(wherein, when the connection site with other structural fragments or substituents is NH, the hydrogen atom on NH is lost to form the connection site).

In another preferred embodiment, the substituents on ring A are groups selected from the group consisting of: H, halogen, cyano, amino, nitro, carbonyl, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₃-C₈carbocycle, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₁₀ester group, substituted or unsubstituted C₁-C₆ amide, and substituted or unsubstituted C₁-C₄alkyl-S(O)₂-.

In another preferred embodiment, the compound has a structure shown in the following formula II:



5 In another preferred embodiment, the compound has a structure shown in the following formula III:



wherein,

10 ring A is selected from the group consisting of substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 4-8 membered carbocycle, and substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 4-8 membered heterocycle;

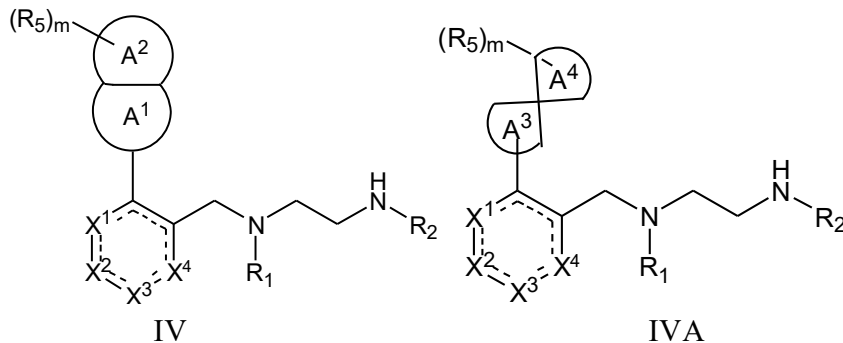
15 ring B is selected from the group consisting of substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-12 membered heteroaryl, substituted or unsubstituted 3-12 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, and substituted or unsubstituted C₃-C₁₂heterocycle;

20 preferably, R³ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-;

25 preferably, R⁴ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-7 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted

-C₁-C₆alkyl-phenyl, substituted or unsubstituted C₃-C₈carbocycle, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-.

In another preferred embodiment, the compound has a structure shown in the following formula IV:



wherein,

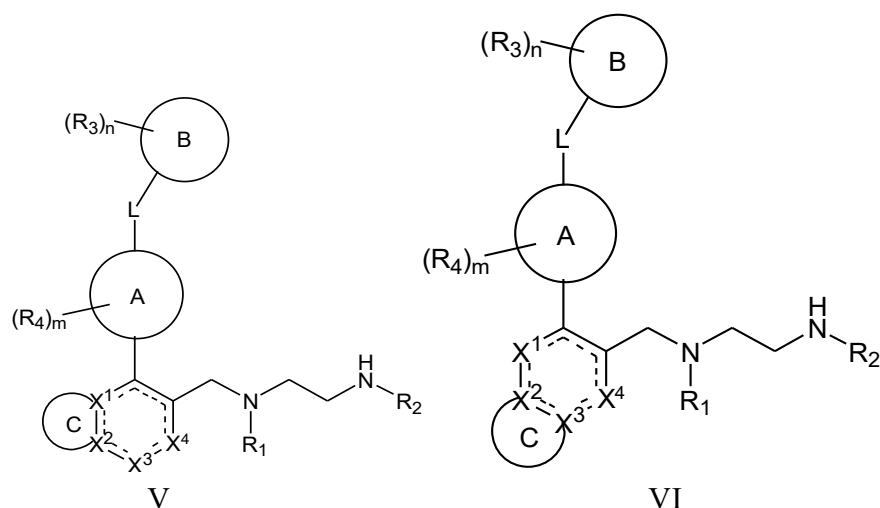
ring A¹ is selected from the group consisting of substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 5-8 membered carbocycle, and substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 5-8 membered heterocycle;

ring A² is selected from the group consisting of substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-12 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, and substituted or unsubstituted C₃-C₁₂carbocycle; and ring A² is fused with ring A¹;

ring A³ and ring A⁴ are each independently selected from the group consisting of substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 5-8 membered carbocycle, and substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 3-8 membered heterocycle;

m is 0, 1, 2, 3 or 4; R⁵ is selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₆-C₁₀aryloxy or heteroaryloxy, substituted or unsubstituted C₆-C₁₀arylamino or heteroarylamino, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-; and R⁵ can be located on ring A¹, ring A², ring A³ or ring A⁴.

In another preferred embodiment, the compound has a structure shown in the following formula V or VI:



wherein, ring C is substituted or unsubstituted phenyl, substituted or unsubstituted 5-7 membered heterocyclyl, or substituted or unsubstituted 5-6 membered heteroaryl;

ring A is selected from the group consisting of substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 5-6 membered carbocycle, and substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 4-8 membered heterocycle;

ring B is selected from the group consisting of substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-12 membered heteroaryl, substituted or unsubstituted 4-12 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, and substituted or unsubstituted C₃-C₁₂carbocycle;

preferably, R³ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-;

preferably, R⁴ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-7 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₃-C₈carbocycle, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-.

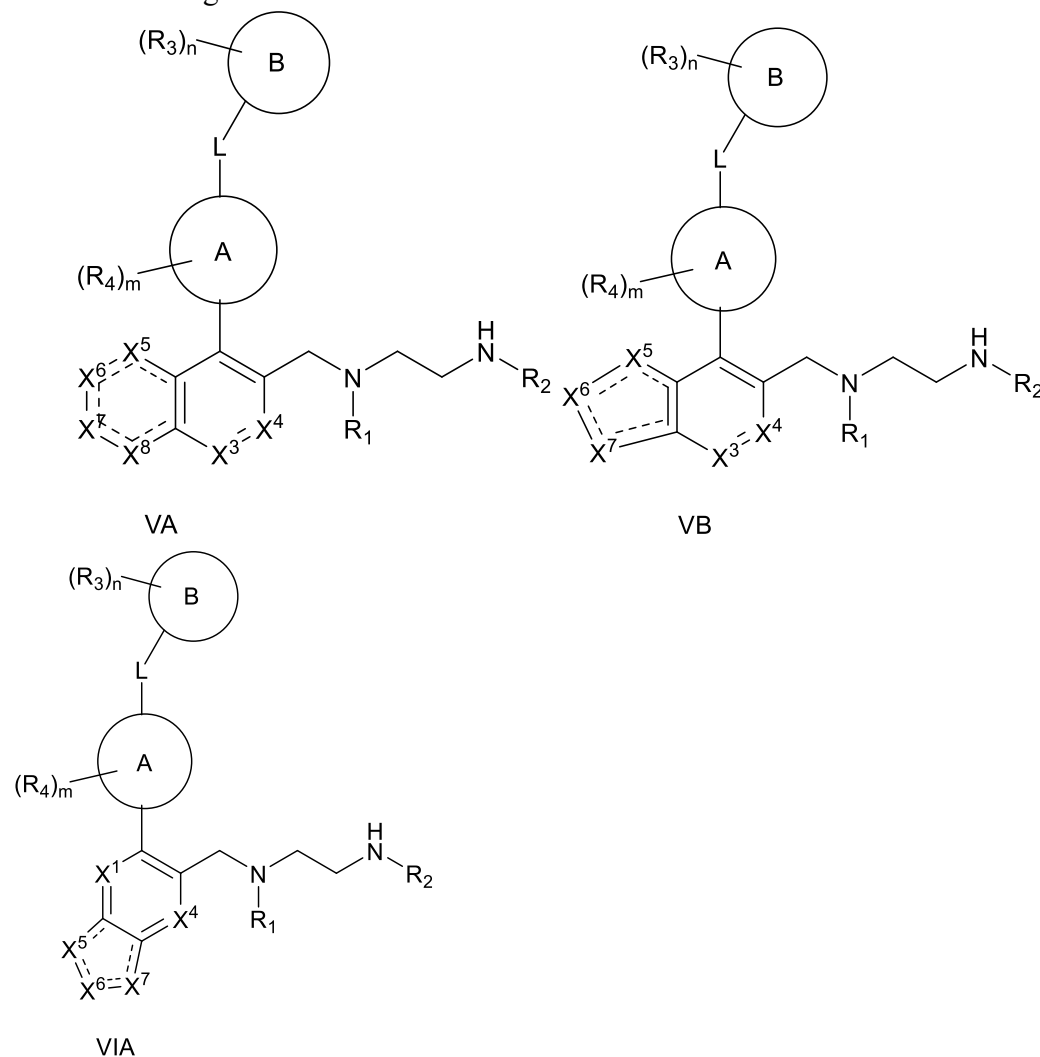
In another preferred embodiment, ring C is selected from the group consisting of benzene ring, 5-7 membered heteroaromatic ring, and 5-7 membered saturated or partially unsaturated heterocycle.

In another preferred embodiment, ring A is selected from the group consisting of substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 5-6 membered carbocycle, and substituted or unsubstituted saturated or partially unsaturated (non-aromatic)

5-7 membered heterocycle.

In another preferred embodiment, ring B is selected from the group consisting of substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-7 membered heteroaryl, substituted or unsubstituted 4-12 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, and substituted or unsubstituted C₃-C₁₂carbocycle.

In another preferred embodiment, the compound of Formula I has a structure as shown in the following formula:



X⁵, X⁶, X⁷, and X⁸ are each independently selected from the group consisting of: C(R)₂, NR, CR and N; the dash lines are chemical bonds or absent.

In the second aspect of the present invention, provided is a pharmaceutical composition, comprising a therapeutically effective amount of the compound of formula I as described in the first aspect of the present invention, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients, adjuvants, accessories and/or diluents.

In the third aspect of the present invention, provided is a use of a compound of formula I as described in the first aspect of the present invention, or a pharmaceutically acceptable salt thereof, in the preparation of a pharmaceutical composition for the treatment or prevention of diseases associated with PRMT; preferably the PRMT is type I PRMT.

In another preferred embodiment, the disease is selected from the group consisting of tumor, cardiovascular disease, neurodegenerative disease, malaria, AIDS, gout, diabetes, renal failure, chronic lung disease, oculopharyngeal muscular dystrophy, cocaine addiction, pulmonary hypertension, amyotrophic lateral sclerosis, and alcoholic cirrhosis.

5 In another preferred embodiment, the tumor is selected from any one of brain cancer, glioblastoma, leukemia, lymphoma, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast cancer, Wilms tumor, Ewing sarcoma, rhabdomyosarcoma, ependymoma, medulloblastoma, colon cancer, stomach cancer, bladder cancer, head and neck cancer, kidney cancer, lung cancer, liver cancer, melanoma, ovarian cancer, pancreatic cancer,
10 prostate cancer, sarcoma, osteosarcoma, giant cell tumor of bone, and thyroid cancer.

It should be understood that within the scope of the present invention, the above-mentioned technical features of the present invention and the technical features specifically described in the following (such as embodiments) can be combined with each
15 other to form a new or preferred technical solution. Limited by space, it will not be repeated here.

Detailed Description of the Invention

Through extensive and in-depth research, the present inventors unexpectedly discovered
20 a class of compounds with PRMT inhibitory effect for the first time. On this basis, the present invention is completed.

Terms

As used herein, the halogen is F, Cl, Br or I.

25 In the present invention, unless otherwise specified, the terms used herein have the ordinary meaning known to those skilled in the art. In the present invention, all chemical formulas are intended to cover any possible optical or geometric isomers (such as R-form, S-form or racemate, or cis-trans isomers of alkenes, etc.) unless otherwise specified.

In the present invention, the term "C₁-C₆ alkyl" refers to a straight or branched alkyl
30 having 1 to 6 carbon atoms, and including without limitation methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl, etc.; preferably, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

In the present invention, the term "C₁-C₆alkoxy" refers to a straight or branched alkoxy
35 with 1 to 6 carbon atoms, including without limitation methoxy, ethoxy, propoxy, isopropoxy and butoxy, etc.

In the present invention, the term "C₂-C₆ alkenyl" refers to a straight or branched alkenyl with 2 to 6 carbon atoms containing a double bond, including without limitation ethenyl, propenyl, butenyl, isobutenyl, pentenyl and hexenyl etc.

In the present invention, the term "C₂-C₆alkynyl" refers to a straight or branched alkynyl
40 group with 2 to 6 carbon atoms containing a triple bond, including without limitation ethynyl, propynyl, butynyl, isobutynyl, pentynyl and hexynyl, etc.

In the present invention, the term "C₃-C₁₀ cycloalkyl" refers to a cyclic alkyl having 3

to 10 carbon atoms on the ring, including without limitation cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and cyclodecyl, etc. The terms "C₃-C₈cycloalkyl", "C₃-C₇ cycloalkyl", and "C₃-C₆cycloalkyl" have similar meanings.

5 In the present invention, the term "C₃-C₁₀ cycloalkenyl" refers to a cyclic alkenyl having 3 to 10 carbon atoms on the ring, including without limitation cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl and cyclodecylene, etc. The term "C₃-C₇ cycloalkenyl" has a similar meaning.

10 In the present invention, the term "C₁-C₁₂ alkoxy carbonyl" refers to an alkoxy carbonyl having 1 to 12 carbon atoms in the alkyl chain, including without limitation methoxy carbonyl, ethoxy carbonyl, propoxy carbonyl, isopropoxy carbonyl, tert-butoxy carbonyl, benzyloxy carbonyl, and the like.

15 In the present invention, the term "C₁-C₁₂ alkylaminocarbonyl" refers to an alkylaminocarbonyl group having 1 to 12 carbon atoms in the alkyl chain, including without limitation methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, isopropylaminocarbonyl, tert-butylaminocarbonyl, benzylaminocarbonyl, dimethylaminocarbonyl, and the like.

In the present invention, the term "C₅-C₉ furanosyl" refers to a furanosyl group with 5 to 9 carbon atoms, wherein the position-1 of the glycosyl is connected to the main chain, including without limitation ribofuranosyl, deoxyribofuranosyl, galactofuranosyl, etc.

20 In the present invention, the term "C₅-C₉ pyranosyl" refers to a pyranosyl group having 5 to 9 carbon atoms, wherein the position-1 of the glycosyl is connected to the main chain, including without limitation the glucopyranosyl, glucuronic acid glucopyranosyl, rhamnopyranosyl, galactopyranosyl, mannopyranosyl, xylopyranosyl, etc.

25 In the present invention, the term "aromatic ring" or "aryl" has the same meaning, preferably "aryl" is "C₆-C₁₂ aryl" or "C₆-C₁₀ aryl". The term "C₆-C₁₂ aryl" refers to an aromatic ring group having 6 to 12 carbon atoms without heteroatoms in the ring, such as phenyl, naphthyl and the like. The term "C₆-C₁₀ aryl" has a similar meaning.

30 In the present invention, the term "heteroaromatic ring" or "heteroaryl" has the same meaning and refers to a heteroaromatic group containing one to more heteroatoms. The heteroatoms herein include oxygen, sulfur and nitrogen. For example, furyl, thienyl, pyridyl, pyrazolyl, pyrrolyl, N-alkylpyrrolyl, pyrimidinyl, pyrazinyl, imidazolyl, tetrazolyl and the like. The heteroaromatic ring may be fused to an aryl, heterocyclyl or cycloalkyl ring, wherein the ring bonded to the parent structure is a heteroaryl ring. Heteroaryl can be optionally substituted or unsubstituted.

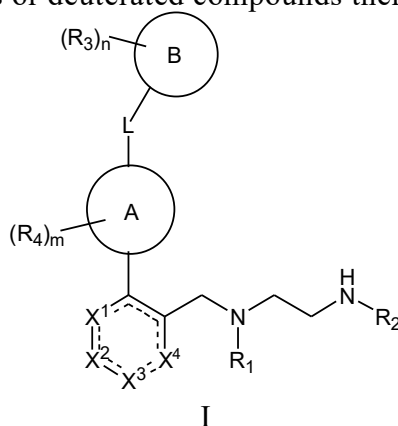
35 In the present invention, the term "3-12 membered heterocyclyl" refers to a saturated or unsaturated 3-12 membered cyclic group containing 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen on the ring, such as dioxolo, etc. The term "3-7 membered heterocyclyl" has a similar meaning.

40 In the present invention, the term "substituted" means that one or more hydrogen atoms on a specific group are replaced by a specific substituent. The specific substituents are the corresponding substituents described above, or the substituents appeared in each example. Unless otherwise specified, a substituted group may have a substituent selected from a

specific group at any substitutable position, and the substituents may be the same or different at each position. A cyclic substituent, such as a heterocycloalkyl, can be attached to another ring, such as a cycloalkyl, to form a spirobicyclic ring system, eg, two rings share a common carbon atom. Those skilled in the art will understand that combinations of substituents contemplated by the present invention are those that are stable or chemically feasible. The substituents are for example (but not limited to): C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, C3-8 cycloalkyl, 3- to 12-membered heterocyclyl, aryl, heteroaryl, halogen, hydroxyl, carboxyl (-COOH), C1-8 aldehyde group, C2-10 acyl, C2-10 ester group, C1-C12 alkoxy, carbonyl, amino, alkoxy, C1-10 sulfonyl, etc.

PRMT inhibitor compounds

The present invention provides a class of compounds with PRMT inhibitory activity, or pharmaceutically acceptable salts or deuterated compounds thereof:



wherein, the definition of each group is as described above. In the present invention, preferred compounds have the structure shown in any one of the example compounds P001-P448.

Pharmaceutical composition and mode of application

Since the compound of the present invention has excellent activity of inhibiting type I PRMT, the compound of the present invention and its various crystal forms, pharmaceutically acceptable inorganic or organic salts, hydrates or solvates, and pharmaceutical compositions containing the compound of the present invention as the main active ingredient can be used to treat, prevent and alleviate related diseases caused by abnormal activity or expression of PRMT.

The pharmaceutical composition of the present invention comprises the compound of the present invention or a pharmacologically acceptable salt thereof within a safe and effective amount range, and a pharmaceutically acceptable excipient or carrier. Wherein, "safe and effective amount" refers to: the amount of the compound is sufficient to obviously improve the condition without causing severe side effects. Usually, the pharmaceutical composition contains 1-2000 mg of the compound of the present invention per dose, more preferably, 5-500 mg of the compound of the present invention per dose. Preferably, the "one dose" is a capsule or tablet.

"Pharmaceutically acceptable carrier" refers to one or more compatible solid or liquid fillers or gel substances, which are suitable for human use and must have sufficient purity and low toxicity. "Compatibility" herein refers to the ability of components of a composition to blend with each other and with the compounds of the invention without significantly reducing the efficacy of the compounds. Examples of pharmaceutically acceptable carriers include cellulose and its derivatives (such as sodium carboxymethyl cellulose, sodium ethyl cellulose, cellulose acetate, etc.), gelatin, talc, solid lubricants (such as stearic acid, Magnesium stearate), calcium sulfate, vegetable oil (such as soybean oil, sesame oil, peanut oil, olive oil, etc.), polyols (such as propylene glycol, glycerin, mannitol, sorbitol), emulsifiers (e.g. Tween etc.[®]), wetting agents (such as sodium dodecyl sulfate), colorants, flavoring agents, stabilizers, antioxidants, preservatives, pyrogen-free water, etc.

The mode of administration of the compounds or pharmaceutical compositions of the present invention are not particularly limited, and representative mode of administration include, but are not limited to, oral, intratumoral, rectal, parenteral (intravenous, intramuscular or subcutaneous), and topical administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In these solid dosage forms, the active compound is mixed with at least one conventional inert excipient (or carrier), such as sodium citrate or dicalcium phosphate, or with the following ingredients: (a) filler or compatibilizer, such as starch, lactose, sucrose, glucose, mannitol and silicic acid; (b) adhesives, such as hydroxymethyl cellulose, alginate, gelatin, polyvinylpyrrolidone, sucrose and gum arabic; (c) moisturizing agents, such as glycerol; (d) disintegrating agents, such as agar, calcium carbonate, potato starch or cassava starch, algic acid, some complex silicates, and sodium carbonate; (e) retarding solvent, such as paraffin; (f) absorption accelerators, such as quaternary amine compounds; (g) wetting agents, such as cetyl alcohol and glycerol monostearate; (h) adsorbents, such as kaolin; and (i) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycol, sodium dodecyl sulfate, or mixtures thereof. In capsules, tablets and pills, dosage forms may also contain buffers.

Solid dosage forms such as tablets, sugar pills, capsules and granules may be prepared using coating and shell materials such as casing and other materials well known in the art. They may comprise an opacifying agent, and the release of the active compound in such a composition may be released in a delayed manner in a part of the digestive tract. Examples of embedding components that can be employed are polymeric substances and wax substances. If necessary, the active compound may also form a microcapsule form with one or more of the excipients described above.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups or tinctures. In addition to the active compounds, the liquid dosage form may contain inert diluents conventionally used in the art, such as water or other solvents, solubilizers and emulsifiers, for example, ethanol, isopropanol, ethyl carbonate, ethyl acetate, propylene glycol, 1,3-butanediol, dimethylformamide and oils, especially cottonseed oil, peanut oil, corn germ oil, olive oil, castor oil and sesame oil, or mixtures thereof.

In addition to these inert diluents, the composition may also contain auxiliaries such as wetting agents, emulsifiers, suspending agents, sweeteners, flavoring agents and spices.

In addition to the active compound, the suspension may comprise suspending agents, such as ethoxylatedisooctadecanol, polyoxyethylene sorbitol and dehydrated sorbitol esters, microcrystalline cellulose, methanolic aluminum, agar, and any mixtures thereof.

The composition for parenteral injection may comprise physiologically acceptable sterile aqueous or anhydrous solutions, dispersions, suspensions or emulsions, and sterile powders for redissolution into sterile injectable solutions or dispersions. Suitable aqueous and non-aqueous carriers, diluents, solvents, or excipients include water, ethanol, polyols, and suitable mixtures thereof.

Dosage forms of the compound of the invention for topical administration include ointments, powder, patches, propellants and inhalants. The active ingredient is mixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers or propellants as may be required.

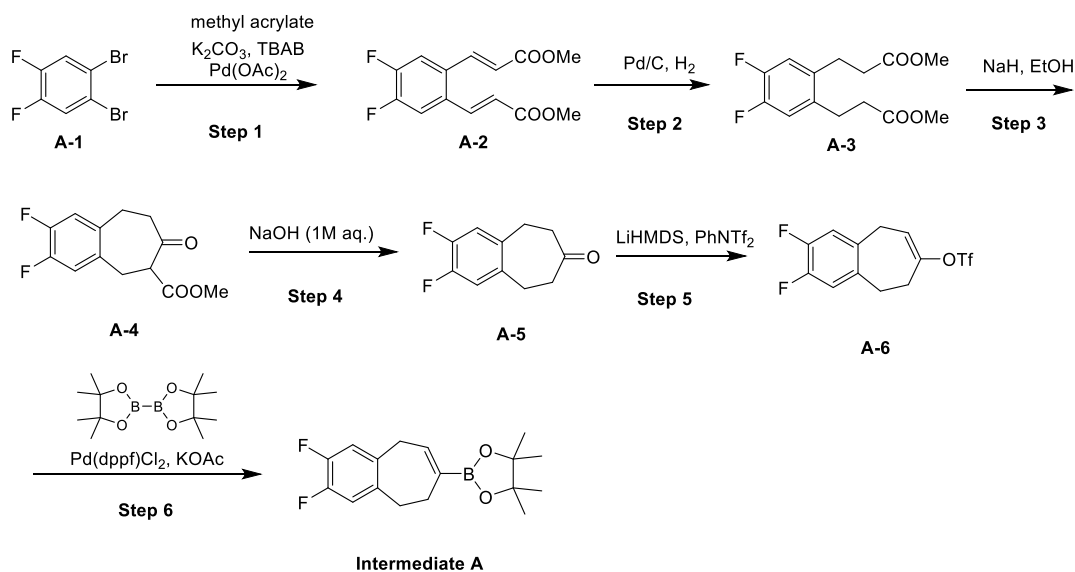
The compound of the present invention can be administered alone or in combination with other pharmaceutically acceptable compounds. In some preferred embodiments, the compounds of the present invention can be administered together with other small molecular compounds to form PROTACs, or with other macromolecular compounds such as monoclonal antibodies to form ADCs.

When using the pharmaceutical composition, a safe and effective amount of the compound of the present invention is administered to mammals in need of treatment (such as humans), where the dosage at the time of administration is the pharmaceutically considered effective dose, which is typically 1 to 2,000 mg per day, more preferably 5 to 500mg per day for a 60 kg body weight human. Of course, the specific dosage should also consider the route of administration, the patient's health condition and other factors, which are within the range of skilled doctors.

The present invention is further described below in conjunction with specific embodiments. It is to be understood that these examples are intended to illustrate the invention only and not to limit the scope of the invention. The experimental methods in the following examples that do not specify specific conditions are usually based on conventional conditions or conditions recommended by the manufacturer. Unless otherwise specified, percentages and portions are calculated by weight.

General synthesis methods:

Intermediate	Synthesis	1:	Synthesis	of
2-(2,3-difluoro-6,9-dihydro-5H-benzo[7]cyclopenten-7-yl)				
-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (intermediate A):				



Step 1: To a solution of 1,2-dibromo-4,5-difluorobenzene (A-1) (2.0 g, 7.36 mmol) and methyl acrylate (1.90 g, 22.1 mmol, 1.99 mL) in dimethylformamide (10 mL) was added tetrabutylammonium bromide (2.37 g, 7.36 mmol), and potassium carbonate (2.54 g, 18.4 mmol). After the reaction solution was replaced with nitrogen for 1 minute, palladium acetate (33.03 mg, 147 mmol), and the reaction solution was stirred at 80 °C for 16 hours. The reaction solution was then filtered, and the filter cake was washed 3 times with ethyl acetate (50 mL). The organic layer was washed with water (100 mL), dried with magnesium sulfate, filtered, and the filtrate was concentrated to dryness under reduced pressure, then purified by column chromatography (silica, 15% ethyl acetate in petroleum ether) to give the compound (2E,2'E)-dimethyl 3,3'-(4,5-difluoro-1,2-phenylene)diacrylate (A-2) (6.0 g, 21.26 mmol, 96.3% yield), as a white solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.93 (d, 2H), 7.39 (t, 2H), 6.31 (d, 2H), 3.85 (s, 6H)

Step 2: To a solution of (2E,2'E)-dimethyl 3,3'-(4,5-difluoro-1,2-phenylene)diacrylate (A-2) (6.0 g, 21.3 mmol) in methanol (150 mL) was added palladium/carbon (1.0 g, 10%), the reaction solution was degassed under reduced pressure and replaced with hydrogen for multiple times, then stirred under a hydrogen balloon atmosphere for 16 hours. The reaction solution was then filtered with diatomite pad and the filter cake was washed with ethyl acetate (50 mL) three times. The filtrate was concentrated to dryness under reduced pressure, then purified by column chromatography (silica, 15% ethyl acetate in petroleum ether) to give the compound dimethyl 3,3'-(4,5-difluoro-1,2-phenylene)dipropionate (A-3) (5.8 g, 20.26 mmol, 95.31% yield), as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 6.98 (t, 2H), 3.71 (s, 6H), 2.94 (t, 4H), 2.61 (t, 4H);

Step 3: A stirred solution of dimethyl 3,3'-(4,5-difluoro-1,2-phenylene)dipropionate (A-3) (1.0 g, 3.49 mmol) in xylene (5 mL) was slowly added at 95 °C to a suspension of NaH (209.59 mg, 5.24 mmol, 60% purity) in xylene (5 mL), with one drop of anhydrous ethanol being added for every 1 mL of the solution of 3,3'-(4,5-difluoro-1,2-phenylene)dipropionate (A-3) in xylene. After addition, the temperature of the reaction was raised to 115 °C and the reaction was continued at this temperature for 1.5 hours. Six reactions were set up in parallel. The completion of the reaction and the generation of the target product were detected by

LC-MS. The 6 reactions were combined, quenched with ice water (30 mL) and 1M hydrochloric acid aqueous solution (30 mL), and extracted 3 times with ethyl acetate (40 mL). The organic layer was dried with magnesium sulfate, filtered, and the filtrate was concentrated to dryness under reduced pressure to give a crude product of methyl 2,3-difluoro-7-oxo-6,7,8,9-tetrahydro-5H-benzo[7]cyclopentene-6-carboxylate (**A-4**) (5.3 g) as a yellow oil, which was used directly in the next step without purification. LCMS: (ESI) $m/z=254.7$ $[M+H]^+$, 268.8 $[M+14]^+$;

Step 4: To a solution of methyl 2,3-difluoro-7-oxo-6,7,8,9-tetrahydro-5H-benzo[7]cyclopentene-6-carboxylate (**A-4**) (5.3 g, 20.85 mmol) in ethanol (60 mL) was added sodium hydroxide (1 M aqueous solution, 62.5 mL), and the reaction solution was reacted for 2 hours at 90 °C. The completion of the reaction and the generation of the target product were detected by LC-MS. The reaction solution was then concentrated to dryness under reduced pressure, diluted with ethyl acetate (30 mL), and washed with water (30 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure, then purified by column chromatography (silica, 12% ethyl acetate in petroleum ether) to give compound 2,3-difluoro-8,9-dihydro-5H-benzo[7]cyclopenten-7(6H)-one (**A-5**) (2.6 g, 13.2 mmol, with a two-step yield of 78.9%), as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.06 (t, 2H), 2.78-2.95 (m, 4H), 2.53-2.69 (m, 4H),

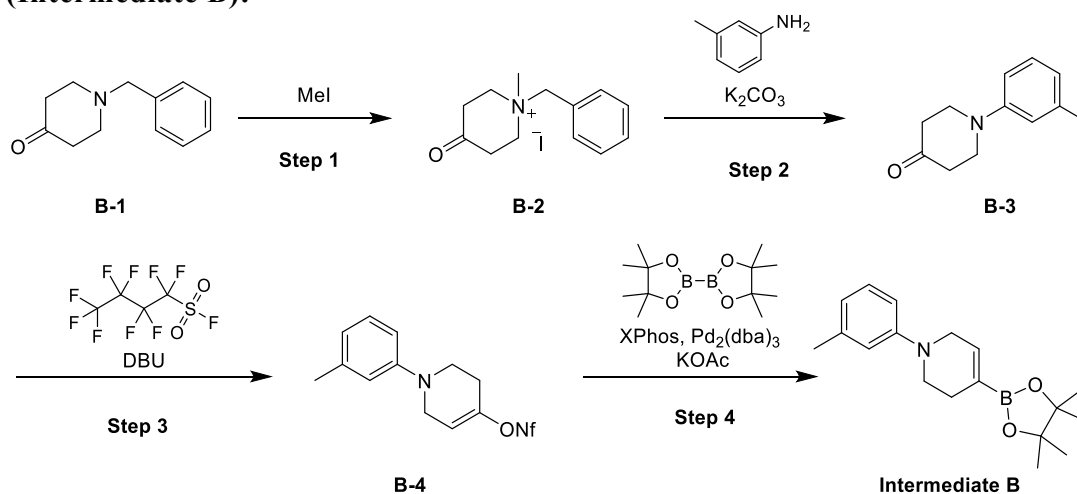
Step 5: To a solution of 2,3-difluoro-8,9-dihydro-5H-benzo[7]cyclopenten-7(6H)-one (**A-5**) (1.0 g, 5.10 mmol) in tetrahydrofuran (10 mL) was added lithium bis(trimethylsilyl)amide (1 M tetrahydrofuran solution, 5.61 mL) at -70 °C, then reacted at -70 °C for 1 h under nitrogen protection. The reaction solution was added with N-phenylbis(trifluoromethanesulfonyl)imide (2.00 g, 5.61 mmol) at -70 °C and then slowly warmed to room temperature for 15 h. The completion of the reaction was confirmed by TLC detection (petroleum ether:ethyl acetate=8:1, R_f =0.8). The reaction solution was then quenched with water (25 mL) and extracted three times with ethyl acetate (15 mL). The organic layer was dried with magnesium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure, then purified by column chromatography (silica, 5% ethyl acetate in petroleum ether) to give compound 2,3-difluoro-6,9-dihydro-5H-benzo[7]cyclopenten-7-yl trifluoromethanesulfonate (**A-6**) (1.27 g, 3.87 mmol, 75.91% yield), as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 6.87-7.09 (m, 2H), 5.89-5.97 (m, 1H), 3.35-3.49 (m, 2H), 2.89-3.02 (m, 2H), 2.55-2.75 (m, 2H);

Step 6: To a solution of 2,3-difluoro-6,9-dihydro-5H-benzo[7]cyclopenten-7-yl trifluoromethanesulfonate (**A-6**) (1.27 g, 3.87 mmol) and bis(pinacolato)diboron (1.08 g, 4.26 mmol) in dioxane (20 mL) was added potassium acetate (1.14 g, 11.61 mmol) and 1,1-bis(diphenylphosphino)ferrocene palladium chloride (283.09 mg, 386.89 μmol), and the reaction solution was replaced with nitrogen for 1 min, then reacted at 100 °C under stirring for 16 hours under nitrogen protection. The complete consumption of the raw material and the generation of new spots were detected by TLC (petroleum ether:ethyl acetate=8:1, R_f =0.8). The reaction solution was then cooled to room temperature, diluted with water (20 mL)

and extracted with ethyl acetate (20 mL) three times. The organic layer was dried with magnesium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure, then purified by column chromatography (silica, 3% ethyl acetate in petroleum ether) to give compound

5 2-(2,3-difluoro-6,9-dihydro-5H-benzo[7]cyclopenten-7-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**Intermediate A**) (880 mg, 2.87 mmol, 74.3% yield), as a yellow solid. ¹H NMR: (400 MHz, CDCl₃) δ(ppm) 6.95 (m, 1H), 6.86 (m, 1H), 6.54-6.69 (m, 1H), 3.45-3.58 (m, 2H), 2.87-3.01 (m, 2H), 2.29-2.54 (m, 2H), 1.25 (s, 12H)

10 Intermediate Synthesis 2: Synthesis of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(m-tolyl)-1,2,3,6-tetrahydropyridine (**Intermediate B**):



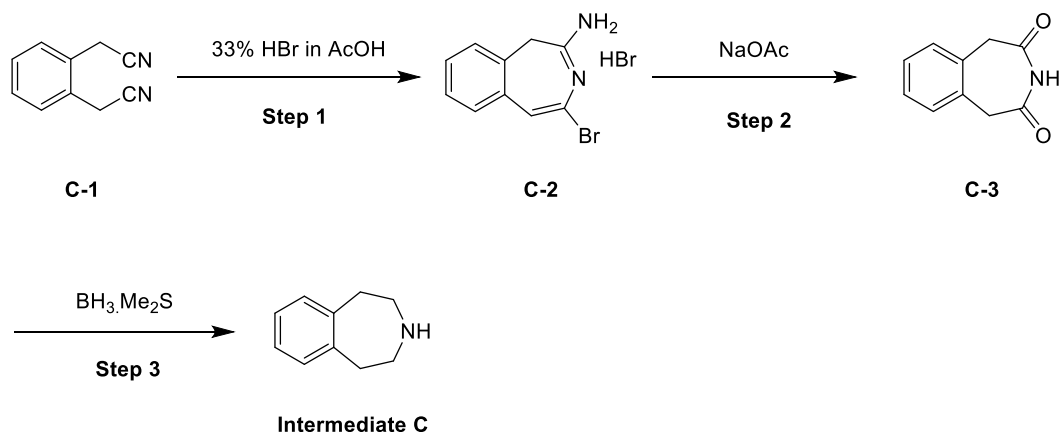
15 **Step 1:** To a solution of 1-benzylpiperidin-4-one (B-1) (100 g, 528 mmol, 1.0 equiv.) in acetone (700 mL) was added iodomethane (90.0 g, 634 mmol, 39.5 mL, 1.2 equiv.), and the reaction solution was stirred at 20 °C for 16 hours, with white solid precipitated. The reaction solution was then filtered, and the filter cake was washed twice with dry acetone (200 mL), collected and concentrated to dryness under reduced pressure to give 1-benzyl-1-methyl-4-oxopiperidin-1-iodide (B-2) (297 g, 897 mmol, 84.86% yield), as an off-white solid, which was used directly in the next step without purification.

20 **Step 2:** A turbid solution of 1-benzyl-1-methyl-4-oxopiperidin-1-iodide (B-2) (162 g, 489 mmol, 1.3 equiv.) in ethanol (400 mL) and water (200 mL) was added in batches into arefluxd (90 °C) 3-methylaniline (40 g, 373 mmol, 1.0 equiv.) and potassium carbonate (7.74 g, 56.0 mmol, 0.15 equiv.) in ethanol (500 mL), and the reaction solution was stirred at 90 °C for another 40 minutes. The completion of the reaction and the generation of new spots were detected by TLC (petroleum ether: ethyl acetate = 4:1, R_f = 0.5). The reaction solution was then diluted with water (300 mL) and extracted three times with dichloromethane (200 mL). The organic layer was dried with magnesium sulfate, filtered, and the filtrate was concentrated to dryness under reduced pressure, then purified by column chromatography (silica, 12% ethyl acetate in petroleum ether) to give compound 1-(m-tolyl)piperidin-4-one (B-3) (59 g, 312 mmol, 83.5% yield) in a yellow syrup form; ¹H NMR (400 MHz, CDCl₃) δ(ppm) 7.21 (t, 1H), 6.79-6.89 (m, 2H), 6.75 (d, 1H), 3.61 (t, 4H), 2.59 (t, 4H), 2.35 (s, 3H)

Step 3: To a solution of 1-(m-tolyl)piperidin-4-one (B-3) (90 g, 475 mmol, 1 equiv.) and 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (216 g, 715 mmol, 1.5 equiv.) in tetrahydrofuran (1200 mL) was added dropwise DBU (217 g, 1.43 mol, 215 mL, 3 equiv.) at 0 °C, and the reaction solution was stirred at 25 °C for 3 hours. The completion of the reaction was detected by LCMS. The reaction solution was then diluted with water (1 liter), adjusted to pH 3~4 with 10 % phosphoric acid, and extracted with methyl tert-butyl ether (1 liter) for 3 times. The organic layer was dried with magnesium sulfate, filtered, and the filtrate was concentrated to dryness under reduced pressure to obtain a rough product. The rough product was dispersed in petroleum ether (1.5 L) and stirred at 20 °C for 1 hour, filtered, and the filtrate was concentrated to dryness under reduced pressure to obtain a crude product of 1-(m-tolyl)-1,2,3,6-tetrahydropyridin-4-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (B-4) (175 g), as a yellow oil, which was used directly in the next step without purification. LCMS: (ESI) m/z=472.1 [M+H]⁺;

Step 4: Two reactions were set up in parallel. To a solution of 1-(m-tolyl)-1,2,3,6-tetrahydropyridin-4-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (B-4) (70 g, 148 mmol, 1.0 eq.), and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bis(1,3,2-dioxaborolan) (42.0 g, 165 mmol, 1.11 equiv.) in 1,4-dioxane (1000 mL) was added potassium acetate (44 g, 448 mmol), then the reaction solution was degassed under reduced pressure and replaced with nitrogen for multiple times, and 2-dicyclohexylphosphino-2,4,6-triisopropylbiphenyl (4.3 g, 9.02 mmol, 0.06 equiv.) and tris(dibenzylideneacetone)dipalladium (4.10 g, 4.47 mmol, 0.03 equiv.) were added, then the reaction solution was stirred at 90 °C under nitrogen protection for 16 hours. The completion of the reaction was detected by LCMS. The reaction solution was then cooled to room temperature, filtered, the filter cake was washed with petroleum ether (500 mL) 3 times, and the filtrate was concentrated to dryness under reduced pressure, then purified by column chromatography (silica, 5% ethyl acetate in petroleum ether) to give a crude product, which was beat with n-pentane (150 mL) to give 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(m-tolyl)-1,2,3,6-tetrahydropyridine (Intermediate B) as a yellow solid (32 g, 101.60 mmol, 34.21% yield, 95% purity). LCMS: (ESI) m/z=300.2 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ(ppm) 7.10-7.22 (m, 1H), 6.70-6.81 (m, 2H), 6.56-6.69 (m, 2H), 3.76-3.83 (m, 2H), 3.33 (t, 2H), 2.38-2.45 (m, 2H), 2.38-2.46 (m, 1H), 2.34 (s, 3H), 1.30 (s, 12H)

Intermediate Synthesis 3: Synthesis of 2,3,4,5-tetrahydro-1H-benzo[d]azepine (Intermediate C).



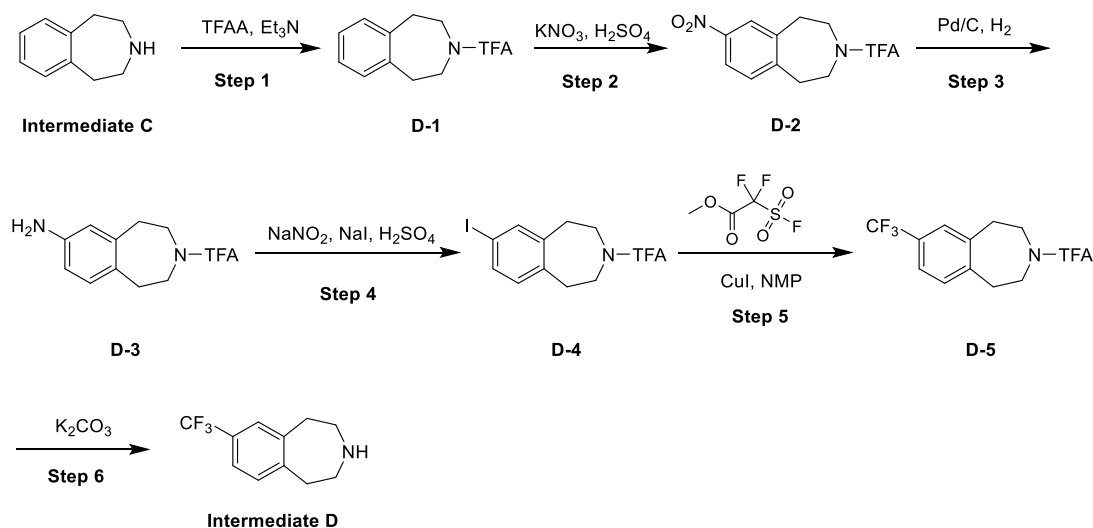
Step 1: To a solution of 2,2'-(1,2-phenylene)diacetonitrile (**C-1**) (50 g, 320.14 mmol) in acetic acid (60 mL) was slowly added hydrogen bromide (196.23 g, 800.34 mmol, 33% hydrogen bromide in acetic acid) for 1 hour at 25 °C. The reaction solution continued stirring for 1 hour. The completion of the reaction was detected by TLC. The suspended reaction solution was then filtered and washed with isopropyl ether to obtain a solid compound, which was dried under reduced pressure to give 4-bromo-1H-benzo[d]azepin-2-amine (**C-2**) as a bright yellow solid. The bright yellow solid crude product was used directly in the next step without purification.

Step 2: A solution of 4-bromo-1H-benzo[d]azepin-2-amine (**C-2**) (88 g, 276.72 mmol, hydrobromide hydrochloride) in water (600 mL) was heated to 85 °C, and sodium acetate (29.51 g, 359.74 mmol) was added step by step. The reaction was heated to 95 °C and stirred for 6 hours. The completion of the reaction was detected by TLC. The reaction solution was then cooled to room temperature, filtered to obtain a solid compound, and the solid compound was washed with water to give the crude product of 1H-benzo[d]azepine-2,4(3H,5H)-dione (**C-3**) (47 g), as a pink solid. This crude product was used directly in the next step without purification.

Step 3: To a solution of 1H-benzo[d]azepine-2,4(3H,5H)-dione (**C-3**) (47 g, 268.29 mmol) in toluene (50 mL) was added slowly dropwise di-methylsulfide borane solution (10 M, 80.49 mL) under nitrogen atmosphere. The pink reaction solution was heated to 110 °C and stirred for 6 hours. TLC ($R_f = 0.40$) detection indicated complete reaction of the raw material. The reaction solution was then cooled to room temperature, methanol (115 mL) was added slowly dropwise, and the reaction solution was heated to 100 °C after addition and stirred for 1 hour. The reaction solution was then cooled to 20 °C, 4M hydrochloric acid-dioxane was added, the pH of the reaction solution was adjusted to 4-5, and the reaction was stirred at 20 °C for 2 hours. The reaction suspension was then filtered to give 2,3,4,5-tetrahydro-1H-benzo[d]azepine (**Intermediate C**) (26 g, 141 mmol, 52.7% yield, hydrochloride) as a pink solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 9.50 (br, 2H), 7.14-7.24 (m, 4H), 3.10-3.20 (m, 8H);

Intermediate Synthesis 4: Synthesis of

7-(trifluoromethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (Intermediate D):



Step 1: To a solution of 2,3,4,5-tetrahydro-1H-benzo[d]azepine (Intermediate C) (11 g free base, 74.72 mmol) in dichloromethane (220 mL) was added triethylamine (9.07 g, 89.7 mmol) at 25 °C under nitrogen protection, and trifluoromethanesulfonic anhydride (18.8 g, 89.7 mmol) was added dropwise at 0 °C and the reaction solution was stirred at 0 °C for 1 hour. The completion of the reaction was detected by LCMS. The reaction solution was then washed once with saturated sodium bicarbonate aqueous solution (200 mL), twice with 1 M hydrochloric acid aqueous solution (200 mL), and once with saturated salt water (200 mL) successively. The organic phase was dried with magnesium sulfate and filtered. The filtrate was concentrated to dryness under reduced pressure, and then purified by column chromatography (silica, 13% ethyl acetate in petroleum ether) to give 1-(4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone (**D-1**) (16 g, 65.8 mmol, 88.0% yield) as a white solid. LCMS: (ESI) $m/z = 244.1$ $[M+H]^+$; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.15-7.24 (m, 4H), 3.77-3.83 (m, 2H), 3.70-3.75 (m, 2H), 2.98-3.04 (m, 4H);

Step 2: Two reactions were set up in parallel. 1-(4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone (**D-1**) (8.0 g, 32.9 mmol) was added to concentrated sulfuric acid (32 mL) at 0 °C and the mixture was stirred for 10 min to obtain a grayish yellow solution. Potassium nitrate (2.66 g, 26.3 mmol) was added in batches over 20 min at 0 °C, then the reaction solution was stirred at 0 °C for 30 minutes. The complete consumption of the raw material was detected by TLC. The reaction solution was then slowly poured into stirred ice water (50 mL) and extracted three times with ethyl acetate (50 mL). The organic layer was washed once with saturated salt water (50 mL), dried with magnesium sulfate, filtered, and the filtrate was concentrated to dryness under reduced pressure, then purified by column chromatography (silica, 15% ethyl acetate in petroleum ether) to give 2,2,2-trifluoro-1-(7-nitro-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)ethanone (**D-2**) (8.6 g, 29.8 mmol, 45.2% yield, 99.7% purity) as a white solid. LCMS: (ESI) $m/z = 288.9$ $[M+H]^+$; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.05-8.10 (m, 2H), 7.32-7.39 (m, 1H), 3.80-3.87 (m, 2H), 3.77 (m, 2H), 3.09-3.17 (m, 4H)

Step 3: To a solution of 2,2,2-trifluoro-1-(7-nitro-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)ethanone (**D-2**) (4.3 g, 14.9 mmol) in methanol (130 mL) was added 10% wet palladium carbon (794 mg, 746 μmol) under nitrogen protection, the suspension was

replaced three times with a hydrogen balloon and the reaction was stirred at 25 °C for 16 hours under hydrogen atmosphere. The completion of the reaction was detected by LCMS. The reaction solution was then filtered, the filtrate was concentrated under reduced pressure to dryness, and then purified by column chromatography (silica, 30% ethyl acetate in petroleum ether) to obtain 1-(7-amino-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone (**D-3**) as a bright yellow solid (6.6 g, 25.5 mmol, 85.4% yield, 99.7% purity). LCMS: (ESI) $m/z=259.0$ $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.94 (dd, 1H), 6.47-6.55 (m, 2H), 3.71-3.78 (m, 2H), 3.57-3.70 (m, 4H), 2.83-2.94 (m, 4H)

Step 4: To a solution of

1-(7-amino-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone (**D-3**) (4.5 g, 17.4 mmol) in a mixed solution of water (58 mL) and sulfuric acid (9.57 g, 97.6 mmol) was added dropwise an aqueous solution (29 mL) of $NaNO_2$ (1.56 g, 22.6 mmol) at 0 °C, and then stirred for 10 minutes. Then an aqueous solution of NaI (3.92 g, 26.1 mmol) in sulfuric acid (1M per liter, 5.8 mL) was added to the above solution. The reaction was naturally warmed to 25 °C and stirred for 16 hours. The complete consumption of the raw material was detected by TLC. The reaction solution was then extracted three times with dichloromethane (100 mL). The organic layer was washed twice with half-saturated sodium thiosulfate aqueous solution (100 mL), dried with magnesium sulfate, filtered, and the filtrate was concentrated to dryness under reduced pressure, and then purified by column chromatography (silica, 4.3% ethyl acetate in petroleum ether) to give 2,2,2-trifluoro-1-(7-iodo-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)ethanone (**D-4**) as a white solid (4.7 g, 12.7 mmol, 73.1% yield). 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46-7.57 (m, 2H), 6.86-6.94 (m, 1H), 3.72-3.83 (m, 2H), 3.62-3.72 (m, 2H), 2.93 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -68.07

Step 5: To a solution of

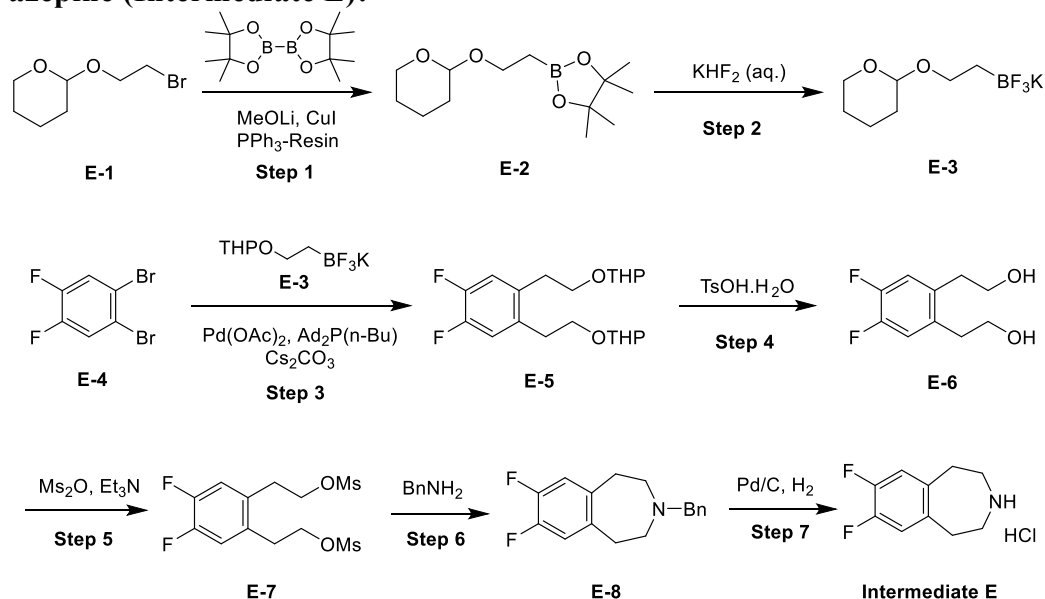
2,2,2-trifluoro-1-(7-iodo-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)ethanone (**D-4**) (250 mg, 677 μ mol) in dimethylformamide (2 mL) was added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (651 mg, 3.39 mmol), cuprous iodide (26 mg, 135 μ mol), and N-methylpyrrolidone (806 mg, 8.13 mmol) in turn at 25 °C under nitrogen atmosphere. The reaction was heated to 80 °C and stirred for 12 hours. The completion of the reaction was detected by LCMS. The reaction solution was then diluted with water (10 mL) and filtered. The filtrate was extracted twice with ethyl acetate (10 mL). The organic layer was dried with magnesium sulfate, filtered, concentrated to dryness under reduced pressure, and then purified by column chromatography (silica, 4% ethyl acetate in petroleum ether) to give 2,2,2-trifluoro-1-(7-(trifluoromethyl)-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)ethanone (**D-5**) as a yellow solid (180 mg, 578 μ mol, 85.4% yield).

Step 6: To a solution of

2,2,2-trifluoro-1-(7-(trifluoromethyl)-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)ethanone (**D-5**) (120 mg, 386 μ mol) in methanol (3 mL) was added potassium carbonate (160 mg, 1.16 mmol) all at once, and the reaction was heated to 50 °C and stirred for 12 hours. The complete consumption of the raw material and the generation of target product were detected by LCMS. The reaction solution was then concentrated to dryness, added with water (5 mL)

and extracted three times with ethyl acetate (5 mL). The organic layer was dried with magnesium sulfate, filtered, and concentrated to dryness under reduced pressure to give a crude product of 7-(trifluoromethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (**Intermediate D**) (80 mg) in a yellow syrup form, which was used directly in the next step without further purification. LCMS: (ESI) $m/z=215.9$ $[M+H]^+$;

Intermediate Synthesis 5: Synthesis of 7,8-difluoro-2,3,4,5-tetrahydro-1H-benzo[d]azepine (Intermediate E**):**



Step 1: To a solution of 2-(2-bromoethoxy)tetrahydro-2H-pyran (**E-1**) (18 g, 86.09 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bis(1,3,2-dioxaborolane) (26.2 g, 103 mmol) in dimethylformamide (350 mL) was added lithium methoxide (6.54 g, 172.18 mmol, 2.0 eq), cuprous iodide (1.64 g, 8.61 mmol) and triphenylphosphine resin (2.25 g, ~3 mmol/g, 8.61 mmol), and the reaction solution was stirred at 25 °C for 12 hours. After the reaction was detected as finished, it was diluted with dichloromethane (200 mL), and filtered with diatomite. The filter cake was washed twice with dichloromethane (100 mL), and the filtrates were combined and concentrated to dryness under reduced pressure, then poured into saturated ammonium chloride solution and extracted with tert-butyl methyl ether (200 mL) three times. The resulting organic phase was washed respectively with water (300 mL) and saturated salt water (300 mL), dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated to dryness under reduced pressure to give a crude product of 4,4,5,5-tetramethyl-2-(2-(((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1,3,2-dioxaborolane (**E-2**) (19.0 g), as a colorless oil, and the crude product was used directly in the next step without further purification. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 4.62 (t, 1H), 3.83-3.94 (m, 2H), 3.46-3.59 (m, 2H), 1.77-1.91 (m, 1H), 1.65-1.74 (m, 1H), 1.45-1.61 (m, 4H), 1.25 (s, 12H), 1.19 (t, 2H).

Step 2: To a solution of 4,4,5,5-tetramethyl-2-(2-(((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1,3,2-dioxaborolane (**E-2**) (19 g, 74.18 mmol) in tetrahydrofuran (540 mL) was added a solution of potassium bifluoride

(17.38 g, 222.53 mmol, 7.33 ml) in water (60 ml), and stirred at 25 °C for 2 hours. The reaction solution was then concentrated to dryness under reduced pressure and lyophilized to obtain a white solid. The solid was washed 4 times with dry acetone (50 mL), filtered and the filtrate was concentrated to dryness under reduced pressure. The resulting solid was purified by beating with tert-butyl methyl ether (100 mL), collected by filtration and dried to give potassium (2-(((tetrahydro-2H-pyran-2-yl)oxy)ethyl)trifluoroborate (**E-3**) (13.5 g, 57.18 mmol, 77.09% yield), as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ(ppm) 4.44 (dd, 1H), 3.72 (ddd, 1H), 3.58 (ddd, 1H), 3.33-3.39 (m, 1H), 3.23 (ddd, 1H), 1.64-1.77 (m, 1H), 1.50-1.60 (m, 1H), 1.29-1.49 (m, 4H), 0.20-0.45 (m, 2H).

Step 3: To a solution of 1,2-dibromo-4,5-difluorobenzene (**E-4**) (2.0 g, 7.36 mmol) and potassium (2-(((tetrahydro-2H-pyran-2-yl)oxy)ethyl)trifluoroborate (**E-3**) (3.99 g, 16.92 mmol) in water (10 mL) and dioxane (50 mL) was added Bis (1-adamantyl) - butyl phosphine (527.49 mg, 1.47 mmol), cesium carbonate (14.38 g, 44.14 mmol) and palladium acetate (495.45 mg, 2.21 mmol), and then replaced with nitrogen for 5 minutes. The reaction was stirred at 100 °C for 16 hours. TLC (petroleum ether: ethyl acetate = 8:1) detection indicated complete consumption of the raw materials and the generation of new spots. The reaction solution was filtered with diatomite, then diluted with water (30 mL) and extracted with ethyl acetate (50 mL) three times. The organic phases were combined and washed with salt water (100 mL), dried with anhydrous magnesium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure, and then purified by column chromatography (silica, 10% ethyl acetate in petroleum ether) to afford 2,2'-((((4,5-difluoro-1,2-phenylene)bis(ethane-2,1-diyl))bis(oxy))bis(tetrahydro-2H-pyran) (**E-5**) (1.25 g, 3.37 mmol, 45.87% yield), as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ(ppm) 7.03 (t, 1H), 6.97-7.09 (m, 1H), 4.56-4.60 (m, 2H), 3.91 (td, 2H), 3.68-3.77 (m, 2H), 3.57 (td, 2H), 3.42-3.52 (m, 2H), 2.91 (t, 4H), 1.75-1.87 (m, 2H), 1.65-1.74 (m, 2H), 1.45-1.63 (m, 8H).

Step 4: To a solution of 2,2'-((((4,5-difluoro-1,2-phenylene)bis(ethane-2,1-diyl))bis(oxy))bis(tetrahydro-2H-pyran) (**E-5**) (1.25 g, 3.37 mmol) in methanol (15 mL) was added p-toluenesulfonic acid monohydrate (801.08 mg, 4.21 mmol, 1.2 equiv). The reaction solution was stirred at 25 °C for 16 hours. The complete consumption of the raw material and the generation of new spots were detected by TLC (petroleum ether: ethyl acetate = 10:1). Solvent was then removed by concentration under reduced pressure, dichloromethane (20 mL) and saturated sodium bicarbonate solution (20 mL) were added, and the aqueous phase was extracted five times with dichloromethane (20 mL). The organic layer was washed with saturated salt water (50 mL), dried with anhydrous magnesium sulfate, and filtered. The filtrate was concentrated to dryness under reduced pressure to give 2,2'-(4,5-difluoro-1,2-phenylene)diethanol (**E-6**) (700 mg, 3.46 mmol, 98.65% yield), as a yellow solid. The crude product was used directly in the next step without purification. ¹H NMR (400 MHz, CDCl₃) δ(ppm) 7.03 (t, 2H), 3.86 (t, 4H), 2.88 (t, 4H), 1.97 (br, 2H).

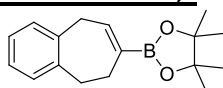
Step 5: To a solution of 2,2'-(4,5-difluoro-1,2-phenylene)diethanol (**E-6**) (700 mg, 3.46 mmol) and triethylamine (1.75 g, 17.31 mmol) in dichloromethane (15 mL) was added

methanesulfonic anhydride (1.51 g, 8.65 mmol) at $^{\circ}\text{C}$, and the reaction solution was stirred at 0-25 $^{\circ}\text{C}$ for 1 hour. The complete consumption of the raw material and the generation of new spots were detected by TLC (petroleum ether: ethyl acetate = 10:1). The reaction was then quenched by dropwise addition of saturated sodium bicarbonate (20 mL), and extracted three times with dichloromethane (20 mL). The combined organic phase was dried, and filtered. The filtrate was concentrated to dryness under reduced pressure to give a crude product of (4,5-difluoro-1,2-phenylene)bis(ethane-2,1-diyl) dimethanesulfonate (**E-7**) (1.32 g), as a yellow solid, which was used directly in the next step without further purification. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.07 (t, 2H), 4.39 (t, 4H), 3.08 (t, 4H), 2.98 (s, 6H)

Step 6: To a solution of (4,5-difluoro-1,2-phenylene)bis(ethane-2,1-diyl) dimethanesulfonate (**E-7**) (1.22 g, 3.40 mmol) in 1,2-dichloroethane (20 mL) was added benzylamine (3.65 g, 34.04 mmol), and the reaction solution was stirred at 50 $^{\circ}\text{C}$ for 16 hrs. LCMS showed completion of reaction. Then the reaction solution was added with saturated sodium bicarbonate (15 mL), and extracted twice with dichloromethane (15 mL). The organic phases were combined, dried with anhydrous magnesium sulfate, and filtered. The filtrate was concentrated to dryness under reduced pressure, and then purified by column chromatography (silica, 5% ethyl acetate in petroleum ether) to give N-benzyl-7,8-difluoro-2,3,4,5-tetrahydro-1H-benzo[d]azepine (**E-8**) (600 mg, 1.98 mmol, 58.04% yield, 90% purity) as a light yellow liquid. LCMS: (ESI) m/z = 273.8 $[\text{M}+\text{H}]^+$.

Step 7: To a solution of N-benzyl-7,8-difluoro-2,3,4,5-tetrahydro-1H-benzo[d]azepine (**E-8**) (600 mg, 2.20 mmol) in hydrochloric acid/methanol (1 ml) in methanol (15 ml) was added 10% palladium/carbon (233.62 mg, 219.52 μmol). The reaction was replaced several times with hydrogen under vacuum, and then stirred under a hydrogen balloon (15 Psi) at 50 $^{\circ}\text{C}$ for 16 hours. LCMS showed the completion of reaction. The reaction solution was concentrated under reduced pressure to remove solvent, to give 7,8-difluoro-2,3,4,5-tetrahydro-1H-benzo[d]azepine (**Intermediate E**) (400 mg hydrochloride crude product) as a white solid, which was used directly in the next step without further purification. LCMS: (ESI) m/z = 184.0 $[\text{M}+\text{H}]^+$, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.83 (br s, 1H), 7.31 (t, 2H), 2.98-3.16 (m, 8H)

Intermediate Synthesis 6: Synthesis of 2-(6,9-dihydro-5H-benzo[7]cyclopenten-7-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate F):

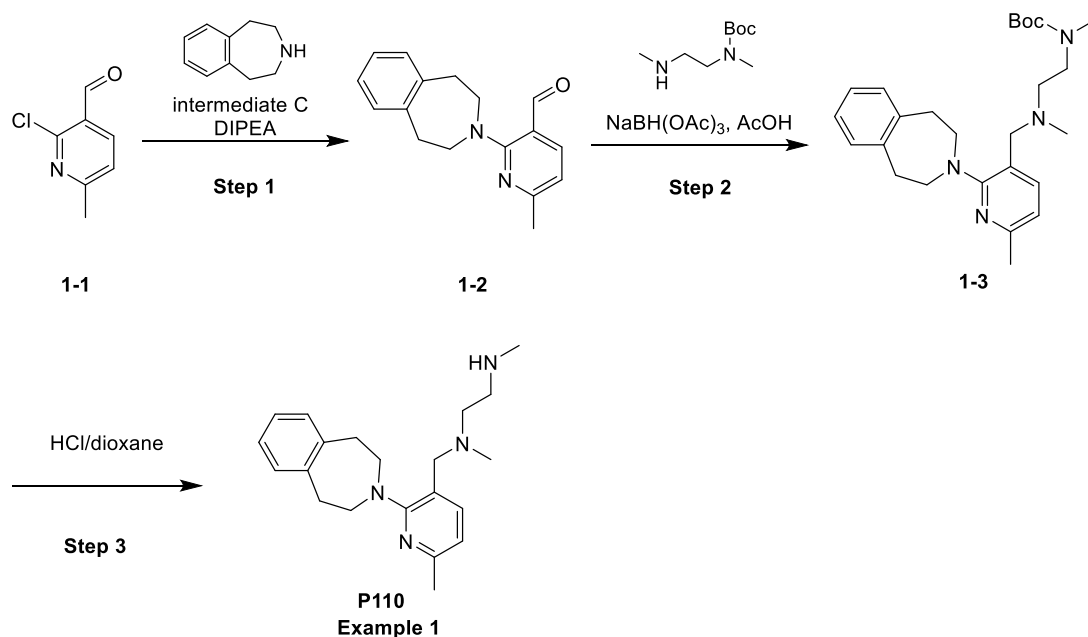


Intermediate F

Intermediate F can be synthesized by referring to the synthesis of Intermediate A. ^1H NMR (400 MHz, CHCl_3) δ (ppm) 7.15-7.18 (m, 2H), 7.04-7.09 (m, 2H), 6.62-6.73 (m, 1H), 3.55-3.62 (m, 2H), 3.01-3.07 (m, 2H), 2.46-2.53 (m, 2H), 1.21-1.27 (m, 12H)

Example 1: Synthesis of (N1-((2-(4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-6-methylpyridin-3-yl)methyl)-N1,N2-dimethylethane-1,2-diamine)

(Compound P110):



Step 1: To a solution of 2-chloro-6-methylnicotinaldehyde (1-1) (100 mg, 643 μmol) and 2,3,4,5-tetrahydro-1H-benzo[d]azepine (**Intermediate C**) (104 mg, 707 μmol) in DMF (2 ml) was added DIPEA (166 mg, 1.29 mmol) under nitrogen protection, and the reaction solution was stirred at 100 °C for 16 hours. LCMS showed completion of reaction. Then the reaction solution was concentrated and purified by column chromatography (silica gel column, 0-7% ethyl acetate/petroleum ether gradient elution) to give compound 2-(4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-6-methylnicotinaldehyde (**1-2**) (90 mg, 314.26 μmol , 48.89% yield, 93% purity) as a yellow solid. LCMS: (ESI) m/z = 267.1 $[\text{M}+\text{H}]^+$;

Step 2: To a solution of 2-(4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-6-methylnicotinaldehyde (**1-2**) (110 mg, 413 μmol) and tert-butyl methyl (2-(methylamino)ethyl)carbamate (78 mg, 413 μmol) in 10 mL of dichloromethane was added dropwise AcOH (25 mg, 413 μmol), and the yellow reaction solution was stirred at 20 °C for 2 hours. Then $\text{NaBH}(\text{OAc})_3$ (263 mg, 1.24 mmol) was added in batches and the yellow reaction solution was stirred at 20 °C for 14 h. LCMS showed that the reaction was finished. The reaction was then quenched by dropwise addition of saturated NaHCO_3 aqueous solution (20 mL) and extracted with dichloromethane (20 mL $\times$ 3). The organic phase was washed with saturated salt water, dried with magnesium sulfate, filtered and concentrated to give a crude product of tert-butyl (2-((2-(4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-6-methylpyridin-3-yl)methyl)(methyl)amino)ethyl(methyl)carbamate (**1-3**) (150 mg, crude), as a yellow mucus, which was used directly in the next step without further purification. LCMS: (ESI) m/z = 439.3 $[\text{M}+\text{H}]^+$;

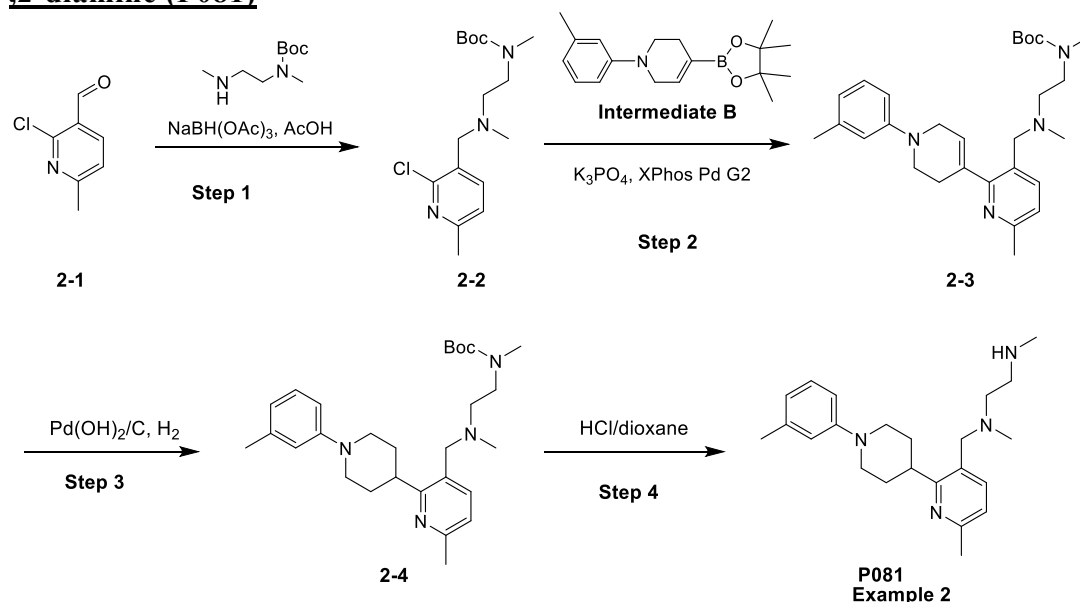
Step 3: To tert-butyl (2-((2-(4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-6-methylpyridin-3-yl)methyl)(methyl)amino)ethyl(methyl)carbamate (**1-3**) (150 mg, 342 μmol) was added carefully a solution of HCl/1,4-dioxane (5 mL), and stirred at room temperature for 16 h. LCMS showed completion

of reaction, and the reaction solution was concentrated to obtain crude product, which was purified by preparative HPLC (column: Boston Green ODS 150×30 mm×5μm; mobile phase: [water (0.05% HCl)-ACN]; B%: 0%-38%, 9 min) and collected and lyophilized at low temperature to obtain

- 5 N1-((2-(4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-6-methylpyridin-3-yl)methyl)-N1,N2-dimethylethane-1,2-diamine (**P110, Example 1**), as a yellow solid (110 mg, 318 μmol, 93.1% yield, 98% purity). LCMS: (ESI) m/z=339.3 [M+H]⁺; ¹H NMR (400 MHz, D₂O) δ(ppm) 8.29 (d, 1H), 7.32 (d, 1H), 7.27 (s, 4H), 4.35 (s, 2H), 3.53 (t, 4H), 3.39 (s, 4H), 3.16 (t, 4H), 2.72 (s, 3H), 2.60 (s, 3H), 2.46 (s, 3H)

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Example 2. Synthesis of compound N¹,N²-dimethyl-N1-((6-methyl-2-(1-(m-tolyl)piperidin-4-yl)pyridin-3-yl)methyl)ethane-1,2-diamine (P081)



- 15 **Step 1:** Compound 2-chloro-6-methylnicotinaldehyde (**2-1**) (10.0 g, 64.3 mmol), tert-butyl methyl (2-(methylamino)ethyl)carbamate (13.3 g, 70.7 mmol) and AcOH (4.25 g, 70.7 mmol) were dissolved in dichloromethane (150 mL) and the reaction was stirred at 25 °C for 2 hours. NaBH(OAc)₃ (40.9 g, 1923 mmol) was then added carefully in batches and the reaction continued to stir at room temperature for 16 hours. LCMS showed the disappearance of raw material disappeared. The reaction was then quenched by careful addition of NaHCO₃ (300 mL) and extracted with dichloromethane (200 mL x 3). The combined organic phase was dried with anhydrous magnesium sulfate, filtered, concentrated, then purified by column chromatography (silica gel column, 0-10% ethyl acetate/petroleum ether gradient elution) and concentrated to give a yellow viscous product tert-butyl
- 20 2-((2-chloro-6-methylpyridin-3-yl)methyl)(methylamino)ethyl(methyl)carbamate (**2-2**) (13.0 g, 38.4 mmol, 59.8% yield). LCMS: (ESI) m/z = 328.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.65-7.78 (m, 1H), 7.09 (d, 1H), 3.60 (s, 2H), 3.25-3.50 (m, 2H), 2.86 (s, 3H), 2.52-2.65 (m, 2H), 2.52 (s, 3H), 2.30 (s, 3H), 1.35-1.49 (m, 9H)
- 25 **Step 2.** To 70 mL of tetrahydrofuran were sequentially added tert-butyl

(2-((2-chloro-6-methylpyridin-3-yl)methyl)(methylamino)ethyl)(methyl)carbamate (**2-2**) (7.02 g, 21.4 mmol),

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(m-tolyl)-1',2,3,6-tetrahydropyridine (**Intermediate B**) (7.05 g, 23.6 mmol), and tripotassium phosphate (9.10 g, 42.9 mmol)

aqueous solution (14 mL). The reaction system was depressurized and replaced with nitrogen for several times and added with XPhos-Pd-G2 (510 mg, 648 μ mol), then heated in an oil bath under nitrogen protection at 85 °C for 30 h. LCMS showed that the raw material disappeared. After cooling to room temperature, the reaction solution was diluted with saturated saline (50 mL) and ethyl acetate (100 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was dried with anhydrous magnesium sulfate, filtered, concentrated, then separated by column chromatography (silica gel column, gradient elution with 0~10~30% of ethyl acetate/dichloromethane), and then concentrated to give tert-butyl methyl(2-(methyl((6-methyl-1'-(m-tolyl)-1

1',2',3',6'-tetrahydro-[2,4'-bipyridin]-3-yl)methyl)amino) ethyl)carbamate (**2-3**) as a yellow viscous liquid (10.9 g, 19.9 mmol, 93.1% yield, 85% purity). LCMS: (ESI) m/z =465.2 $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.70 (d, 1H), 7.18 (t, 1H), 6.99-7.08 (m, 1H), 6.81 (s, 1H), 6.78-6.81 (m, 1H), 6.66 (d, 1H), 5.84-5.93 (m, 1H), 3.86-3.93 (m, 2H), 3.56 (t, 2H), 3.51 (s, 2H), 3.21-3.41 (m, 2H), 2.82 (s, 3H), 2.62-2.71 (m, 2H), 2.54 (s, 3H), 2.39-2.52 (m, 2H), 2.35 (s, 3H), 2.20 (s, 3H), 1.34-1.54 (m, 9H)

Step 3: To a solution of tert-butyl methyl(2-(methyl((6-methyl-1'-(m-tolyl)-1',2',3',6'-tetrahydro-[2,4'-bipyridin]-3-yl)methyl)amino)ethyl)carbamate (**2-3**) (7.84 g, 16.9 mmol) in 250 mL of ethyl acetate was added 10% wetPd(OH)₂/C (3.16 g) under the nitrogen protection, and the system was replaced several times with a hydrogen balloon and then reacted under stirring at room temperature for 36 h under hydrogen protection. The completion of reaction was monitored by LCMS. The reaction solution was then filtered through diatomite, and washed with ethyl acetate. The combined organic phases were concentrated, then purified by column chromatography (silica gel column, 0~25% ethyl acetate/dichloromethane gradient elution) to give tert-butyl methyl (2-(methyl

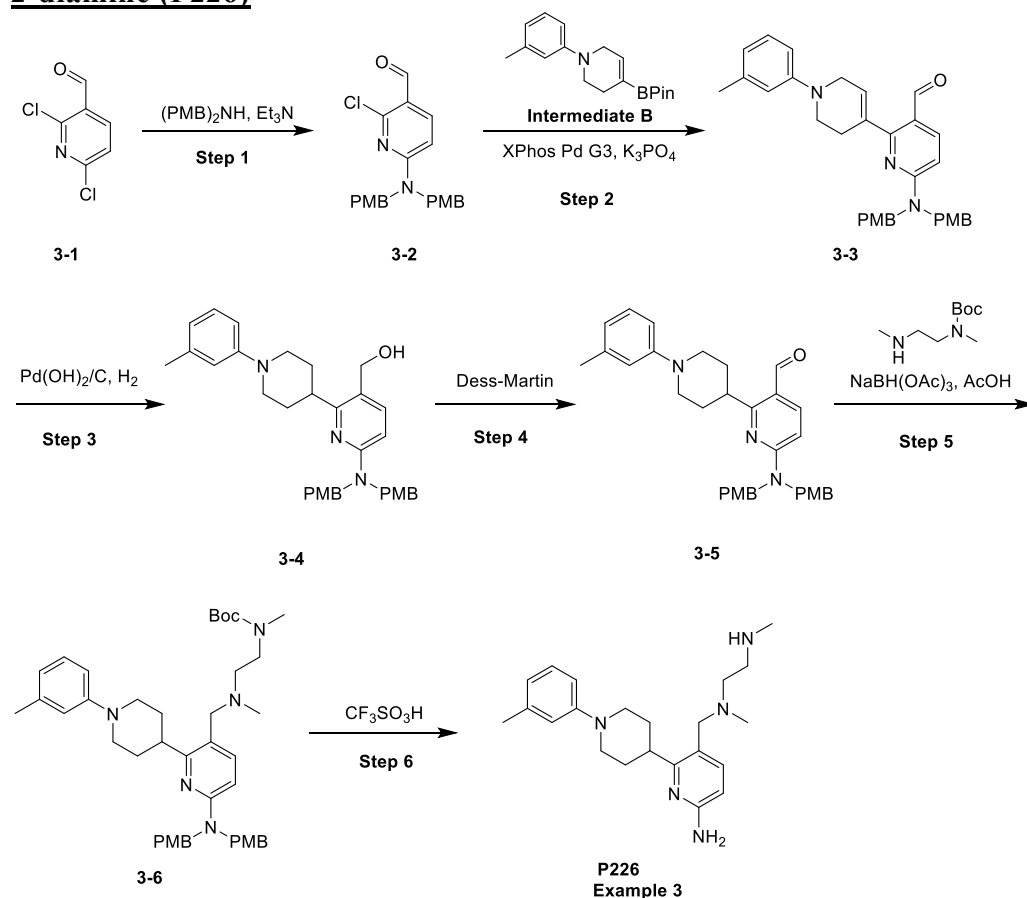
((6-methyl-2-(1-(m-tolyl)piperidin-4-yl)pyridin-3-yl)methyl)amino)ethyl)carbamate (**2-4**), as a yellow mucus (8.86 g, 18.0 mmol, 76.9% yield). LCMS: (ESI) m/z = 467.4 $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45 (d, 1H), 7.17 (t, 1H), 6.92 (d, 1H), 6.82 (s, 1H), 6.78-6.81 (m, 1H), 6.67 (d, 1H), 3.76-3.86 (m, 2H), 3.50 (s, 2H), 3.23-3.43 (m, 2H), 3.03-3.17 (m, 1H), 2.84 (s, 3H), 2.73-2.83 (m, 2H), 2.49-2.63 (m, 1H), 2.49 (s, 3H), 2.33 (s, 3H), 2.14-2.29 (m, 5H), 1.75-1.84 (m, 2H), 1.33-1.51 (m, 9H)

Step 4: To a solution of tert-butyl methyl (2-(methyl((6-methyl-2-(1-(m-tolyl)piperidin-4-yl)pyridin-3-yl)methyl)amino)ethyl)carbamate (**2-4**) (11.7 g, 25.1 mmol) in methanol (70 mL) was added dropwise HCl/1,4-dioxane (4 M, 75 mL) under stirring, and the reaction was stirred under nitrogen protection at room temperature for 16 h. The completion of reaction was monitored by LCMS. The reaction solution was then concentrated, and added with about 200 mL of methanol, and then

spun-dried under reduced pressure. The operation repeated twice to remove hydrochloric acid. The concentrate was diluted with methanol and decolorized by heating with activated charcoal, cooled and filtered at room temperature and washed with methanol, then concentrated to about 100 ml. Isopropanol was added to replace methanol and concentrated to 250 ml. The reaction emulsion was heated at 85 °C for 30 minutes, stirred at 30 °C for 10 hours and cooled to room temperature. After filtration, the solids were washed sequentially with isopropanol (100 mL) and n-pentane (200 mL x 2), and then collected and dried under vacuum. The solid product was dissolved in 150 mL of water, filtered, and the filtrate was lyophilized to give

N^1,N^2 -dimethyl- N^1 -((6-methyl-2-(1-(m-tolyl)piperidin-4-yl)pyridin-3-yl)methyl)ethane-1,2-diamine (**P081**, **Example 2**), as a white solid (hydrochloride, 9.8 g, 19.1 mmol, 76.2% yield, 99.9% purity). LCMS: (ESI) $m/z=367.3$ $[M+H]^+$; 1H NMR (400 MHz, D_2O) δ (ppm) 8.52 (d, 1H), 7.83 (d, 1H), 7.52 (s, 1H), 7.43-7.51 (m, 2H), 7.36-7.42 (m, 1H), 4.72 (s, 2H), 3.93-4.07 (m, 3H), 3.82-3.91 (m, 2H), 3.67-3.76 (m, 2H), 3.55-3.63 (m, 2H), 2.85 (s, 3H), 2.81 (s, 3H), 2.80 (s, 3H), 2.46-2.60 (m, 2H), 2.39 (s, 3H), 2.31-2.39 (m, 2H)

Example 3. Synthesis of N^1 -((6-amino-2-(1-(m-tolyl)piperidin-4-yl)pyridin-3-yl)methyl)- N^1,N^2 -dimethylethane-1,2-diamine (**P226**)



Step 1: To a solution of 2,6-dichloronicotinaldehyde (**3-1**) (25 g, 142 mmol) and bis(4-methoxybenzyl)amine (40.2 g, 156 mmol) in DMF (200 mL) was added triethylamine

(17.2 g, 170 mmol, 23.7 mL), and the reaction solution was stirred at 50 °C for 16 h. The completion of reaction was monitored by LCMS. The mixture was poured into 200 mL of ice water and extracted with ethyl acetate (400 mL x 1, 200 mL x 2). The combined organic phases were washed with saturated salt water, dried with anhydrous magnesium sulfate, filtered, concentrated, and then purified by column chromatography (silica gel column, 0-20% ethyl acetate/(petroleum ether:dichloromethane=5:1) gradient elution) to give compound 6-(bis(4-methoxybenzyl)amino)-2-chloronicotinaldehyde (**3-2**), as a white solid (50 g, 124.83 mmol, 87.88% yield, 99.08% purity). LCMS: (ESI) m/z =397.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6), δ (ppm) 10.02 (s, 1H), 7.86 (d, 1H), 7.27 - 7.12 (m, 4H), 6.90 (d, 4H), 6.73 (d, 1H), 4.78 (br, 4H), 3.73 (s, 6H)

Step 2: To a reaction flask was added 6-(bis(4-methoxybenzyl)amino)-2-chloronicotinaldehyde (**3-2**) (800 mg, 2.02 mmol), 1-(*m*-tolyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine (**Intermediate B**) (1.02 g, 2.40 mmol, 70% purity), tetrahydrofuran (6 mL) and potassium phosphate aqueous solution (856 mg of potassium phosphate dissolved in 1 mL of water) in turn, and the reaction system was depressurized and replaced with nitrogen for several times and then added with XPhos-Pd-G3 (37 mg, 43.71 μ mol) under nitrogen protection. The reaction was heated to 70 °C in an oil bath under stirring for 2.5 h under nitrogen protection, and the generation of product was monitored by LCMS. After cooling to room temperature, the reaction solution was added with saturated salt water and extracted three times with ethyl acetate. The organic phases were combined and dried with anhydrous magnesium sulfate, filtered, concentrated, and then separated and purified by column chromatography (silica gel column, 0~10~15% gradient elution of ethyl acetate/petroleum ether) to give a product of 6-(bis(4-methoxybenzyl)amino)-1'-(*m*-tolyl)-1', 2', 3', 6'-tetrahydro-[2,4'-bipyridyl]-3-carboxaldehyde (**3-3**) (1.01 g, 1.50 mmol, 74.2% yield, 79% purity), as a yellow mucus. LCMS: (ESI) m/z =534.3 $[M+H]^+$;

Step 3: To a reaction flask was added 6-(bis(4-methoxybenzyl)amino)-1'-(*m*-tolyl)-1',2',3',6'-tetrahydro-[2,4'-bipyridyl]-3-carboxaldehyde (**3-3**) (801 mg, 1.50 mmol) and ethyl acetate (50 mL), and Pd(OH) $_2$ /C (450 mg, 10% Pd(OH) $_2$ /C) was added under nitrogen protection. The reaction system was replaced with hydrogen and then stirred under hydrogen atmosphere (hydrogen balloon) at room temperature for 18 hours. The reaction solution was then filtrated, concentrated and purified by column chromatography (silica gel column, 0-25% ethyl acetate/petroleum ether gradient elution) to give (6-(bis(4-methoxybenzyl)amino)-2-(1-(*m*-tolyl)piperidin-4-yl)pyridin-3-yl)methanol (**3-4**), as a yellow mucus (695 mg, 1.23 mmol, 64.9% yield, 95% purity). LCMS: (ESI) m/z =538.3 $[M+H]^+$; 1H NMR (400 MHz, CDCl $_3$) δ (ppm) 7.34 (d, 1H), 7.09-7.24 (m, 5H), 6.77-6.92 (m, 6H), 6.68 (br d, 1H), 6.29 (d, 1H), 4.73 (s, 4H), 4.65 (d, 2H), 3.81 (s, 6H), 3.72-3.81 (m, 1H), 2.99-3.13 (m, 1H), 2.75-2.88 (m, 2H), 2.33 (s, 3H), 2.15-2.30 (m, 2H), 1.80-1.92 (m, 2H), 1.40 (t, 1H).

Step 4: Compound (6-(bis(4-methoxybenzyl)amino)-2-(1-(*m*-tolyl)piperidin-4-yl)pyridin-3-yl)methanol (**3-4**)

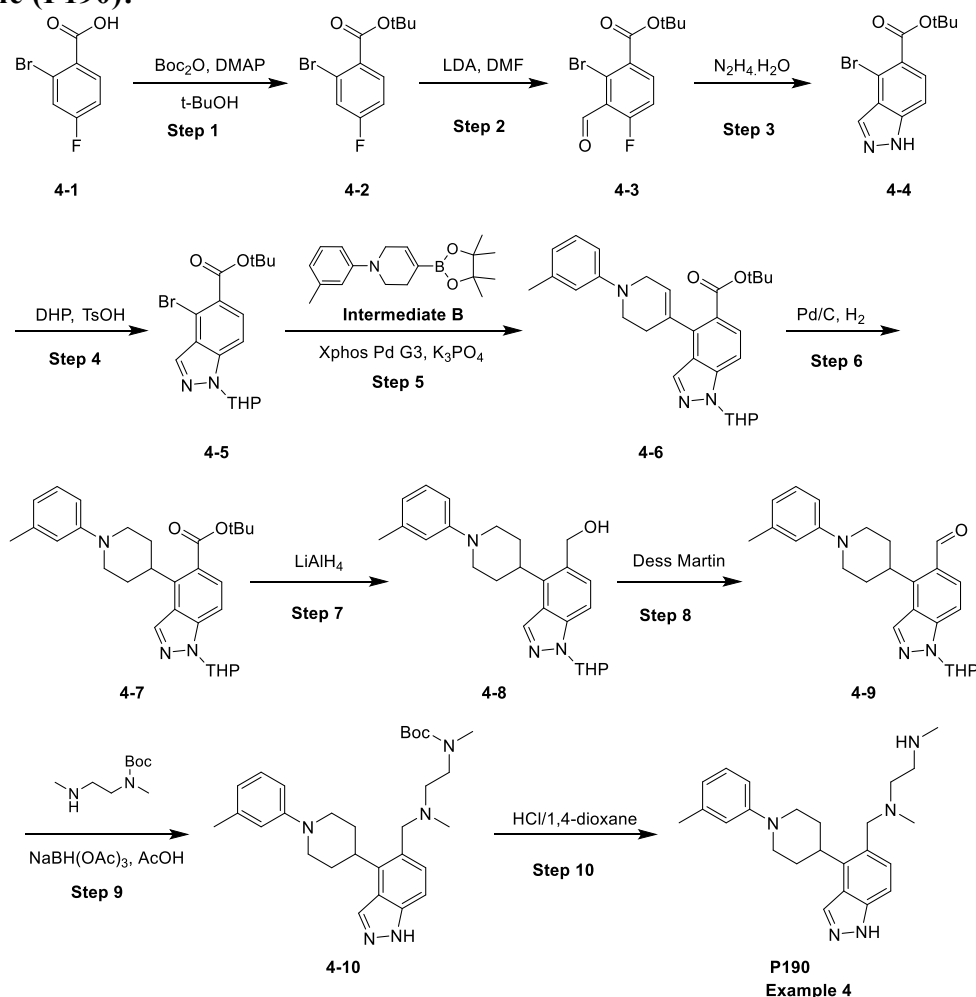
(440 mg, 818 μmol) was added to 10 mL of dichloromethane and Dess-Martin periodinane (347 mg, 818 μmol) was added under an ice bath. The reaction solution was stirred at room temperature for 16 hours. The reaction was quenched by the addition of 20 mL of 10% sodium thiosulfate aqueous solution. After stirring for half an hour, the reaction solution was added with 50 mL of saturated sodium bicarbonate aqueous solution and extracted three times with dichloromethane. The combined organic phases were washed with saturated salt water and saturated sodium bicarbonate aqueous solution in turn, dried with anhydrous magnesium sulfate, filtered, concentrated, and then separated and purified by column chromatography (silica gel column 0~16.8% ethyl acetate/petroleum ether gradient elution) to give 6-(bis(4-methoxybenzyl)amino)-2-(1-(m-tolyl)piperidin-4-yl)nicotinaldehyde (**3-5**), as a yellow mucus (250 mg, 373 μmol , 45.6% yield). LCMS: (ESI) $m/z=536.2$ $[\text{M}+\text{H}]^+$;

Step 5: To a reaction flask was added 5 mL of dichloromethane, and then 6-(bis(4-methoxybenzyl)amino)-2-(1-(m-tolyl)piperidin-4-yl)nicotinaldehyde (**3-5**) (250 mg, 466.70 μmol), tert-butyl methyl (2-(methylamino)ethyl)carbamate (88 mg, 466 μmol), and AcOH (28.03 mg, 466.70 μM) in turn and stirred at room temperature for 2 hours. $\text{NaBH}(\text{OAc})_3$ (297 mg, 1.40 mmol) was added in batches, and stirring was continued for 14 hours. The reaction was then quenched by careful dropwise addition of 20 mL of saturated sodium bicarbonate aqueous solution, and extracted with dichloromethane three times after stirring. The combined organic phases were washed with saturated salt water, dried with anhydrous magnesium sulfate, then filtrated, concentrated and purified by column chromatography (silica gel column, 0~17% tetrahydrofuran/petroleum ether gradient elution) to give compound tert-butyl 2-((6-(bis(4-methoxybenzyl)amino)-2-(1-(m-tolyl)piperidin-4-yl)pyridin-3-yl)m-ethyl)(methylamino)ethyl(methyl)carbamate (**3-6**), as a yellow mucus (60 mg, 83.1 μmol , 17.80% yield, 98% purity). LCMS: (ESI) $m/z=708.4$ $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.24 (d, 1H), 7.10-7.19 (m, 5H), 6.74-6.88 (m, 6H), 6.65 (d, 1H), 6.25 (d, 1H), 4.69 (s, 4H), 3.79 (s, 6H), 3.70-3.79 (m, 2H), 3.41 (s, 2H), 3.21-3.41 (m, 2H), 2.98-3.09 (m, 1H), 2.84 (s, 3H), 2.72-2.84 (m, 2H), 2.44-2.59 (m, 2H), 2.31 (s, 3H), 2.09-2.27 (m, 5H), 1.78-1.87 (m, 2H), 1.36-1.49 (m, 9H).

Step 6: To a solution of Compound tert-butyl 2-((6-(bis(4-methoxybenzyl)amino)-2-(1-(m-tolyl)piperidin-4-yl)pyridin-3-yl)m-ethyl)(methylamino)ethyl(methyl)carbamate (**3-6**) (60 mg, 84.7 μmol) in 1 mL of trifluoroacetic acid was added trifluoromethanesulfonic acid (29 mg, 194 μmol), and the reaction was stirred under nitrogen protection at room temperature for 16 hours. The reaction mixture was concentrated, then purified and separated by preparative HPLC (Column: Boston Green ODS 150 $\times$ 30mm $\times$ 5 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 0%-25%, 9 min). The target product was lyophilized to give N^1 -((6-amino-2-(1-(m-tolyl)piperidin-4-yl)pyridin-3-yl)methyl)- N^1, N^2 -dimethylethane-1,2-diamine (**P226**, **Example 3**), as a yellow solid (22 mg, 58.7 μmol , 69.2% yield). LCMS: (ESI) $m/z=368.3$ $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, D_2O) δ (ppm) 7.91 (d, 1H), 7.43-7.51 (m, 2H), 7.36-7.43 (m, 2H), 6.98 (d, 1H), 4.40 (s, 2H), 3.78-3.89 (m, 4H), 3.63-3.72 (m, 1H), 3.49-3.62 (m, 4H), 2.78 (s, 6H), 2.39 (s, 3H), 2.31-2.44 (m, 2H), 2.18-2.30 (m, 2H)

Example 4. Synthesis of

N¹,N²-dimethyl-N¹-((4-(1-(m-tolyl)piperidin-4-yl)-1H-indazol-5-yl)methyl)ethane-1,2-diamine (P190):



Step 1: To a solution of 2-bromo-4-fluorobenzoic acid (**4-1**) (23 g, 105 mmol) in tert-butanol (200 mL) was added 4-dimethylaminopyridine (12.8 g, 105 mmol) and di-tert-butyl dicarbonate (68.8 g, 315 mmol, 3.0 equiv.) at room temperature (vented), and the reaction solution was reacted under nitrogen protection at 90 °C for 2 hours. Complete consumption of the raw material and the generation of new spot were detected by TLC. The reaction solution was then diluted with water (100 mL) and extracted twice with ethyl acetate (150 mL). The organic layer was washed once with saturated salt water (80 mL), dried with magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and then purified by column chromatography (silica, petroleum ether: ethyl acetate = 10:1) to give tert-butyl 2-bromo-4-fluorobenzoate (**4-2**), as a colorless liquid (26.8 g, 95.0 mmol, 90.4% yield, 97.5% purity). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.77 (dd, 1H), 7.37 (dd, 1H), 7.02-7.10 (m, 1H), 1.61 (s, 9H).

Step 2: Synthesis of lithium diisopropylamide: to a solution of diisopropylamine (5.15 g, 50.9 mmol, 7.19 mL) in tetrahydrofuran (100 mL) was added dropwise n-butyllithium (2.5 M, 17.45 mL) at -70 °C, after addition, the reaction solution was warmed to room temperature

and stirred for half an hour to give a yellow solution of diisopropylamide. A solution of tert-butyl 2-bromo-4-fluorobenzoate (**4-2**) (10 g, 36.35 mmol) dissolved in tetrahydrofuran (20 mL) was added dropwise to freshly prepared lithium diisopropylamide at -75 °C, and the reaction solution was reacted at -75 °C for 1.5 hours. Dimethylformamide (10.6 g, 145 mmol) was added to the reaction solution at -75 °C to continue to react for 0.5 hours. Complete consumption of the raw material and the generation of new spot were detected by TLC. Then the reaction was quenched with acetic acid (20 mL) at -70 °C, diluted with water (150 mL) and extracted twice with ethyl acetate (200 mL). The organic layer was washed with saturated salt water (100 mL), dried with magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and then purified by column chromatography (silica, 3% ethyl acetate in petroleum ether) to give tert-butyl 2-bromo-4-fluoro-3-formylbenzoate (**4-3**), as a white solid (8.7 g, 27.7 mmol, 76.2% yield). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 10.39 (s, 1H), 7.80 (dd, 1H), 7.19 (t, 1H), 1.63 (s, 9H).

Step 3: To a solution of tert-butyl 2-bromo-4-fluoro-3-formylbenzoate (**4-3**) (8.7 g, 28.7 mmol) in ethylene glycol dimethyl ether (100 mL) was added hydrazine hydrate (31.6 g, 537 mmol, 85%, 18.7 equiv.), and the reaction solution was stirred at 90 °C for 1 hour. Complete consumption of the raw material and the generation of target product were detected by LCMS. The reaction solution was then cooled, diluted with water (100 mL) and extracted twice with ethyl acetate (150 mL). The organic layer was washed with saturated salt water (100 mL), dried with magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and then purified by column chromatography (silica, 3% ethyl acetate in petroleum ether) to give tert-butyl 4-bromo-1H-indazole-5-carboxylate (**4-4**), as a yellow solid (4.5 g, 15.1 mmol, 52.7% yield). LCMS: (ESI) m/z = 296.9/298.9 [M+H]⁺;

Step 4: To a solution of tert-butyl 4-bromo-1H-indazole-5-carboxylate (**4-4**) (4.5 g, 15.14 mmol) and 3,4-dihydro-2H-pyran (3.82 g, 45.43 mmol, 4.15 mL) in dichloromethane (60 mL) was added p-toluenesulfonic acid monohydrate (288 mg, 1.51 mmol), and the reaction solution was stirred at 15 °C for 1 hour. Complete consumption of the raw material and generation of the target product were detected by LC-MS. The reaction solution was then diluted with water (50 mL) and extracted twice with ethyl acetate (100 mL). The organic layer was washed with saturated salt water (80 mL), dried with magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and then purified by column chromatography (silica, 3% ethyl acetate in petroleum ether) to give tert-butyl 4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-5-carboxylate (**4-5**) in a yellow syrup form (4.5 g, 11.6 mmol, 76.7% yield). LCMS: (ESI) m/z = 240.9/242.9 [M+H-THP-tBu]⁺; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.16 (s, 1H), 7.81 (d, 1H), 7.55 (d, 1H), 5.72 (dd, 1H), 3.93-4.03 (m, 1H), 3.67-3.80 (m, 1H), 2.43-2.59 (m, 1H), 2.12-2.21 (m, 1H), 2.02-2.12 (m, 1H), 1.66-1.85 (m, 3H), 1.64 (s, 9H).

Step 5: To a solution of tert-butyl 4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-5-carboxylate (**4-5**) (1.0 g, 2.62 mmol, 1.0 equiv.) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(m-tolyl)-1,2,3,6-tetrahydropyridine (**Intermediate B**) (863 mg, 2.89 mmol) in tetrahydrofuran (8 mL) was added potassium

phosphate(1.67 g, 7.87 mmol)aqueous solution(2 mL). The reaction was degassed under reduced pressure and replaced with nitrogen for multiple times.(2-dicyclohexylphosphine-2,4,6-triaisopropyl-1,1-biphenyl) [2- (2-amino-1,1-biphenyl)] palladium (II) methanesulfonate (XPhos Pd-G3) (67 mg, 78.7 μ mol) was added. The reaction solution was stirred at 80°C for 16 hours under nitrogen protection. The completion of reaction and generation of new product were detected by LCMS. The reaction solution was diluted with water(30 mL), and extracted with ethyl acetate(20 mL) three times. The organic layer was washed with saturated salt water(20 mL), dried with magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and then purified by column chromatography (silica, 3% ethyl acetate in petroleum ether) to give tert-butyl 1-(tetrahydro-2H-pyran-2-yl)-4-(1-(m-tolyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole-5-carboxylate (**4-6**)(800 mg, 1.55 mmol, 59.0% yield) in yellow syrup form. LCMS:(ESI) m/z = 474.4 $[M+H]^+$;

Step 6: To a solution of tert-butyl 1-(tetrahydro-2H-pyran-2-yl)-4-(1-(m-tolyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole-5-carboxylate (**4-6**) (800 mg, 1.69 mmol) in methanol (160 mL) was added 10% Pd/C (150 mg), and the reaction solution was degassed under reduced pressure and replaced with hydrogen several times, then stirred at 50 °C for 32 h under hydrogen balloon atmosphere. The generation of target product was detected by LCMS. The reaction solution was then filtrated, and the filtrate was concentrated to dryness under reduced pressure, then purified by column chromatography (silica, 30% ethyl acetate in petroleum ether) to give tert-butyl 1-(tetrahydro-2H-pyran-2-yl)-4-(1-(m-tolyl)piperidin-4-yl)-1H-indazole-5-carboxylate (**4-7**) in a yellow syrup form (630 mg, 1.24 mmol, 73.2% yield). LCMS: (ESI) m/z = 476.3 $[M+H]^+$; RT=0.857 min

^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.31 (s, 1H), 7.64 (d, 1H), 7.45 (d, 1H), 7.19 (t, 1H), 6.80-6.91 (m, 2H), 6.71 (d, 1H), 5.71 (dd, 1H), 3.99-4.07 (m, 1H), 3.86-3.94 (m, 2H), 3.65-3.79 (m, 2H), 2.82-3.93 (m, 2H), 2.51-2.65 (m, 1H), 2.37-2.49 (m, 2H), 2.35 (s, 3H), 2.11-2.22 (m, 1H), 2.04-2.10 (m, 1H), 1.93-2.02 (m, 2H), 1.71-1.85 (m, 2H), 1.64-1.71 (m, 1H), 1.63 (s, 9H)

Step 7: To a solution of tert-butyl 1-(tetrahydro-2H-pyran-2-yl)-4-(1-(m-tolyl)piperidin-4-yl)-1H-indazole-5-carboxylate (**4-7**) (630 mg, 1.32 mmol) in tetrahydrofuran (6 mL) was added dropwise lithium aluminiumhydride (1 M in THF, 5.5 mL) at -5 °C, and the reaction solution was stirred at 20 °C for 3 hours. The complete consumption of the material and the generation of new spots were detected by TLC (petroleum ether / ethyl acetate = 1:1). The reaction solution was then quenched dropwise with water (10 mL) at -5 °C, diluted with water (5 mL) and extracted twice with ethyl acetate (30 mL). The organic layer was washed with saturated salt water(20 mL), dried with magnesium sulfate, and filtered. The filtrate was concentrated to dryness under reduced pressure, then purified by column chromatography (silica, 50% ethyl acetate in petroleum ether) to give 1-(tetrahydro-2H-pyran-2-yl)-4-(1-(m-tolyl)piperidin-4-yl)-1H-indazole-5-carboxylate (**4-8**), as a white solid(500 mg, 849 μ mol, 64.1% yield). LCMS: (ESI) m/z = 406.3 $[M+H]^+$;

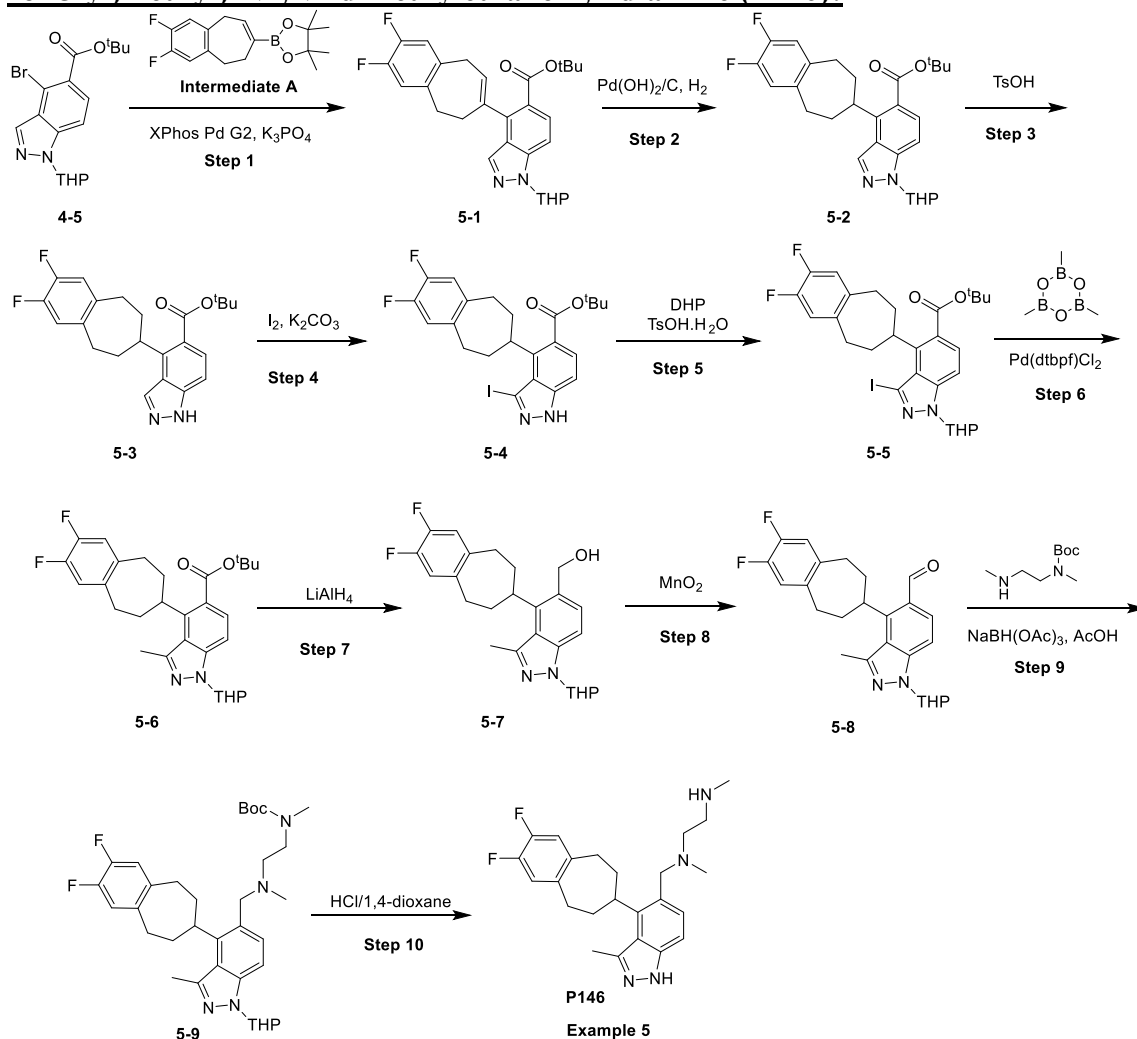
Step 8: To a solution of 1-(tetrahydro-2H-pyran-2-yl)-4-(1-(m-tolyl)piperidin-4-yl)-1H-indazol-5-yl)methanol (**4-8**) (200 mg, 493.18 μ mol) in dichloromethane (10 ml) was added Dess-Martin periodinane (220 mg, 518 μ mol), and the reaction solution was reacted at 25 °C for 6 hours. The complete consumption of the raw material and generation of target product were detected by LC-MS. The reaction solution was then quenched with 10% sodium thiosulfate solution (20 mL) and stirred at room temperature for 0.5 h, then added with saturated sodium bicarbonate (50 mL) and extracted three times with dichloromethane (50 mL). The organic layer was washed with saturated salt water (50 mL), dried with magnesium sulfate, and filtered. The filtrate was concentrated to dryness under reduced pressure, and then purified by column chromatography (silica, 30% ethyl acetate in petroleum ether) to give 1-(tetrahydro-2H-pyran-2-yl)-4-(1-(m-tolyl)piperidin-4-yl)-1H-indazole-5-carboxaldehyde (**4-9**) in a yellow syrup form (140 mg, 293 μ mol, 59.4% yield). LCMS: (ESI) m/z = 404.3 $[M+H]^+$;

Step 9: To a solution of 1-(tetrahydro-2H-pyran-2-yl)-4-(1-(m-tolyl)piperidin-4-yl)-1H-indazole-5-carboxaldehyde (**4-9**) (200 mg, 496 μ mol) and tert-butyl methyl (2-(methylamino)ethyl)carbamate (112 mg, 595 μ mol) in dichloromethane (5 ml) was added acetic acid (36 mg, 595 μ mol), and the reaction solution was stirred at 20 °C for 2 hours. Then sodium triacetoxyborohydride (315 mg, 1.49 mmol, 3 equiv.) was added, and the reaction solution was stirred at 20 °C for 14 hours. The complete consumption of raw materials and generation of target product were detected by LC-MS. The reaction solution was then quenched with saturated sodium bicarbonate solution (10 mL), diluted with water (5 mL), extracted twice with dichloromethane (20 mL), dried with magnesium sulfate, and filtered. The filtrate was concentrated to dryness under reduced pressure, and then purified by column chromatography (silica, 50% ethyl acetate in dichloromethane) to give tert-butyl methyl (2-(methyl((1-(tetrahydro-2H-pyran-2-yl)-4-(1-(m-tolyl)piperidin-4-yl)-1H-indazol-5-yl)methylamino)ethyl)carbamate (**4-10**) (210 mg, 365 μ mol, 73.6% yield) in a yellow syrup form. LCMS: (ESI) m/z = 576.5 $[M+H]^+$;

Step 10: To a solution of tert-butyl methyl (2-(methyl((1-(tetrahydro-2H-pyran-2-yl)-4-(1-(m-tolyl)piperidin-4-yl)-1H-indazol-5-yl)methylamino)ethyl)carbamate (**4-10**) (210 mg, 365 μ mol) in methanol (2 ml) was added HCl/1,4-dioxane (4 M, 2.10 mL), and the reaction solution was stirred at 25 °C for 16 hours. The complete consumption of raw material and the generation of target product were detected by LC-MS. The reaction solution was concentrated to dryness under reduced pressure, and then purified by preparative liquid chromatography (Boston Green ODS column, 5 μ m silica, 30 mm diameter, 150 mm length; a mixture of water (containing 0.05% hydrochloric acid) and acetonitrile with decreasing polarity was used as eluent) to give N1,N2-dimethyl-N1-(((4-(1-(m-tolyl)piperidin-4-yl))-1H-indazol-5-yl)methyl)ethane-1,2-diamine (**P190**, **Example 4**) as a white solid (hydrochloride, 105 mg, 245 μ mol, 67.3% yield). LCMS: (ESI) m/z = 392.2 $[M+H]^+$; ^1H NMR (400 MHz, D_2O) δ (ppm) 8.63 (s, 1H), 7.61 (d, 1H), 7.54 (s, 1H), 7.42-7.51 (m, 3H),

7.36 (d, 1H), 4.74 (s, 2H), 3.86-4.02 (m, 2H), 3.65-3.84 (m, 5H), 3.52-3.64 (m, 2H), 2.87 (s, 3H), 2.70-2.94 (m, 2H), 2.78 (s, 3H), 2.37 (s, 3H), 2.09-2.19 (m, 2H)

Example 5. Synthesis of N1-((4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-3-methyl-1H-indazol-5-yl)methyl)-N1,N2-dimethylethane-1,2-diamine (P146):



Step 1: To a reaction flask was added a solution of tert-Butyl 4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-5-carboxylate (**4-5**) (1.95 g, 5.11 mmol), (2,3-difluoro-6,9-dihydro-5H-benzo[7]cyclopentan-7-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**Intermediate A**) (1.80 g, 5.88 mmol, 1.15 equiv), toluene (45 ml) and potassium phosphate (2.18 g, 10.3 mmol) in water (6.5 mL), and the reaction was replaced with nitrogen several times, and then added with chloro(2-dicyclohexylphosphino-2,4,6-triisopropyl-1,1-biphenyl)[2-(2-amino-1,1-biphenyl)]palladium(II) (0.03 equiv). The reaction solution was stirred at 60 °C for 24 hours under nitrogen protection. The generation of target product was detected by LCMS. The reaction solution was then cooled to 25 °C, dissolved with water (50 mL) and ethyl acetate (50 mL). The organic phase was separated and then extracted three times with ethyl acetate (50 mL). The organic phases were combined, dried with magnesium sulfate, and filtered. The

filtrate was concentrated to dryness under reduced pressure, then purified by column chromatography (silica, 15% ethyl acetate in petroleum ether) to give a crude product of tert-butyl

4-(2,3-difluoro-6,9-dihydro-5H-benzo[7]cyclopenten-7-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-5-carboxylate (**5-1**), as a yellow oil. LCMS: (ESI) $m/z = 481.2$ $[M+H]^+$;

Step 2: The crude product of the previous step, tert-butyl 4-(2,3-difluoro-6,9-dihydro-5H-benzo[7]cyclopenten-7-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-5-carboxylate (**5-1**), was dissolved in ethyl acetate (50 mL) and palladium hydroxide/carbon (520 mg, 10%) was added under nitrogen atmosphere. The reaction solution was replaced several times with hydrogen and stirred for 12 h at 30 °C. The consumption of the raw material and the generation of target product were detected by LCMS. The reaction solution was then filtered to give tert-butyl 4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-5-carboxylate (**5-2**) as a white solid, which was used directly in the next step without further purification. LCMS: (ESI) $m/z = 399.3$ $[M+H-THP]^+$; 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.98 (s, 1H), 7.64 (d, 1H), 7.43 (d, 1H), 6.94-7.05 (m, 2H), 5.70 (dd, 1H), 3.98-4.07 (m, 1H), 3.89-3.98 (m, 1H), 3.69-3.80 (m, 1H), 2.91-3.06 (m, 2H), 2.76-2.91 (m, 2H), 2.46-2.59 (m, 1H), 2.11-2.23 (m, 3H), 1.95-2.10 (m, 3H), 1.66-1.84 (m, 4H), 1.65 (s, 9H)

Step 3: To a solution of tert-butyl 4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-5-carboxylate (**5-2**) (1.9 g, 3.94 mmol) in methanol (30 mL) and tetrahydrofuran (30 mL) was added p-toluenesulfonic acid monohydrate (297 mg, 1.56 mmol), and the reaction solution was stirred at 30 °C for 3.5 days. The generation of target product and the raw material remained were detected by LCMS. The reaction solution was quenched with saturated sodium bicarbonate solution (20 mL) and concentrated under reduced pressure to remove methanol. Then ethyl acetate (100 mL) and water (50 mL) were added, and the organic phase was separated and extracted twice with ethyl acetate (50 mL). The organic phases were combined and dried with anhydrous magnesium sulfate, and filtered. The filtrate was concentrated to dryness under reduced pressure, then purified by thin layer chromatography (silica, 35% ethyl acetate in petroleum ether), then concentrated to dryness under reduced pressure to give tert-butyl 4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-1H-indazole-5-carboxylate (**5-3**) as a white solid (827 mg, 2.08 mmol, 52.7% yield). LCMS: (ESI) $m/z = 399.2$ $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.06 (s, 1H), 7.65 (d, 1H), 7.34 (d, 1H), 7.00 (t, 2H), 3.90-4.02 (m, 1H), 2.92-3.06 (m, 2H), 2.76-2.90 (m, 2H), 2.14-2.27 (m, 2H), 1.98-2.11 (m, 2H), 1.64 (s, 9H)

Step 4: To a solution of tert-butyl 4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-1H-indazole-5-carboxylate (**5-3**) (424 mg, 1.06 mmol) in dimethylformamide (10 mL, previously added with potassium carbonate (458 mg, 3.31 mmol) was added iodine (459 mg, 1.81 mmol), and the reaction solution was stirred at 15 ~20 °C for 16 hours. LCMS indicated 69% of the target product

and 30% of the remaining raw material. Additional iodine (135 mg, 532 μmol) and potassium carbonate (180 mg, 1.30 mmol) were added to the reaction solution and stirring was continued at 15 ~30 °C for 3 hours. LCMS indicated 10% of the remaining raw material and the generation of target product. It was combined with the previous 50 mg of the crude product for process. Ethyl acetate (50 mL) and 10 % sodium thiosulfate solution (50 mL) were added to the reaction solution, the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (50 mL) three times. The organic phases were combined and washed once with 10% sodium thiosulfate solution, three times with 10 % lithium chloride (25 mL), and once with saturated salt water (50 mL), dried, filtered, and concentrated under reduced pressure to give the crude product tert-butyl 4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-3-iodo-1H-indazole-5-carboxylate (**5-4**) as a light yellow foam, which was used directly in the next step without further purification. LCMS: (ESI) m/z = 525.0 $[\text{M}+\text{H}]^+$;

Step 5: To a solution of tert-butyl 4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-3-iodo-1H-indazole-5-carboxylate (**5-4**) (589 mg, 1.12 mmol.) and 3,4-dihydropyran (420 mg, 4.99 mmol.) in dichloromethane (15 mL) was added p-toluenesulfonic acid (50 mg, 263 μmol , 0.23 equiv.) under an ice bath at a temperature of 0 to 5 °C, and the reaction solution was stirred for 3 hours at 15-20 °C. The complete consumption of raw material and the generation of target product were detected by LCMS. The reaction solution was then partitioned in 5 % sodium bicarbonate solution (50 mL) and dichloromethane (50 mL). The organic phase was separated and the aqueous phase was extracted twice with dichloromethane (50 mL). The organic phases were combined and dried with magnesium sulfate, filtered and concentrated to dryness under reduced pressure, and then purified by column chromatography (silica, 12% ethyl acetate in petroleum ether) to give tert-butyl 4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-indazole-5-carboxylate (**5-5**) as a white solid (564 mg, 742 μmol , 66.0% yield, 80% purity). LCMS: (ESI) m/z = 525.1 $[\text{M}+\text{H}-\text{THP}]^+$; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.46 (d, 1H), 7.40 (d, 1H), 6.97 (t, 2H), 5.67 (dd, 1H), 4.52-4.67 (m, 1H), 3.95-4.03 (m, 1H), 3.67-3.80 (m, 1H), 3.05-3.16 (m, 2H), 2.80 (dd, 2H), 2.42-2.62 (m, 1H), 2.04-2.27 (m, 6H), 1.68-1.79 (m, 3H), 1.27-1.44 (m, 9H)

Step 6: Two reactions were set up in parallel: tert-butyl 4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-indazole-5-carboxylate (**5-5**) (225 mg, 370 μmol , 1.0 eq.), 1,4-dioxane (5 mL) and potassium phosphate (236 mg, 1.11 mmol) were dissolved in water (1 mL), and the reaction solution was replaced with nitrogen, added with 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (292 mg, 1.16 mmol, 50% in THF) and [1,1-bis(di-tert-butylphosphino)ferrocene]palladium dichloride (17 mg, 26.1 μmol , 0.07 eq.). Then the reaction was stirred at 80 °C for 2 hours under nitrogen protection. The complete consumption of raw material and the generation of target product were detected by LCMS. The reaction solution was cooled to 20 °C and partitioned in saturated salt water (50 mL) and ethyl acetate (50 mL), the organic layer was separated and the aqueous phase was extracted twice with ethyl acetate (50 mL). The organic

phases were combined, dried with magnesium sulfate, filtered and concentrated to dryness under reduced pressure, then purified by column chromatography (silica, 0-5%-7% ethyl acetate in petroleum ether) to give a deiodinated by-product tert-butyl 4-(2,3-difluoro-6,9-dihydro-5H-benzo[7]cyclopenten-7-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-5-carboxylate (**5-1**) as a bright yellow oil (124 mg, 257 μ mol, 34.7% yield) and the target product tert-butyl 4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-3-methyl-1-(tetrahydro-2H-pyran-2-yl)-indazole-5-carboxylate (**5-6**) as a bright yellow oil (244 mg, 442 μ mol, 59.8% yield). LCMS: (ESI) m/z =497.2 $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38 (d, 1H), 7.33 (d, 1H), 6.97 (t, 2H), 5.60 (dd, 1H), 4.02-4.09 (m, 1H), 3.81-3.92 (m, 1H), 3.68-3.78 (m, 1H), 2.87-2.99 (m, 2H), 2.80-2.87 (m, 2H), 2.80 (s, 3H), 2.48-2.61 (m, 1H), 2.19-2.33 (m, 2H), 2.06-2.18 (m, 3H), 1.95-2.04 (m, 1H), 1.70-1.84 (m, 2H), 1.62-1.70 (m, 2H), 1.58 (s, 9H).

Step 7: To a reaction flask was added tert-butyl 4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-3-methyl-1-(tetrahydro-2H-pyran-2-yl)-indazole-5-carboxylate (**5-6**) (239 mg, 481 μ mol) and tetrahydrofuran (8 ml), and Lithium tetrahydroaluminum (1 M tetrahydrofuran solution, 0.9 mL) was added at 15~2 °C, then the reaction solution continued to stir for 2 hours. TLC detected that the raw material was still present and new spots were formed. Lithium tetrahydroaluminum (1 M tetrahydrofuran, 300 μ l) was continued to be added and the reaction solution was stirred for 1 hour at 15-20 °C. TLC (petroleum ether: Ethyl acetate = 3:1) detected that most of the raw material was consumed and new spots were formed. The reaction solution was quenched with water (50 mL) and 15% sodium hydroxide solution, dissolved with ethyl acetate (50 mL), dried with magnesium sulfate, and stirred for 10 minutes, then filtered, concentrated to dryness under reduced pressure to give a crude product of (4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-3-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)methanol (**5-7**) (221 mg, 518 μ mol) as a yellow solid. The crude product was used directly in the next step without further purification. LCMS: (ESI) m/z = 427.3 $[M+H]^+$;

Step 8: To a solution of (4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-3-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)methanol (**5-7**) (210 mg, 492 μ mol) in dichloromethane (15 ml) was added manganese dioxide (530 mg, 6.10 mmol). The reaction solution was stirred at 40 °C for 3.5 hours and then filtered and concentrated under reduced pressure to give a crude product of 4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-3-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-5-carboxaldehyde (**5-8**) (210 mg, 495 μ mol) as an off-white solid. The crude product was used directly in the next step without further purification. LCMS: (ESI) m/z = 425.1 $[M+H]^+$;

Step 9: A solution of 4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-3-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-5-carboxaldehyde (**5-8**) (204 mg, 480 μ mol), tert-butyl methyl

(2-(methylamino)ethyl)carbamate (186 mg, 987 μ mol) and acetic acid (62 mg, 1.03 mmol, 2.15 equiv.) in dichloromethane (3 mL) was stirred at 25 °C for 2 h, then sodium triethoxycarbonylborohydride (340 mg, 1.60 mmol) was added. The reaction solution was stirred at 25 °C for 14 hours. The consumption of the raw material and the generation of target product were detected by LCMS. The reaction solution was partitioned in 5 % sodium bicarbonate solution (15 mL) and dichloromethane. The organic phase was separated and the aqueous phase was extracted three times with ethyl acetate (10 mL). The organic phases were combined, dried with magnesium sulfate, filtered, concentrated to dryness under reduced pressure, then purified by column chromatography (silica, 30% ethyl acetate in

dichloromethane) to give tert-butyl

(2-((4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-3-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)methyl)(methylamino)ethyl)(methyl)carbamate (**5-9**) (204 mg, 325 μ mol, 67.6% yield) as a bright yellow oil. LCMS: (ESI) m/z =597.4 $[M+H]^+$;

Step 10: To a solution of tert-butyl

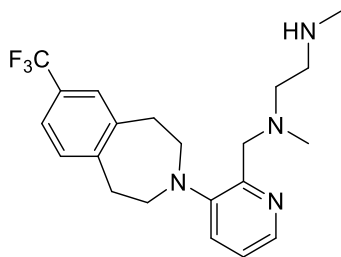
(2-((4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-3-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)methyl)(methylamino)ethyl)(methyl)carbamate (**5-9**) (202 mg, 338 μ mol) in methanol was added HCl/1,4-dioxane (4 M, 15 mL), and the reaction solution was stirred at 10-15 °C for 12 hours. The complete consumption of raw material and the generation of target product were detected by LC-MS. The reaction solution was then

concentrated to dryness under reduced pressure, then purified by reversed phase preparative liquid phase chromatography (YMC-Actus Triart C18 column, 5 μ m silica, 30 mm diameter, 150 mm length; a mixture of water (containing 0.05% ammonia) and acetonitrile with decreasing polarity was used as eluent) to give

N1-((4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-3-methyl-1H-indazol-5-yl)methyl)-N1,N2-dimethylethane-1,2-diamine (**P146, Example 5**) as a white solid (Hydrochloride, 105 mg, 214 μ mol, 63.3% yield, 99% purity). LCMS: (ESI) m/z =413.4 $[M+H]^+$; 1H NMR (400 MHz, CD_3OD) tautomer mixture δ (ppm) 7.84 (d, 0.5H), 7.71 (d, 0.5H), 7.49-7.55 (m, 1H), 7.08-7.17 (m, 2H), 4.74-4.84 (m, 1H), 4.36-4.74 (m, 1H), 4.08-4.20 (m, 0.5H), 3.74-3.87 (m, 1.5H), 3.63-3.72 (m, 1H), 3.43-3.63 (m, 2H), 3.29-3.37 (m, 1H), 2.99-3.05 (m, 2H), 2.96 (s, 1.5H), 2.83-2.87 (m, 1H), 2.83 (s, 1.5H), 2.81 (s, 3H), 2.74 (s, 1.5H), 2.26 (s, 1.5H), 2.09-2.26 (m, 2H), 1.84-2.08 (m, 2H); ^{19}F NMR (376 MHz, CD_3OD) tautomer mixture δ (ppm) -144.96, -145.32

Example 6: Synthesis of

N¹,N²-dimethyl-N¹-((3-(7-(trifluoromethyl)-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)pyr-idin-2-yl)methyl)ethane-1,2-diamine (P088)

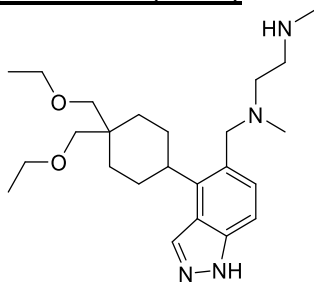


P088

Example 6

Compound P088 was synthesized as described in Example 1 using 3-fluoropyridinecarboxaldehyde and Intermediate D. LCMS: (ESI) $m/z=393.4$ $[M+H]^+$; 1H NMR (400 MHz, D_2O) δ (ppm) 8.25 (d, 1H), 7.91 (d, 1H), 7.61 (dd, 1H), 7.50 (s, 1H), 7.47 (d, 1H), 7.32 (d, 1H), 4.24 (s, 2H), 3.28-3.36 (m, 2H), 3.15-3.20 (m, 2H), 3.06-3.13 (m, 8H), 2.71 (s, 3H), 2.43 (s, 3H)

Example 7: Synthesis of N1-((4-(4,4-bis(ethoxymethyl)cyclohexyl)-1H-indazol-5-yl)methyl)-N1,N2-dimethylethane-1,2-diamine (P266)

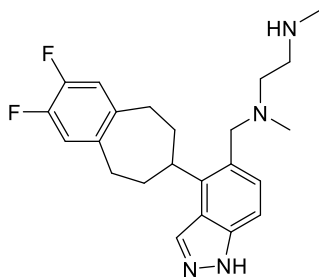


P266

Example 7

Compound P266 was synthesized as described in Example 4 using intermediate 4-4 and 2-(4,4-bis(ethoxymethyl)cyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. LCMS: (ESI) $m/z=417.4$ $[M+H]^+$; 1H NMR (400 MHz, D_2O) δ (ppm) 8.30 (s, 1H), 7.52 (d, 1H), 7.39 (d, 1H), 4.60 (s, 2H), 3.65 (s, 2H), 3.62 (q, 2H), 3.58-3.65 (m, 2H), 3.55 (q, 2H), 3.48-3.57 (m, 2H), 3.30 (s, 2H), 2.92-3.05 (m, 1H), 2.82 (s, 3H), 2.75 (s, 3H), 1.97-2.14 (m, 2H), 1.63-1.75 (m, 2H), 1.48-1.58 (m, 2H), 1.33-1.46 (m, 2H), 1.20 (t, 3H), 1.16 (t, 3H)

Example 8: Synthesis of N1-((4-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-1H-indazol-5-yl)methyl)-N1,N2-dimethylethane-1,2-diamine (P167)

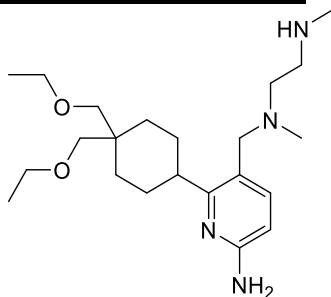


P167

Example 8

Compound **P167** was synthesized as described in **Example 4** using **Intermediate 4-5** and **Intermediate A**. LCMS: (ESI) $m/z=399.2$ $[M+H]^+$; 1H NMR (400 MHz, D_2O) δ (ppm) 8.05 (s, 1H), 7.56 (d, 1H), 7.45 (d, 1H), 7.05 (t, 2H), 4.71 (s, 2H), 3.65-3.78 (m, 2H), 3.54-3.63 (m, 2H), 3.39-3.52 (m, 1H), 2.95-3.08 (m, 2H), 2.90 (s, 3H), 2.75-2.85 (m, 2H), 2.80 (s, 3H) 1.88-2.12 (m, 4H)

Example 9. Synthesis of N1-((6-amino-2-(4,4-bis(ethoxymethyl)cyclohexyl)pyridin-3-yl)methyl)-N1,N2-dimethylethane-1,2-diamine (P293)

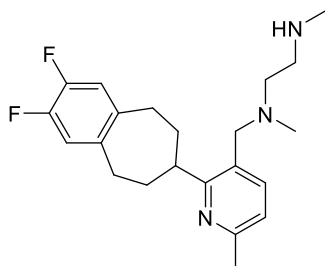


P293

Example 9

Compound **P293** was synthesized as described in **Example 3**, using **intermediate 3-2** and 2-(4,4-bis(ethoxymethyl)cyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. LCMS: (ESI) $m/z=393.3$ $[M+H]^+$; 1H NMR (400 MHz, CD_3OD) δ (ppm) 8.41 (s, 2H), 7.61 (d, 1H), 6.57 (d, 1H), 3.56 (s, 2H), 3.54 (q, 2H), 3.49 (s, 2H), 3.48 (q, 2H), 3.24 (s, 2H), 3.10-3.16 (m, 2H), 2.87-2.98 (m, 1H), 2.67-2.71 (m, 2H), 2.67 (s, 3H), 2.24 (s, 3H), 1.81-1.91 (m, 2H), 1.74-1.81 (m, 2H), 1.50-1.62 (m, 2H), 1.33-1.44 (m, 2H), 1.20 (t, 2H), 1.18 (t, 2H)

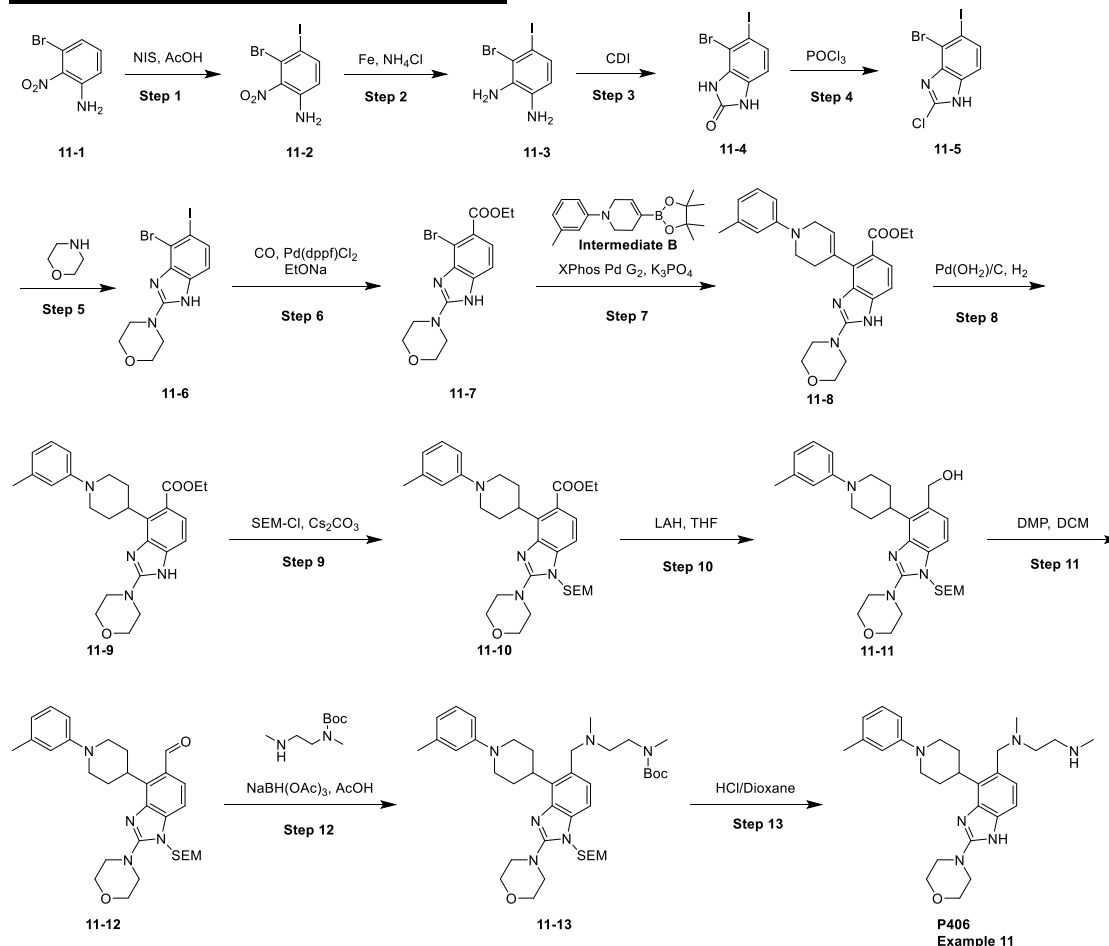
Example 10. Synthesis of N1-((2-(2,3-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]cyclopenten-7-yl)-6-methylpyridin-3-yl)methyl)-N1,N2-dimethylethane-1,2-diamine (P038)



P038
Example 10

Compound **P038** was synthesized as described in Example 2, using **Intermediate 2-2** and **Intermediate A**. LCMS: (ESI) $m/z=374.2$ $[M+H]^+$; 1H NMR (400 MHz, D_2O) δ (ppm) 8.49 (d, 1H), 7.73 (d, 1H), 7.07 (t, 2H), 4.61 (s, 2H), 3.57-3.70 (m, 3H), 3.48-3.56 (m, 2H), 2.92-3.06 (m, 2H), 2.81-2.89 (m, 2H), 2.78 (s, 3H), 2.77 (s, 3H), 2.70 (s, 3H), 2.01-2.13 (m, 2H), 1.74-1.91 (m, 2H)

Example 11: Synthesis of the compound N,N'-dimethyl-N'-[2-morpholin-4-[1-(m-tolyl)-4-piperidinyl]-1H-benzod[imidazol-5-yl]methyl]ethane-1,2-diamine (P406):



10

15

Step 1: A mixture of 2-nitro-3-bromoaniline (11-1) (150 g, 691.18 mmol), N-iodosuccinimide (171 g, 760.05 mmol) and acetic acid (1500 ml) was heated and refluxed for about 2 hours, and cooled after the reactant 11-1 was converted. The reaction solution was then poured into 3600 ml of water, and the precipitate was filtered, dried in vacuum, dissolved in ethyl acetate, washed with water and saturated salt water in turn, and extracted

with ethyl acetate. The combined organic phases were dried with anhydrous magnesium sulfate; filtered and concentrated, then separated by silica gel column chromatography to give 178 g 2-nitro-3-bromo-4-iodoaniline (**11-2**) as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ(ppm) 7.66 (d, 1H), 6.70 (d, 1H), 6.23 (s, 2H).

Step 2: To a solution of compound 2-nitro-3-bromo-4-iodoaniline (**11-2**) (80.0 g, 233.29 mmol) in a mixed system of tetrahydrofuran (640 ml)/ethanol (640 ml)/water (320 ml) was added NH₄Cl (187 g, 3.50 mol), and the mixture was heated to 90 °C and iron powder (52.1 g, 933.17 mmol) was added slowly in batches. Heating was continued for 2 hours until the reaction was complete. The reaction solution was then cooled to 60 °C, stirred with diatomite for 10 min, cooled to room temperature and filtered; the filtrate was extracted with ethyl acetate, concentrated to remove most of the water-soluble solvent and then dissolved in a large amount of ethyl acetate, and washed with saturated salt water; the organic phase was dried after extraction, filtered and concentrated to give a crude product of 3-bromo-4-iodo-phenylenediamine (**11-3**) as a brown solid (73.8 g, 224.04 mmol, 96.03% yield, 933.17 mmol), which was used directly in the next step without further purification. LCMS: (ESI) m/z = 314.8 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) 6.92 (d, 1H), 6.35 (d, 1H), 4.99 (s, 2H), 4.90 (s, 2H).

Step 3: A solution of compound 3-bromo-4-iodo-phenylenediamine (**11-3**) (35.0 g, 111.85 mmol) in tetrahydrofuran (350 mL) was cooled in an ice bath, and carbonyl diimidazole (27.2 g, 167.77 mmol) was added; then the reaction solution was gradually warmed to room temperature and stirred for about 2 hours until the reaction was complete. The reaction solution was concentrated and added with water to beat (500 mL) for half an hour, filtered and lyophilized to give a crude product of 4-bromo-5-iodo-1,3-dihydro-2H-benzo[d]imidazol-2-one (**11-4**), as a brown solid (37.8 g, 111.53 mmol, 99.72% yield), which was used directly in the next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) 11.12 (s, 1H), 11.02 (s, 1H), 7.47 (d, 1H), 6.75 (d, 1H).

Step 4: The compound 4-bromo-5-iodo-1,3-dihydro-2H-benzo[d]imidazol-2-one (**11-4**) (28.0 g, 82.61 mmol) was carefully added to phosphoryl trichloride (130 mL). The mixture was heated to 100 °C for 3 hours, and then heated to 120 °C for 16 hours until the reaction was essentially complete. The mixture was cooled to room temperature and distilled under pressure to half volume. After carefully pouring in batches into 2 liters of ice water, the pH was carefully adjusted to 8 with potassium carbonate under stirring. A brown solid was precipitated, filtered and dried to give a crude product of 2-chloro-4-bromo-5-iodo-1H-benzo[d]imidazole (**11-5**) (30.0 g, crude), which was used directly in the next step without further purification. LCMS: (ESI) m/z = 358.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) 13.77 (br s, 1H), 7.72 (d, 1H), 7.32 (br d, 1H).

Step 5: To a suspension of compound 2-chloro-4-bromo-5-iodo-1H-benzo[d]imidazole (**11-5**) (30.0 g, 83.95 mmol, 2.05 mL) in isopropanol (150 mL) and tetrahydrofuran (150 mL) was added morpholine (37.0 g, 424.70 mmol, 37.37 mL), and the mixture was heated to 90 °C for 4 days and then cooled to room temperature after complete conversion of the raw material. The organic solvent was spun off, then beaten in water (300 mL); the solids were

filtered and purified by silica gel column chromatography to give a brown mucus, which was beating in ethanol to give 30.1 g of a yellow solid crude product, and further recrystallized in ethanol to give 2-(4-morpholinyl)-4-bromo-5-iodo-1H-benzo[d]imidazole (**11-6**) as a white solid (15.5 g, 37.99 mmol, 45.25% yield). LCMS: (ESI) $m/z = 407.9, 409.9 [M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ (ppm) 11.82 (s, 0.85H), 11.40 (s, 0.15H), 7.48 (d, 0.15H), 7.40 (d, 0.85H), 6.97-7.05 (m, 1H), 3.65-3.81 (m, 4H), 3.44-3.59 (m, 4H).

Step 6: 2-(4-morpholinyl)-4-bromo-5-iodo-1H-benzo[d]imidazole (**11-6**) (15.5 g, 37.99 mmol) was added to a solution of sodium ethoxide (20% purity, 180 mL) in ethanol. The reaction solution was deoxygenated and replaced 3 times with CO (balloon), then added with Pd(dppf)Cl₂ (1.11 g, 1.52 mmol), deoxygenated again and replaced 3 times with CO; the system was heated to 45 °C to react for 16 hours. The reaction was then cooled in an ice bath and quenched by careful addition of acetic acid (8 mL, pH = 6-7), concentrated, diluted with ethyl acetate, washed and extracted with saturated sodium bicarbonate and saturated salt water; the organic phase was dried with anhydrous magnesium sulfate, filtered and concentrated, then purified by silica gel column chromatography to give ethyl 4-bromo-2-(4-morpholinyl)-1H-benzo[d]imidazole-5-carboxylate (**11-7**) (16.5 g, 46.58 mmol, 77.12% yield), as a light yellow amorphous solid. LCMS: (ESI) $m/z = 356.0 [M+H]^+$

Step 7: The compound ethyl 4-bromo-2-(4-morpholinyl)-1H-benzo[d]imidazole-5-carboxylate (**11-7**) (16.5 g, 46.58 mmol),

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(m-tolyl)-1,2,3,6-tetrahydropyridine (**Intermediate B**) (15.3 g, 51.24 mmol), and potassium phosphate (19.8 g, 93.17 mmol) were added to tetrahydrofuran (165 mL) and water (33 mL), the reaction solution was replaced with nitrogen, XPhos-PD-G2 (1.10 g, 1.40 mmol) was added, and the reaction was heated at 65 °C for 5 h under nitrogen protection. The reaction solution was cooled to 40 °C, then added with sodium diethylcarbamothionylthiolate (997.25 mg, 5.82 mmol) and continued to stir for 1 hour, then diluted with water (200 mL), and extracted with ethyl acetate. The organic phase was dried with anhydrous magnesium sulfate, filtered and concentrated, and the crude product was purified by silica gel column chromatography to give ethyl 2-(4-morpholinyl)-4-(1-m-tolyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-benzo[d]imidazole-5-carboxylate (**11-8**) (18.5 g, 41.43 mmol, 88.94%), as a yellow solid. LCMS: (ESI) $m/z = 447.3 [M+H]^+$; 1H NMR (400 MHz, CDCl₃) δ (ppm) 9.59 (br s, 1H), 7.89 (d, 1H), 7.35 (d, 1H), 7.23 (t, 1H), 6.86-6.98 (m, 2H), 6.81 (br d, 1H), 5.75 (br s, 1H), 4.33 (q, 2H), 3.76-3.87 (m, 6H), 3.50-3.64 (m, 6H), 2.88 (br d, 2H), 2.65 (br s, 2H), 2.37 (s, 3H), 1.39 (t, 3H).

Step 8: To a suspension of compound ethyl 2-(4-morpholinyl)-4-(1-m-tolyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-benzo[d]imidazole-5-carboxylate (**11-8**) (18.5 g, 41.43 mmol) in tetrahydrofuran (600 mL) was added Pd(OH)₂/C (7.0 g, 41.43 mmol, 10% purity), and the reaction was replaced with hydrogen and then reacted for 16 hours at 30 °C under hydrogen atmosphere (balloon) until the reaction was fundamental finished. The reaction solution was filtered and the filter cake was washed with tetrahydrofuran (200 mL*2). The combined filtrate was concentrated and dried to give a crude product ethyl

2-(4-morpholinyl)-4-(1-m-tolyl-4-piperidinyl)-3H-benzo[d]imidazole-5-carboxylate (**11-9**) (19 g), which was used directly in the next step without further purification. LCMS: (ESI) $m/z=449.3[M+H]^+$.

Step 9: To a solution of compound ethyl

5 2-(4-morpholinyl)-4-(1-m-tolyl-4-piperidinyl)-3H-benzo[d]imidazole-5-carboxylate (**11-9**) (19 g, 42.36 mmol) in CH_3CN (550 mL) was added cesium carbonate (69.0 g, 211.79 mmol), and SEM-Cl (19 g, 113.96 mmol, 20.17 mL) was added dropwise under stirring. The reaction mixture was reacted at 30°C for 24 hours, and then the reaction was basically complete. The mixture was then filtered, washed with ethyl acetate, and the combined organic phases were
10 concentrated, then purified by silica gel column chromatography to obtain compound ethyl 2-(4-morpholinyl)-4-(1-m-tolyl-4-piperidinyl)-1-(2-trimethylsilylethoxymethylene)benzo[d]imidazole-5-carboxylate (**11-10**) as a colorless oil (22.3 g, 38.53 mmol, 90.96% yield). LCMS: (ESI) $m/z = 580.2 [M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59 (d, 1H), 7.08-7.21 (m, 2H), 6.82-6.89 (m, 2H), 6.65 (d, 1H), 5.29 (s, 2H), 4.40 (q, 2H), 3.91 (br d, 2H), 3.81-3.87 (m, 4H), 3.64-3.76 (m, 4H), 3.38-3.47 (m, 4H), 2.98-3.12 (m, 2H), 2.85-2.96 (m, 2H), 2.35 (s, 3H), 1.79 (br d, 2H), 1.44 (t, 3H), 0.05 (s, 2H), 0.02 (s, 8H)

Step 10: To a solution of aluminum lithium hydride (3.0 g, 79.05 mmol, 79.05 ml) in tetrahydrofuran (300 ml) was added dropwise a solution of compound ethyl 2-(4-morpholinyl)-4-(1-m-tolyl-4-piperidinyl)-1-(2-trimethylsilylethoxymethylene)benzo[d]imidazole-5-carboxylate (**11-10**) (22.0 g, 38.01 mmol) in tetrahydrofuran (100 ml) under an ice bath, then gradually returned to room temperature after the dropwise addition, and heated to 30 °C for 1 hour. The reaction was basically complete. The reaction was then quenched by carefully dripping 3 ml of water, 3 ml of 15% sodium hydroxide aqueous solution, and 6 ml of water under an ice bath, then stirred and dried with anhydrous magnesium sulfate at room
25 temperature for 15 minutes, and then filtered. The organic phase was concentrated to obtain a crude product of 2-(4-morpholinyl)-4-(1-m-tolyl-4-piperidinyl)-1-(2-trimethylsilylethoxymethylene)benzo[d]imidazole-5-methanol (**11-11**) (19.3 g, 35.96 mmol, 94.60% yield) as a colorless viscous liquid, which was directly used in the next step without further purification. LCMS: (ESI) $m/z = 537.3 [M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.28 (s, 1H), 7.10-7.22 (m, 3H), 6.83-6.92 (m, 2H), 6.68 (d, 1H), 5.23-5.34 (m, 2H), 4.85 (s, 2H), 3.90 (br d, 2H), 3.80-3.86 (m, 4H), 3.75-3.80 (m, 1H), 3.67-3.75 (m, 2H), 3.39-3.47 (m, 4H), 3.27-3.38 (m, 1H), 3.06 (m, 2H), 2.88-2.99 (m, 2H), 2.35 (s, 3H), 0.95-1.01 (m, 2H), 0.05 (s, 2H), 0.02 (s, 8H).

Step 11: To a solution of compound

35 2-(4-morpholinyl)-4-(1-m-tolyl-4-piperidinyl)-1-(2-trimethylsilylethoxymethylene)benzo[d]imidazole-5-methanol (**11-11**) (9.5 g, 17.70 mmol) in dichloromethane (200 ml) was added DMP (9.01 g, 21.24 mmol, 6.58 ml), then reacted at 30°C with stirring for half an hour; the reaction was basically complete. 100 mL of saturated sodium bicarbonate aqueous solution and 100 mL of sodium thiosulfate were added and the reaction was stirred for 30 min. The
40 organic phase was dried with anhydrous magnesium sulfate after dichloromethane extraction, filtered, concentrated and then purified by silica gel column to give compound 2-(4-morpholinyl)-4-(1-m-tolyl-4-piperidinyl)-1-(2-trimethylsilyl

ethoxymethylene)benzo[d]imidazole-5-carbaldehyde (**11-12**) as a beige white amorphous solid (11.7 g, 21.88 mmol, 61.81% yield). LCMS: (ESI) $m/z = 535.3 [M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.50 (s, 1H), 7.75 (d, 1H), 7.25 (d, 1H), 7.19 (t, 1H), 6.81-6.90 (m, 2H), 6.67 (d, 1H), 5.31 (s, 2H), 4.10-4.16 (m, 1H), 3.92 (br d, 2H), 3.80-3.88 (m, 4H), 3.69-3.77 (m, 2H), 3.39-3.49 (m, 4H), 2.90-3.08 (m, 4H), 2.36 (s, 3H), 1.82 (br d, 2H), 0.94-1.04 (m, 2H), 0.00-0.07 (m, 9H).

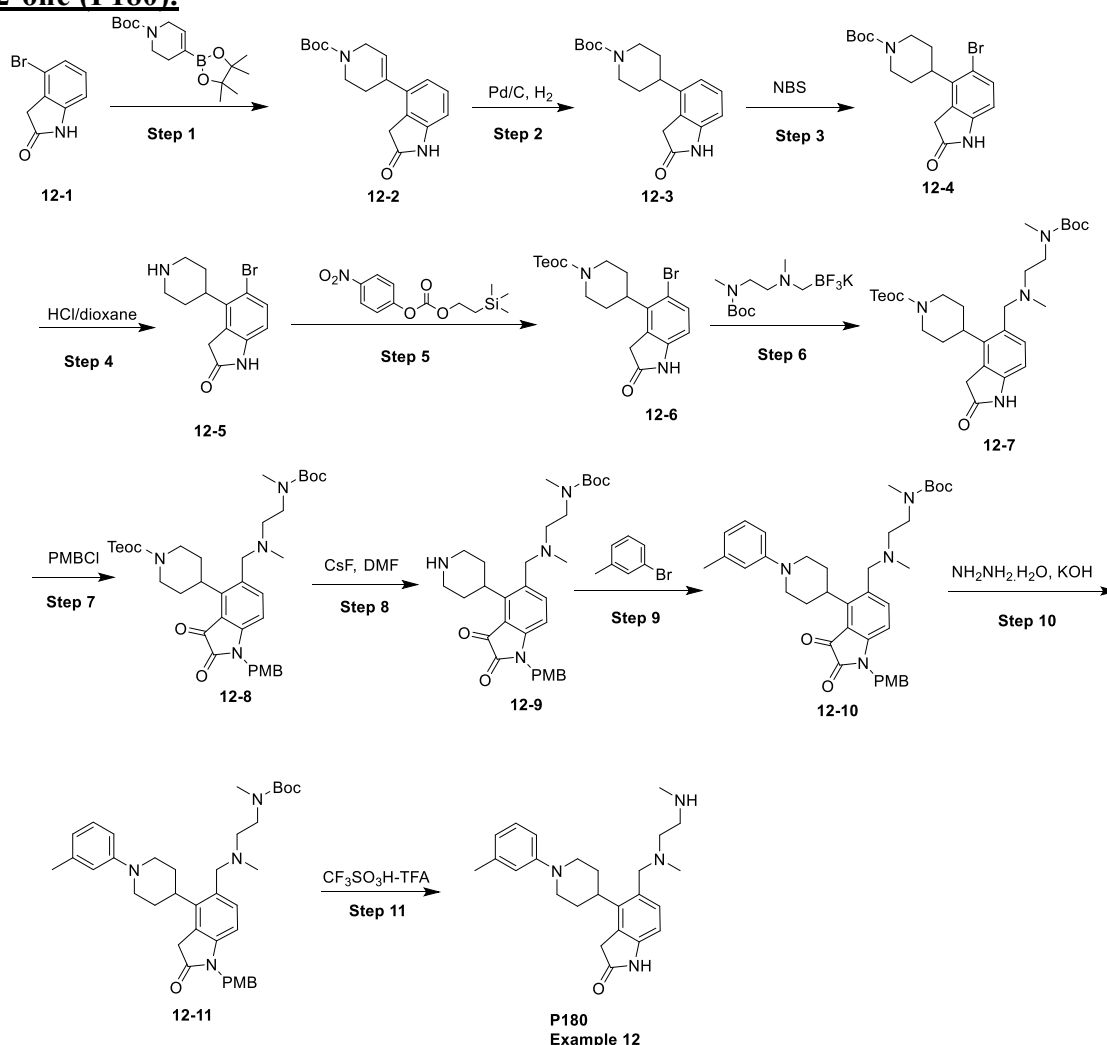
Step 12: To a solution of compound 2-(4-morpholinyl)-4-(1-m-tolyl-4-piperidinyl)-1-(2-trimethylsilyl ethoxymethylene)benzo[d]imidazole-5-carbaldehyde (**11-12**) (10.7 g, 20.01 mmol) and tert-butyl N-methyl-N-[2-(methylamino) ethyl] carbamate (4.52 g, 24.01 mmol) in 150 ml of dichloromethane was added acetic acid (1.44 g, 24.01 mmol, 1.37 ml), and the reaction solution was stirred at 30 °C for 1 hour, then sodium acetate borohydride (12.7 g, 60.03 mmol) was added in batches, and the reaction was stirred at 30°C for 15 hours until the reaction was basically complete. The reaction was quenched by careful addition of 100 mL of saturated sodium bicarbonate aqueous solution and stirred for 1 hour, then extracted with dichloromethane. The combined organic phase was dried with anhydrous magnesium sulfate, filtered, and concentrated, then purified by silica gel column chromatography to obtain the product

N-tert-butoxycarbonyl-N,N'-dimethyl-N'-[[2-morpholinyl-4-[1-(m-tolyl)-4-piperidinyl]-1H-benzo[d]imidazol-5-yl]methyl]ethane-1,2-diamine (**11-13**) (10.6 g, 14.99 mmol, 68.12% yield) and by-product 2-(4-morpholinyl)-4-(1-m-tolyl-4-piperidinyl)-1-(2-trimethylsilylethoxymethylene)benzo[d]imidazole-5-methanol (**11-11**) (1.9 g, 3.54 mmol, 17.69% yield). LCMS: (ESI) $m/z = 535.3 [M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.17 (t, 1H), 7.04 (s, 2H), 6.83-6.89 (m, 2H), 6.65 (d, 1H), 5.25 (s, 2H), 3.89 (br d, 2H), 3.78-3.85 (m, 4H), 3.68-3.76 (m, 2H), 3.61 (s, 2H), 3.37-3.44 (m, 5H), 3.30 (br s, 2H), 3.02 (m, 2H), 2.80-2.91 (m, 5H), 2.46-2.64 (m, 2H), 2.34 (s, 3H), 2.22 (br s, 3H), 1.69 (br d, 2H), 1.36-1.45 (m, 9H), 0.92-1.00 (m, 2H), -0.02-0.03 (m, 9H).

Step 13: To a solution of compound N-tert-butoxycarbonyl-N,N'-dimethyl-N'-[[2-morpholinyl-4-[1-(m-tolyl)-4-piperidinyl]-1H-benzo[d]imidazol-5-yl]methyl]ethane-1,2-diamine (**11-13**) (10.6 g, 14.99 mmol) in 50 mL of 1,4-dioxane was added a solution of HCl/dioxane (50 mL) and stirred at 70°C for 2 hours to precipitate white solid. After cooling to room temperature, 10 ml of methanol was added. After concentration, 50 ml of methanol was added, and 500 ml of isopropyl ether was added dropwise under stirring to get white precipitates, which continued to be under stirring at room temperature for 16 hours; then filtered and lyophilized to give N,N'-dimethyl-N'-[[2-morpholinyl-4-[1-(m-tolyl)-4-piperidinyl]-1H-benzo[d]imidazol-5-yl]methyl]ethane-1,2-diamine hydrochloride as a white solid (quantitatively determined as hydrochloride coefficient of 4). LCMS: (ESI) $m/z = 477.3 [M+H]^+$; 1H NMR (400 MHz, D_2O) δ (ppm) 7.33-7.55 (m, 6H), 3.89-4.02 (m, 6H), 3.69-3.87 (m, 9H), 3.54-3.66 (m, 2H), 2.87 (s, 3H), 2.80 (s, 3H), 2.60-2.77 (m, 2H), 2.39 (s, 3H), 2.21 (br d, 2H)

To a solution of N,N'-dimethyl-N'-[[2-morpholinyl-4-[1-(m-tolyl)-4-piperidinyl]-1H-benzo[d]imidazol-5-yl]methyl]ethane-1,2-diamine hydrochloride (400 mg) in 5 ml of water was carefully added dropwise saturated sodium carbonate aqueous solution to adjust the pH to 8-10, then extracted with ethyl acetate. The organic phase was washed with saturated salt water and dried with anhydrous magnesium sulfate, filtered, and concentrated; then the crude product was lyophilized to give N,N'-dimethyl-N'-[[2-morpholinyl-4-[1-(m-tolyl)-4-piperidinyl]-1H-benzo[d]imidazol-5-yl]methyl]ethane-1,2-diamine (**P406, Example 11**) as a light yellow free compound (270 mg, 0.566 mmol, 88.15% yield). LCMS: (ESI) $m/z = 477.3 [M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ (ppm) 11.28 (br s, 1H), 7.08 (t, 1H), 6.94 (br d, 1H), 6.80 (s, 1H), 6.75 (br t, 2H), 6.55 (br d, 1H), 3.84 (br d, 2H), 3.68 (br s, 4H), 3.48 (s, 2H), 3.05-3.29 (m, 6H), 2.92 (m, 2H), 2.69-2.80 (m, 2H), 2.55-2.63 (m, 2H), 2.41-2.48 (m, 2H), 2.26 (d, 6H), 2.03 (s, 3H), 1.50 (br d, 2H).

EXAMPLE 12: Synthesis of compound 5-((methyl(2-(methylamino)ethyl)amino)methyl)-4-(1-methylphenyl)piperidin-4-yl)indol in-2-one (P180).



Step 1: Compound 4-bromoindolin-2-one (**12-1**) (2.00 g, 9.43 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.92 g, 9.43 mmol) and potassium phosphate (6.01 g, 28.30 mmol) were added to a mixture of 100 mL of tetrahydrofuran and 20 mL of water, and XphosPd G3 (239 mg, 0.28 mmol) was added after nitrogen replacement. The reaction was heated to 65 °C and stirred under nitrogen protection for 2 hours after another nitrogen replacement. The reaction solution was then diluted with saturated salt water and extracted with ethyl acetate; the combined organic phases were dried with anhydrous magnesium sulfate, filtered, and concentrated; then the crude product was purified by silica gel column chromatography to give compound 4-(1-tert-butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)-indolin-2-one (**12-2**) as a brown solid (2.8 g, 8.91 mmol, 94.43% yield). LCMS: (ESI) m/z = 214.9 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ (ppm) 10.40 (s, 1H), 7.16 (t, 1H), 6.88 (d, 1H), 6.73 (d, 1H), 5.96 (br s, 1H), 3.98 (br s, 2H), 3.54 (s, 2H), 3.46-3.53 (m, 2H), 2.41 (br d, 2H), 1.44 (s, 9H).

Step 2: Compound 4-(1-tert-butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)-indolin-2-one (**12-2**) (2.30 g, 7.32 mmol) was added to 50 mL of methanol, and 10% palladium-carbon (460 mg, 0.43 mmol) was added after nitrogen replacement. The reaction solution was stirred at room temperature for 16 hours under hydrogen atmosphere (balloon) after hydrogen replacement. When the reaction was basically complete, it was filtered and washed with methanol; the filtrate was concentrated to give a yellow crude product of 4-(1-tert-butoxycarbonyl-piperidin-4-yl)-indolin-2-one (**12-3**) (2.2 g, 6.95 mmol, 95.04% yield), which was used directly in the next step without further purification. LCMS: (ESI) m/z = 216.9 $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.55 (br s, 1H), 7.22 (t, 1H), 6.89 (d, 1H), 6.78 (d, 1H), 4.28 (br s, 2H), 3.52 (s, 2H), 2.83 (br t, 2H), 2.63 (tt, 1H), 1.75-1.82 (m, 2H), 1.61-1.73 (m, 2H), 1.51 (s, 9H).

Step 3: To a solution of the crude product of 4-(1-tert-butoxycarbonyl-piperidin-4-yl)-indolin-2-one (**12-3**) (3.70 g, 11.69 mmol) in 100 mL of dichloromethane was added N-bromosuccinimide (2.29 g, 12.86 mmol, 1.1 eq) in batches, and the reaction was stirred at room temperature for 16 hours, and the reaction was basically complete. The reaction solution was then carefully added with 50 mL of 15% potassium carbonate aqueous solution under stirring; the organic phase was washed with saturated salt water after dichloromethane extraction, dried with anhydrous magnesium sulfate, filtered, concentrated and then pulped with ethyl acetate at room temperature to give a crude product of 4-(1-tert-butoxycarbonyl-piperidin-4-yl)-5-bromo-indolin-2-one (**12-4**) (3.60 g, 9.11 mmol, 77.88% yield) as a white solid, which was used directly in the next step without further purification. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.90 (br s, 1H), 7.47 (d, 1H), 6.67 (d, 1H), 4.28 (br d, 2H), 3.65 (s, 2H), 3.37 (br s, 1H), 2.83 (br t, 2H), 1.78 (br d, 4H), 1.51 (s, 9H).

Step 4: To a solution of the crude product of 4-(1-tert-butoxycarbonyl-piperidin-4-yl)-5-bromo-indolin-2-one (**12-4**) (3.60 g, 9.11 mmol) in 20 mL of 1,4-dioxane was added a solution of 20 mL of 4M hydrochloric acid in 1,4-dioxane, and stirred at room temperature for 16 hours and the reaction was basically

complete. After filtration, the filter cake was washed with methyl tert-butyl ether, concentrated and dried to give a white crude product of 5-bromo-4-(piperidin-4-yl)indolin-2-one (**12-5**) hydrochloride (3.00 g, 9.05 mmol, 99.33% yield), which was used directly in the next step without further purification. LCMS: (ESI) $m/z=295.0[M+H]^+$; 1H NMR(400 MHz,D₂O) δ (ppm) 7.42(d,1H), 6.66(d,1H), 3.57-3.65(m, 2H), 3.46(br d,2H), 3.36(br s,1H), 3.07(m,2H), 1.64-2.30(m,4H).

Step 5: To a stirred suspension of compound 5-bromo-4-(piperidin-4-yl)indolin-2-one (**12-5**) hydrochloride (1.90 g, 5.73 mmol) in acetonitrile (20 mL) was added N,N-diisopropylethylamine (1.55 g, 12.03 mmol, 2.10 mL), and ethyl (4-nitrophenyl) 2-trimethylsilyl ethyl carbonate (1.79 g, 6.30 mmol) was added dropwise. The reaction solution was stirred at room temperature for 15 h and then filtered; the filter cake was washed with acetonitrile. The combined mother liquors were concentrated, and then purified by silica gel column chromatography to give 5-bromo-4-(1-trimethylsilylethoxycarbonyl-piperidin-4-yl)-indolin-2-one (**12-6**) as a yellow solid (2.50 g, 5.40 mmol, 94.34% yield, 95% purity). LCMS: (ESI) $m/z = 413.1 [M-2Me+H]^+$

Step 6: To a mixture of the compound 5-bromo-4-(1-trimethylsilylethoxycarbonyl-piperidin-4-yl)-indolin-2-one (**12-6**) (2.00 g, 4.55 mmol), anhydrous [2-(tert-butoxycarbonylmethylethylamino)(methyl)amino]potassium methylborontrifluoride (4.21 g, 13.65 mmol), potassium phosphate (2.90 g, 13.65 mmol), and RuphosPd G2 (353 mg, 0.455 mmol) were added to a mixture of 40 mL of tetrahydrofuran and 4 mL of water. The reaction was replaced with nitrogen, and heated to 80 °C under nitrogen protection for 16 h and the reaction was basically complete. After cooling to room temperature, 30 ml of saturated saline was added; the organic phase was extracted with ethyl acetate and dried with anhydrous magnesium sulfate, filtered and concentrated, then purified by silica gel column chromatography to give compound 2-trimethylsilyl ethyl-4-(5-(((2-((tert-butoxycarbonyl)(methyl)amino)ethyl)(methyl)amino)methyl-2-oxoindol in-4-yl)piperidine-1-carboxylate (**12-7**) as a yellow viscous liquid (2.8 g, 4.49 mmol, 98.73% yield, 90% purity). LCMS:(ESI) $m/z= 561.5 [M+H]^+$.

Step 7: A mixture of compound 2-trimethylsilyl ethyl-4-(5-(((2-((tert-butoxycarbonyl)(methyl)amino)ethyl)(methyl)amino)methyl-2-oxoindol in-4-yl)piperidine-1-carboxylate (**12-7**) (1.50 g, 2.41 mmol, 90% purity) and cesium carbonate (5.00 g, 15.35 mmol) was added to 20 mL of acetonitrile and stirred for 3 h; then 4-methoxybenzyl chloride (565 mg, 3.61 mmol, 0.49 mL) was added dropwise, and the reaction was basically complete after stirring for 1 h at room temperature. After filtration, the filtrate was concentrated, and then purified by silica gel column chromatography to give compound 2-trimethylsilyl ethyl-4-(5-(((2-((tert-butoxycarbonyl)(methyl)amino)ethyl)(methyl)amino)methyl)-1-(4-methoxybenzyl)-2,3-dioxoindolin-4-yl)piperidine-1-carboxylate (**12-8**) as a yellow solid (1.32 g, 1.46 mmol, 60.76% yield, 77% purity). LCMS: (ESI) $m/z = 695.6 [M+H]^+$.

Step 8: To a solution of compound 2-trimethylsilyl ethyl-4-(5-(((2-((tert-butoxycarbonyl)(methyl)amino)ethyl)(methyl)amino)methyl)-1-(4-methoxybenzyl)-2,3-dioxoindolin-4-yl)piperidine-1-carboxylate (**12-8**) (2.10 g, 2.33 mmol, 77%

purity) in 30 mL of N,N- dimethylformamide was added cesium fluoride (1.77 g, 11.63 mmol, 0.43 mL), and the reaction was heated to 65 °C and stirred for 5 hours and the reaction was basically complete. After cooling to room temperature, the reaction was diluted with water, adjusted to pH 3~4 with 10% phosphoric acid aqueous solution, extracted with methyl tert-butyl ether and washed. The aqueous phase was adjusted to pH 12 with 10M sodium hydroxide aqueous solution, and extracted with ethyl acetate. The organic phase was dried with anhydrous magnesium sulfate, filtered, concentrated and then vacuum-dried to obtain a crude product of tert-butyl (2-(((1-(4-methoxybenzyl)-2,3-dioxo-4-(piperidin-4-yl)indolin-5-yl)methyl)(methylamino)ethyl)(methyl)carbamate (**12-9**) as a yellow solid (1.40 g, 2.16 mmol, 92.87% yield, 85% purity), which was used directly in the next step without further purification. LCMS: (ESI) $m/z = 551.4 [M+H]^+$.

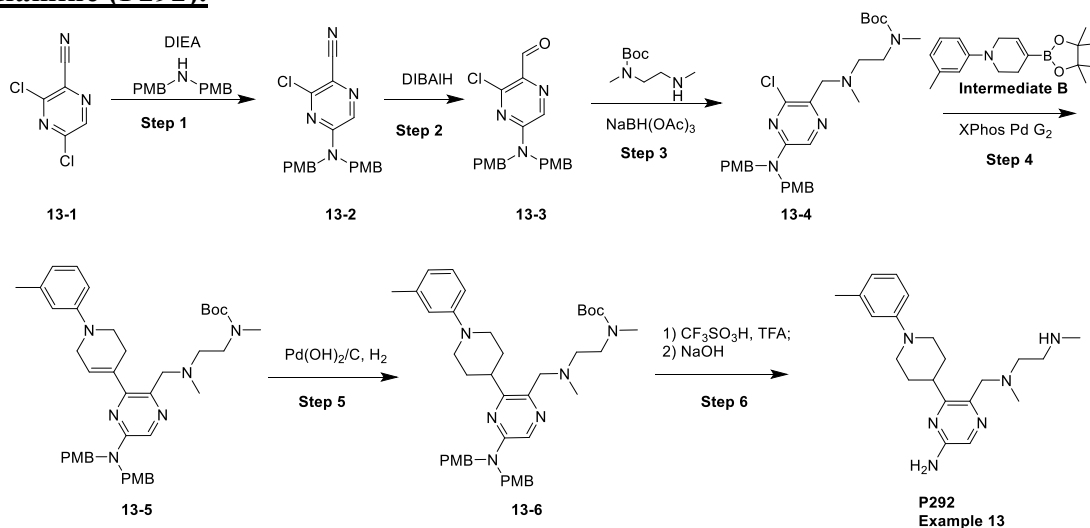
Step 9: To a mixture of compound tert-butyl (2-(((1-(4-methoxybenzyl)-2,3-dioxo-4-(piperidin-4-yl)indolin-5-yl)methyl)(methylamino)ethyl)(methyl)carbamate (**12-9**) (1.30 g, 2.36 mmol), m-bromo-toluene (605 mg, 3.54 mmol, 0.43 mL) and cesium carbonate (1.54 g, 4.72 mmol) was added 20 mL of toluene. The reaction solution was replaced with nitrogen, and added with RuPhosPd G3 (200 mg, 0.24 mmol). Then the reaction solution was replaced with nitrogen and heated to 100 °C with stirring for 16 hours; the reaction was essentially complete. After filtration, it was concentrated and purified by silica gel column chromatography to give compound tert-butyl (2-(((1-(4-methoxybenzyl)-2,3-dioxo-4-(1-m-tolylpiperidin-4-yl)indolin-5-yl)methyl)(methylamino)ethyl)(methyl)carbamate (**12-10**) as an orange solid (900 mg, 1.40 mmol, 59.49% yield, 100% purity). LCMS: (ESI) $m/z = 641.4 [M+H]^+$. ¹H NMR (400 MHz, CD₃OD) δ (ppm) 7.45 (br s, 1H), 7.33 (br d, 2H), 7.13 (t, 1H), 6.72-6.94 (m, 5H), 6.67 (d, 1H), 3.68-3.91 (m, 5H), 3.52 (s, 2H), 3.25-3.40 (m, 5H), 2.67-2.91 (m, 4H), 2.37-2.67 (m, 4H), 2.09-2.36 (m, 7H), 1.60 (br d, 2H), 1.17-1.41 (m, 9H).

Step 10: To a solution of compound tert-butyl (2-(((1-(4-methoxybenzyl)-2,3-dioxo-4-(1-m-tolylpiperidin-4-yl)indolin-5-yl)methyl)(methylamino)ethyl)(methyl)carbamate (**12-10**) (190 mg, 0.30 mmol) in 5 mL of ethanol was added hydrazine hydrate (5.15 g, 87.44 mmol, 5.00 mL, 85% purity) and potassium hydroxide (332 mg, 5.93 mmol), and the mixture was heated to 80 °C and stirred for 3 hours, the reaction was essentially complete. Most of the ethanol was removed by concentration, the aqueous phase was extracted with ethyl acetate, and the combined organic phases were dried with anhydrous magnesium sulfate, filtered and concentrated to obtain a crude product of tert-butyl (2-(((1-(4-methoxybenzyl)-2-oxo-4-(1-m-tolylpiperidin-4-yl)indolin-5-yl)methyl)(methylamino)ethyl)(methyl)carbamate (**12-11**) (220 mg) as a yellow viscous liquid, which was used directly in the next step without further purification. LCMS: (ESI) $m/z = 627.5 [M+H]^+$.

Step 11: To a stirred solution of compound tert-butyl (2-(((1-(4-methoxybenzyl)-2-oxo-4-(1-m-tolylpiperidin-4-yl)indolin-5-yl)methyl)(methylamino)ethyl)(methyl)carbamate (**12-11**) (220 mg, 0.32 mmol, 92% purity) in 5 mL of

trifluoroacetic acid was added dropwise trifluoromethanesulfonic acid (200 mg, 1.33 mmol, 0.12 mL), and the reaction solution was stirred at room temperature for 5 hours and then heated to 40 °C for 30 hours; the reaction was essentially complete. The reaction solution was then concentrated and diluted with 5 mL of dichloromethane and extracted with 0.5 M diluted hydrochloric acid aqueous solution. The combined aqueous phases were adjusted to pH 12 with 1 M sodium hydroxide aqueous solution and then extracted with dichloromethane. The combined organic phases were dried with anhydrous magnesium sulfate, filtered and concentrated to give a free base product of 5-((methyl(2-(methylamino)ethyl)amino)methyl)-4-(1-m-tolyl)piperidin-4-yl)indolin-2-one (**P180**). To a stirred solution of the product in 2 mL of 1,4-dioxane was added dropwise 2 mL of 4 M hydrochloric acid-1,4-dioxane solution. The reaction solution was then concentrated and lyophilized to give 5-((methyl(2-(methylamino)ethyl)amino)methyl)-4-(1-methylphenyl)piperidin-4-yl)indolin-2-one (**P180**, **Example 12**) hydrochloride, as a white solid (80 mg, 48.12% yield, quantitative hydrochloride coefficient of 3). LCMS: (ESI) $m/z = 407.3 [M+H]^+$. ^1H NMR (400 MHz, D_2O) δ (ppm) 7.46 (s, 1H), 7.39-7.44 (m, 2H), 7.37 (d, 1H), 7.31-7.36 (m, 1H), 6.97 (d, 1H), 4.55 (s, 2H), 3.78-3.92 (m, 4H), 3.70-3.77 (m, 2H), 3.59-3.70 (m, 2H), 3.48-3.57 (m, 2H), 3.41 (br t, 1H), 2.83 (s, 3H), 2.73 (s, 3H), 2.41-2.59 (m, 2H), 2.34 (s, 3H), 2.07 (br d, 2H).

EXAMPLE 13 Synthesis of the compound N-((5-amino-3-(1-(m-tolyl)piperidin-4-yl)pyrazin-2-yl)methyl)-N,N'-dimethyl-1,2-ethylenediamine (P292**).**



Step 1: To a solution of compound 2-cyano-3, 5-dichloropyrazine (**13-1**) (145 g, 833.39 mmol) in 1000 mL of N,N-dimethylformamide was added dropwise diisopropylethylamine (109 g, 843.37 mmol, 146.90 mL) at room temperature, and to which a solution of di(4-methoxybenzyl)amine (217.50 g, 845.23 mmol) in 500 mL of N,N-dimethylformamide was added dropwise under stirring after cooling to 5-10 °C. The reaction solution was then slowly warmed to room temperature with continuous stirring for 3 hours, and the reaction was essentially complete. The reaction solution was then poured into 5000 ml of ice-water mixture and stirred for 5 minutes to precipitate solid. After filtration, the solid was dissolved

in 4000 ml of ethyl acetate and then washed with saturated salt water; the organic phase was dried with anhydrous magnesium sulfate, filtrated and concentrated. The crude product was beating with 700 ml of methyl tert-butyl ether at 20 °C for 16 hours, filtered and dried to give compound 2-cyano-3-chloro-5-(bis(4-methoxybenzyl)amino)pyrazine (**13-2**) as a yellow solid, which was directly used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.87 (s, 1H), 7.14 (br d, 4H), 6.85-6.92 (m, 4H), 4.75 (br s, 4H), 3.81 (s, 6H).

Step 2: A solution of compound 2-cyano-3-chloro-5-(bis(4-methoxybenzyl)amino)pyrazine (**13-2**) in 600 mL of tetrahydrofuran was cooled to -78 °C under nitrogen protection, and DIBALH (1 mole/liter, 548 mL) was added dropwise under stirring. The reaction continued stirring for 2 hours until the reaction was almost complete. The reaction was quenched by carefully adding 500 ml of 10% acetic acid aqueous solution under stirring at -78 °C. The reaction was then slowly warmed to room temperature, filtered through diatomite and washed with ethyl acetate. The filtrate was extracted with ethyl acetate, and the combined organic phases were adjusted to pH 8-9 with saturated sodium bicarbonate aqueous solution. The separated organic phases were washed with saturated salt water, and dried with anhydrous magnesium sulfate, filtered, and concentrated. Then the product was beating with methyl tert-butyl ether/petroleum ether (1:2, v/v) for 3 hours to give 5-(bis(4-methoxybenzyl)amino)-3-chloro-pyrazine-2-carboxaldehyde (**13-3**) (100 g, 252.35 mmol, 92.69% yield) as a yellow solid, which was used in the next step directly. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 10.15 (s, 1H), 8.03 (s, 1H), 7.12-7.20 (m, 4H), 6.86-6.91 (m, 4H), 4.71-4.87 (m, 4H), 3.81 (s, 6H).

Step 3: To a solution of compound 5-(bis(4-methoxybenzyl)amino)-3-chloro-pyrazine-2-carbaldehyde (**13-3**) (53.0 g, 133.21 mmol) and N-tert-butyloxycarbonyl-N,N'-dimethylethylenediamine (30.0 g, 159.35 mmol) in 1000 ml of dichloromethane was added acetic acid (9.60 g, 159.86 mmol, 9.14 mL), then sodium borohydride acetate (71.0 g, 335.00 mmol) was added in batches at room temperature, and the reaction continued stirring for 2 h. The reaction was then quenched by careful addition of 1,000 mL of saturated sodium carbonate aqueous solution, then extracted with ethyl acetate; the organic phase was washed with saturated salt water, dried with anhydrous magnesium sulfate, filtered, concentrated, then purified by silica gel column chromatography to give compound tert-butyl (2-((((5-(bis(4-methoxybenzyl)amino)-3-chloropyrazin-2-yl)(methyl)amino)ethyl)(methyl)carbamate (**13-4**) as a yellow mucus (112 g, 196.45 mmol, 73.73% yield); the crude product was used directly in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.83 (s, 1H), 7.15 (d, 4H), 6.83-6.89 (m, 4H), 4.62-4.73 (m, 4H), 3.80 (s, 6H), 3.69 (br s, 2H), 3.36 (br s, 2H), 2.85 (s, 3H), 2.63 (br s, 2H), 2.34 (s, 3H), 1.44 (s, 9H).

Step 4: A mixture of compound tert-butyl (2-((((5-(bis(4-methoxybenzyl)amino)-3-chloropyrazin-2-yl)(methyl)amino)ethyl)(methyl)carbamate (**13-4**) (37 g, 64.90 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(m-tolyl)-1,2,3,6-tetrahydropyridine (**Intermediate B**) (25 g, 83.55 mmol) and potassium phosphate (35 g, 164.89 mmol) was

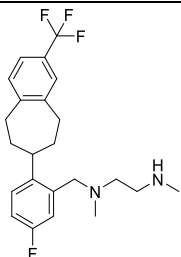
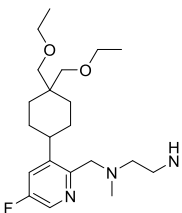
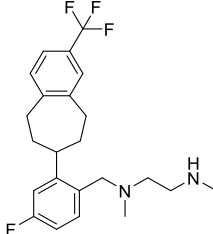
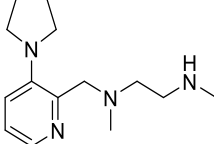
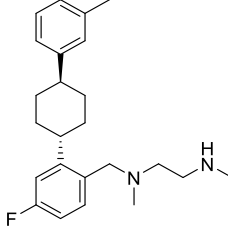
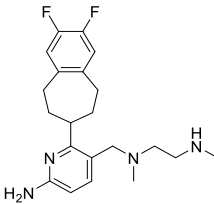
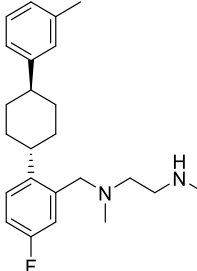
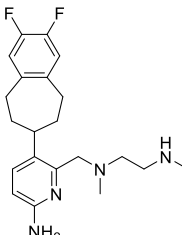
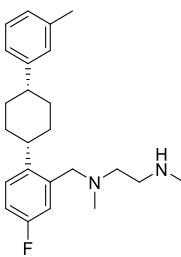
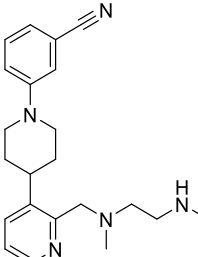
added to tetrahydrofuran (250 mL) and water (50 mL), and the reaction solution was replaced with nitrogen followed by the addition of XPhos-Pd-G2 (1.65 g, 1.95 mmol), then heated to 65 °C with stirring under nitrogen protection for 16 hours; the reaction was essentially completed. To the mixture was added 500 ml of saturated saline and extracted with ethyl acetate; the organic phase was dried with anhydrous magnesium sulfate, filtered, concentrated and then dissolved with 500 ml of methyl tert-butyl ether, washed with 10% phosphoric acid aqueous solution (150 ml x 3), and the aqueous phase was adjusted to pH 13-14 with 10-15% sodium hydroxide aqueous solution. After extraction with ethyl acetate, the organic phase was dried with anhydrous magnesium sulfate, filtered and concentrated to give 101 g of brown viscous crude product tert-butyl (2-(((5-(bis(4-methoxybenzyl)amino)-3-(1-(m-tolyl)-1,2,3,6-tetrahydropyridin-4-yl)pyrazin-2-yl)methyl)(methyl)amino)ethyl)(methyl)carbamate (**13-5**), which was used directly in the next step. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.84 (s, 1H), 7.13-7.19 (m, 4H), 6.85 (br d, 4H), 6.77-6.82 (m, 2H), 6.67 (br d, 1H), 6.57 (br s, 1H), 4.72 (s, 4H), 4.13 (q, 1H), 3.93 (br s, 2H), 3.80 (s, 6H), 3.54-3.64 (m, 2H), 3.49 (br t, 2H), 3.20-3.39 (m, 1H), 2.69-2.85 (m, 5H), 2.48-2.66 (m, 2H), 2.35 (s, 3H), 2.28 (br s, 2H), 2.05 (s, 1H), 1.47 (br s, 1H), 1.43 (br s, 9H).

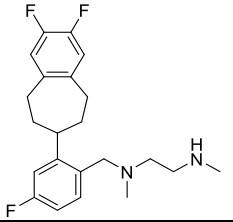
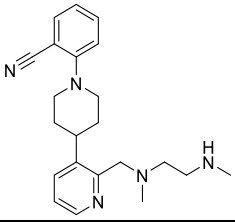
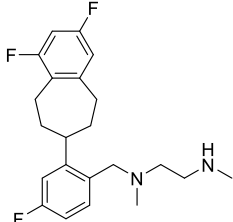
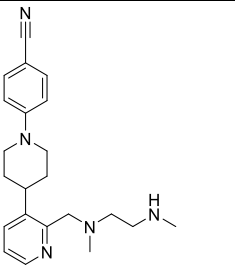
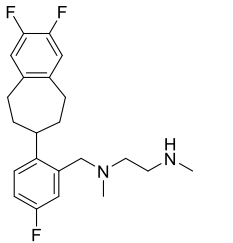
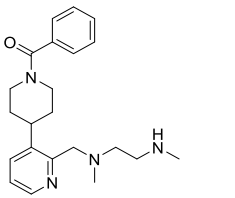
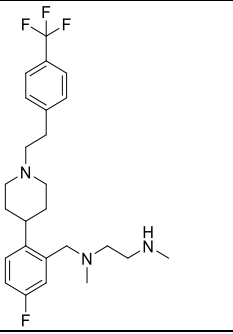
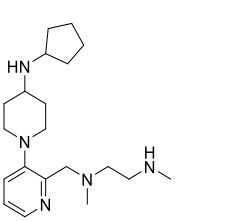
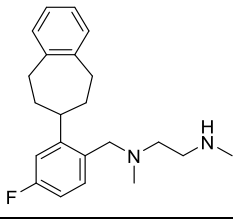
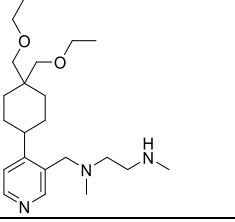
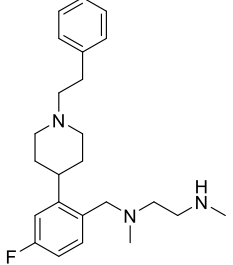
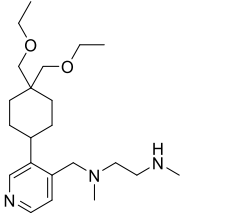
Step 5: To a solution of compound tert-butyl (2-(((5-(bis(4-methoxybenzyl)amino)-3-(1-(m-tolyl)-1,2,3,6-tetrahydropyridin-4-yl)pyrazin-2-yl)methyl)(methyl)amino)ethyl)(methyl)carbamate (**13-5**) (46.5 g, 65.78 mmol) in 600 ml of tetrahydrofuran was added palladium hydroxide/C (15 g, 21.36 mmol, 20% purity) under nitrogen protection, then stirred under hydrogen atmosphere (balloon) at room temperature for 4 days after hydrogen replacement. After filtration, the concentrated crude product was purified by silica gel column chromatography to give compound tert-butyl (2-(((5-(bis(4-methoxybenzyl)amino)-3-(1-(m-tolyl)piperidin-4-yl)pyrazin-2-yl)methyl)(methyl)amino)ethyl)(methyl)carbamate (**13-6**) as a yellow viscous liquid (83.5 g, 117.78 mmol, 89.53% yield). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.75 (s, 1H), 7.10-7.19 (m, 5H), 6.77-6.90 (m, 6H), 6.67 (d, 1H), 4.69 (s, 4H), 3.79 (s, 7H), 3.60 (br s, 2H), 3.25-3.42 (m, 2H), 3.09 (br s, 1H), 2.74-2.85 (m, 5H), 2.48-2.65 (m, 2H), 2.32 (s, 3H), 2.27 (br s, 3H), 2.14 (dq, 2H), 2.05 (s, 1H), 1.86 (br d, 2H), 1.41 (br s, 9H).

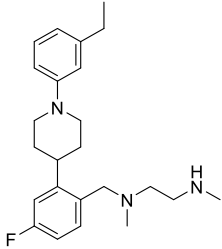
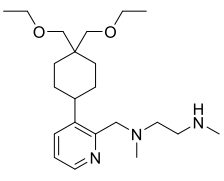
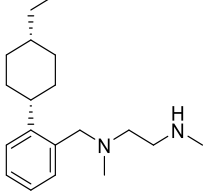
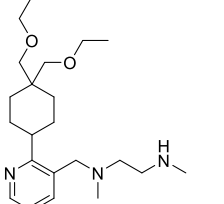
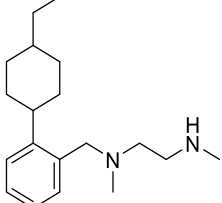
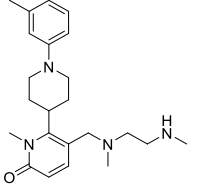
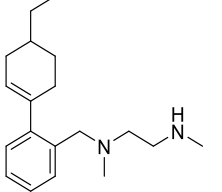
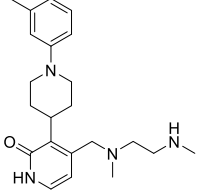
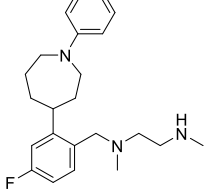
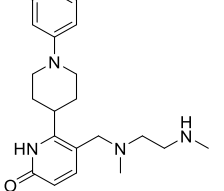
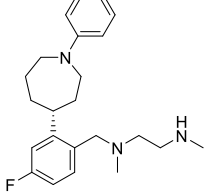
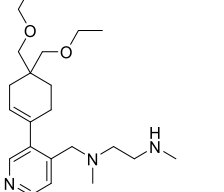
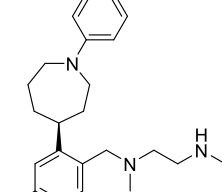
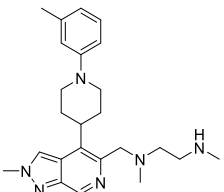
Step 6: To a compound tert-butyl (2-(((5-(bis(4-methoxybenzyl)amino)-3-(1-(m-tolyl)piperidin-4-yl)pyrazin-2-yl)methyl)(methyl)amino)ethyl)(methyl)carbamate (**13-6**) (56 g, 78.99 mmol) was added 300 mL of trifluoroacetic acid and then trifluoromethanesulfonic acid (30.0 g, 199.90 mmol, 17.65 mL), and the reaction solution was essentially complete after stirring at room temperature for 16 h. The reaction solution was then concentrated under reduced pressure, added with 1 liter of water and then 2 liters of ethyl acetate, and stirred until the solid was dissolved. After separation and extraction, the organic phase was extracted with 1M hydrochloric acid solution, and the aqueous phase was neutralized with 30% sodium hydroxide aqueous solution to pH 9, and then extracted with ethyl acetate; the organic phase was dried, concentrated, then purified by silica gel column chromatography to give compound N-((5-amino-3-(1-(m-tolyl)piperidin-4-yl)pyrazin-2-yl)methyl)-2-yl)methyl)-N,N'-dimethyl-1,2-ethylenediamine (**P292**, **Example 13**), as a white solid. LCMS: (ESI) m/z = 369.3

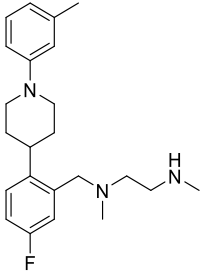
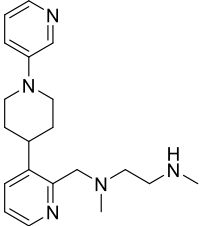
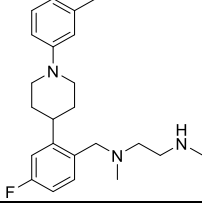
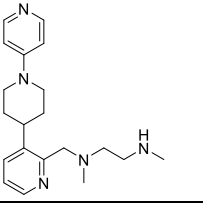
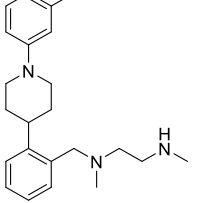
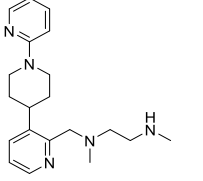
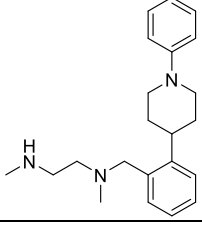
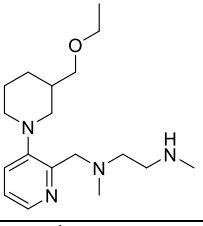
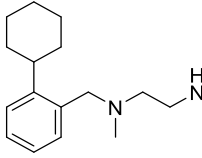
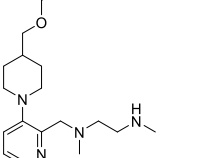
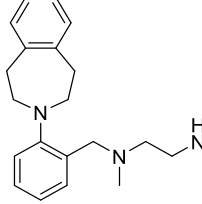
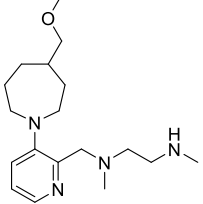
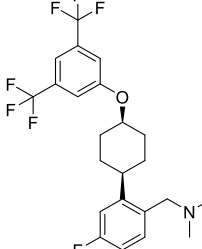
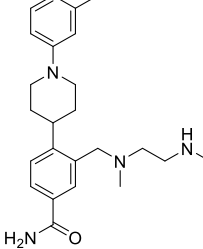
[M+H]⁺ ; ¹H NMR (400 MHz, methanol-d₄) δ (ppm) 7.90 (s, 1H), 7.62 (s, 1H), 7.56 (br d, 1H), 7.46 (t, 1H), 7.33 (d, 1H), 6.02 (s, 3H), 5.01 (br s, 25H), 4.50 (s, 2H), 3.88-3.99 (m, 2H), 3.74 (br d, 2H), 3.42-3.63 (m, 5H), 2.90 (s, 3H), 2.81 (s, 3H), 2.41-2.56 (m, 5H), 2.19-2.32 (m, 20H), 2.13 (br d, 3H).

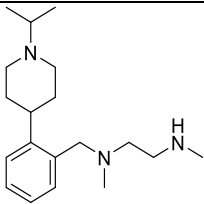
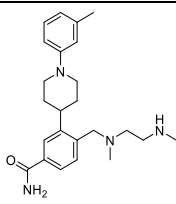
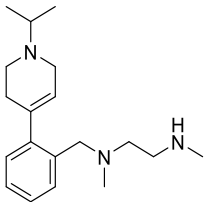
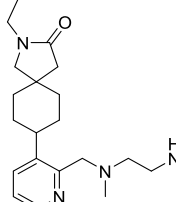
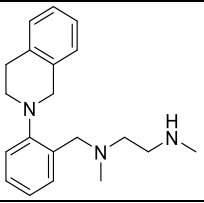
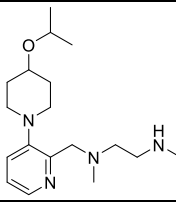
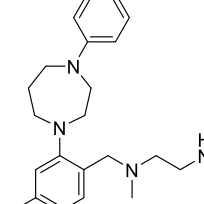
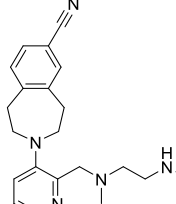
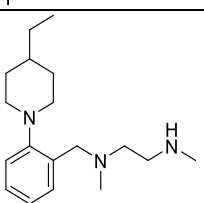
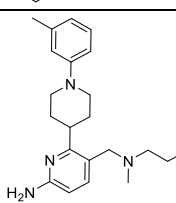
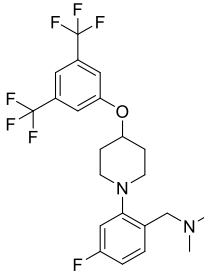
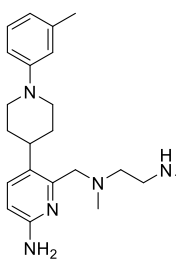
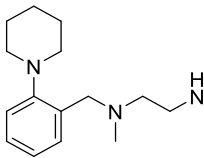
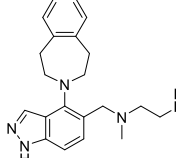
5 Similar methods as described above were used to synthesize the compounds P001-P448, the characterization data of which were shown in the right column:

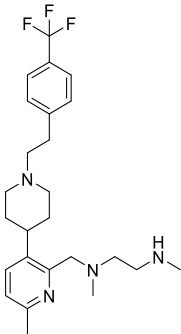
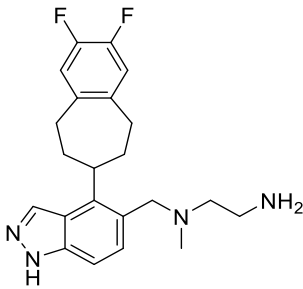
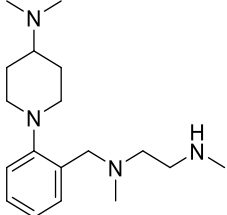
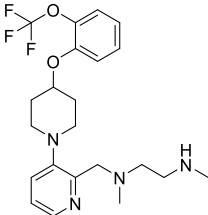
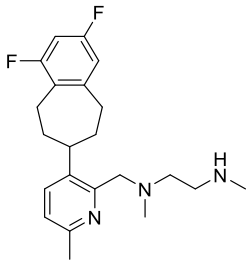
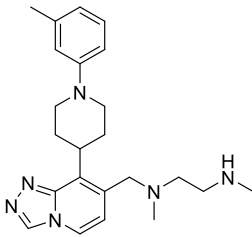
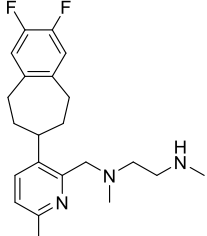
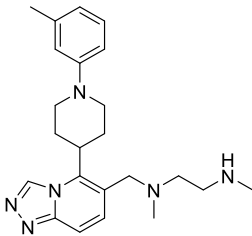
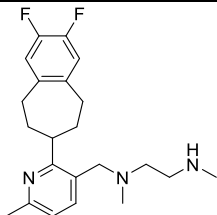
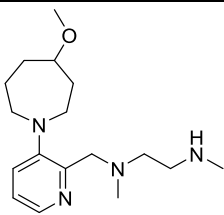
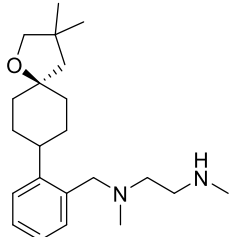
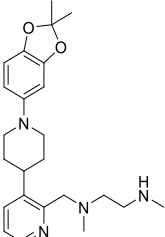
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P006		369.2	P200		364.3

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P009		377.2	P203		367.3
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P012		384.2	P206		378.2

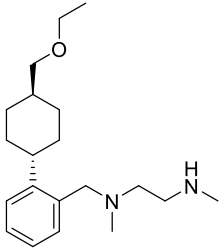
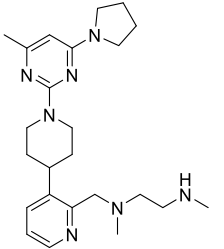
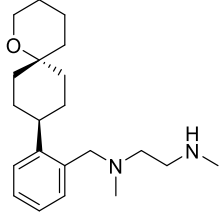
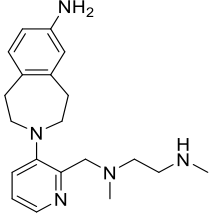
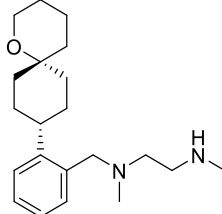
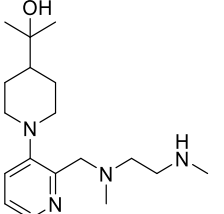
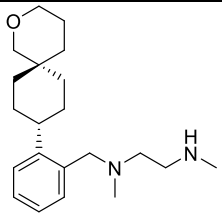
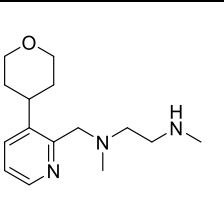
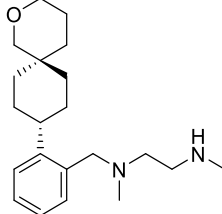
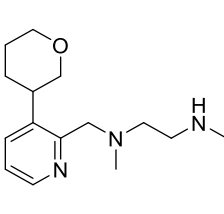
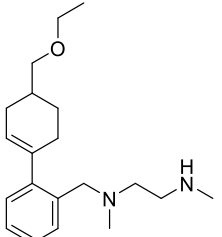
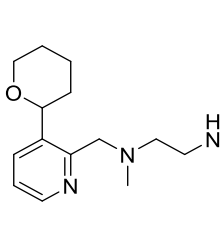
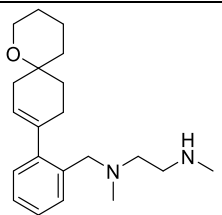
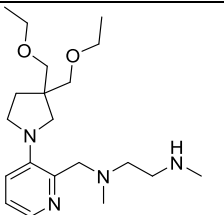
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P017		370.3	P211		369.2
P018		370.3	P212		376.1
P019		370.3	P213		

Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z	Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z
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P021		370.4	P215		340.2
P022		351.9	P216		340.3
P023		338.3	P217		321.0
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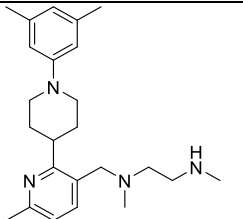
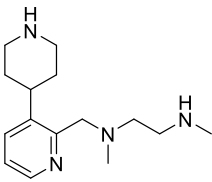
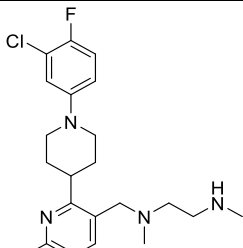
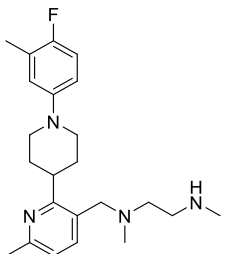
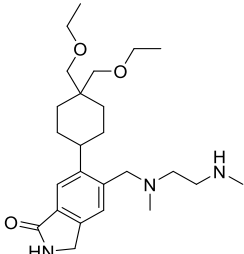
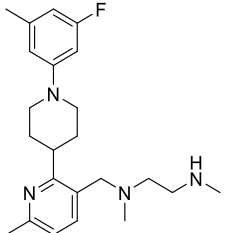
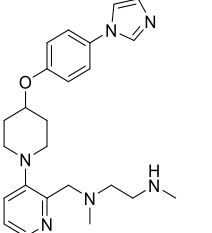
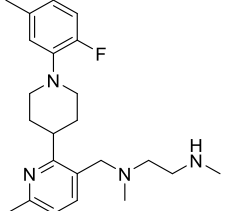
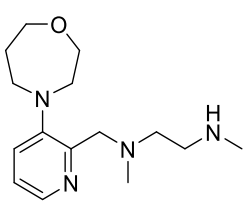
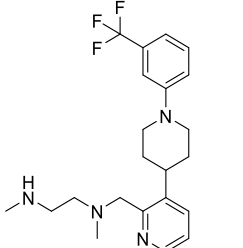
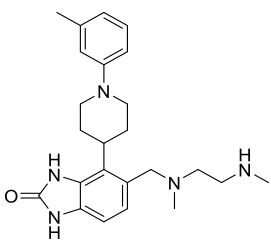
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P028		302.3	P222		359.4
P029		310.2	P224		320.9
P030		371.3	P225		350.3
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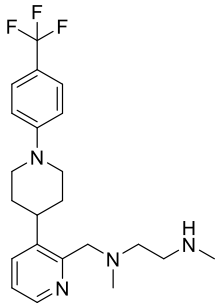
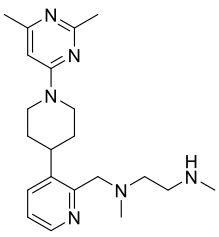
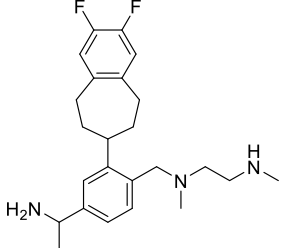
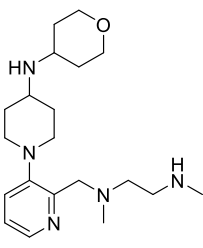
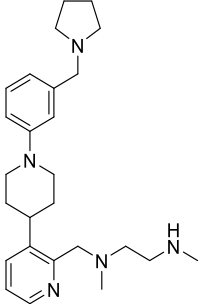
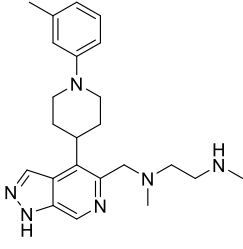
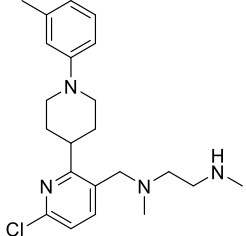
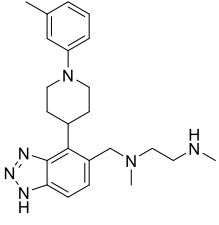
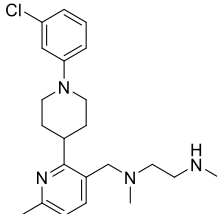
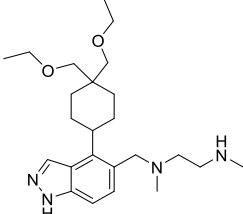
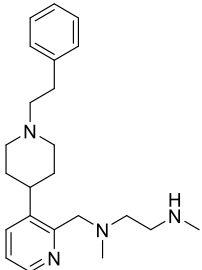
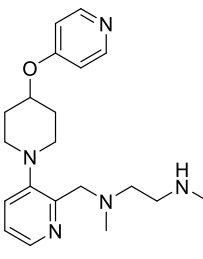
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P036		374.3	P231		
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P038		374.2	P233		306.9
P039		345.1	P234		411.4

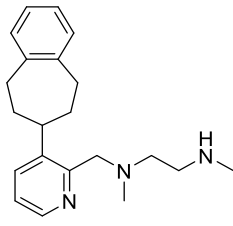
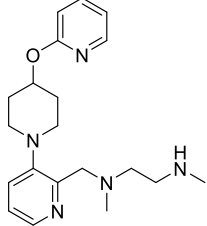
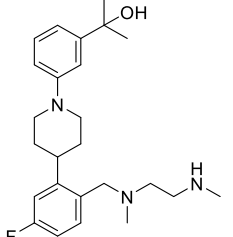
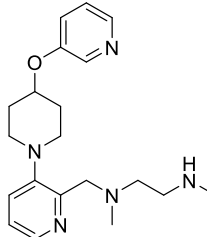
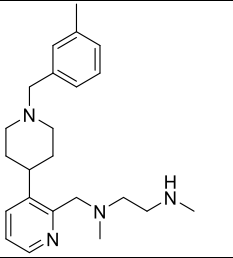
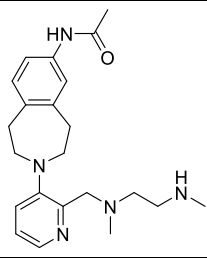
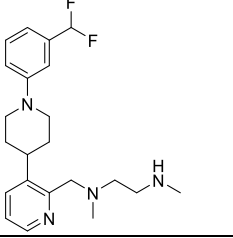
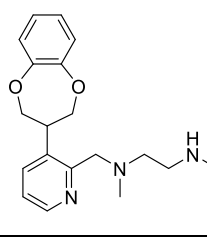
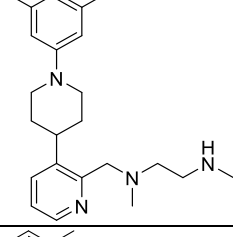
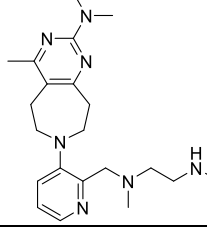
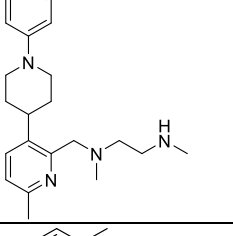
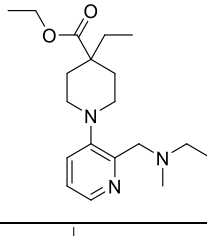
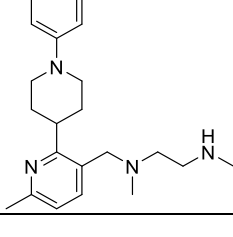
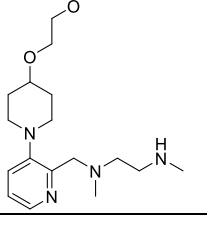
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P042		343.3	P236		379.3
P043			P237		
P044		395.3	P238		385.0
P046		403.3	P239		405.2
P047		401.3	P240		434.3
P048		319.3	P241		

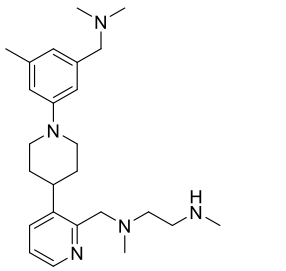
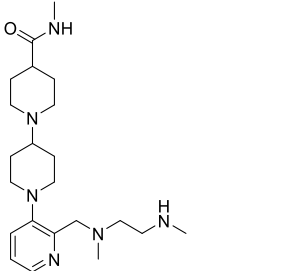
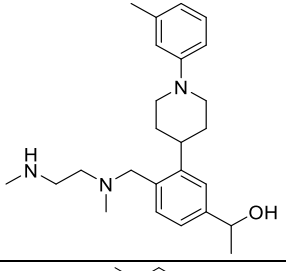
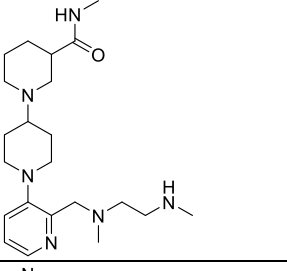
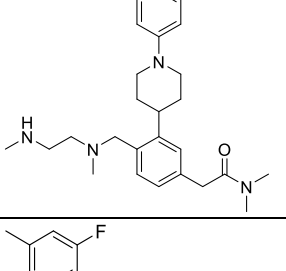
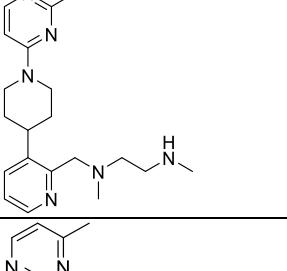
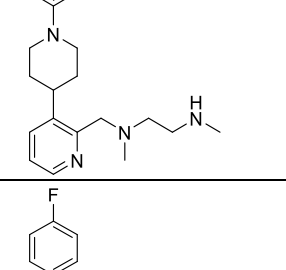
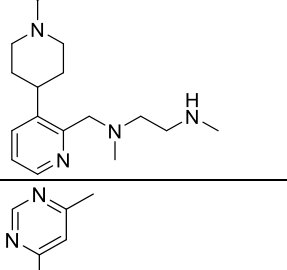
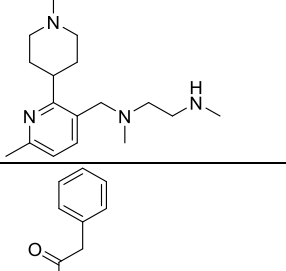
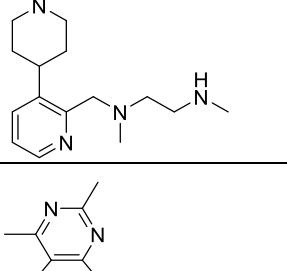
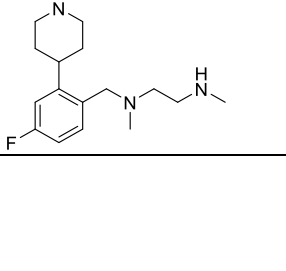
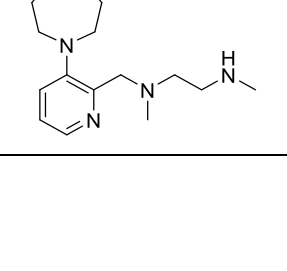
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P050		331.1	P243		340.3
P051		331.1	P244		320.9
P052		331.1	P245		264.2
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P054		317.1	P247		264.2
P055		329.1	P248		365.0

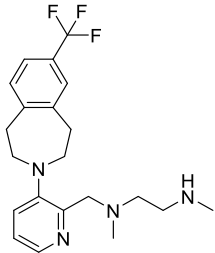
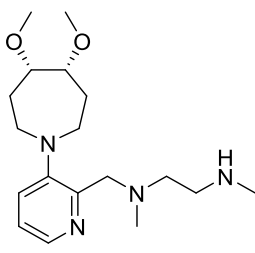
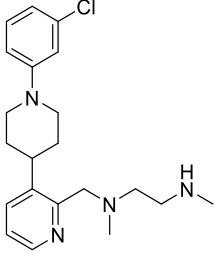
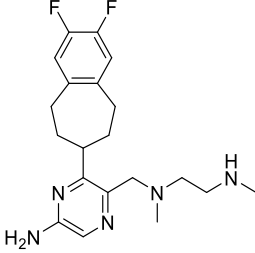
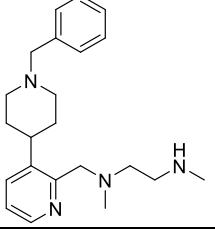
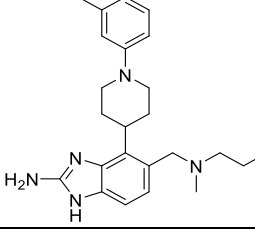
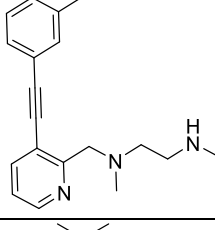
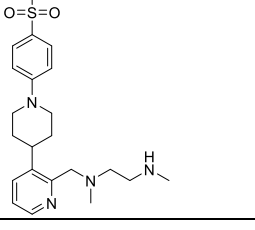
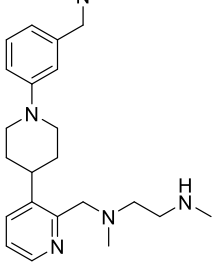
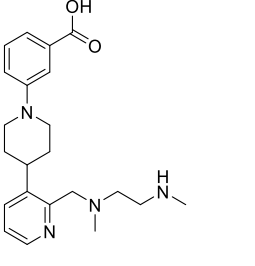
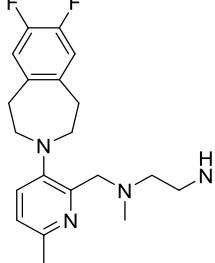
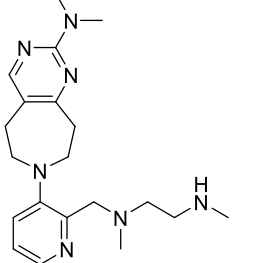
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P058		401.3	P251		410.0
P059		381.0	P252		410.3
P060		317.1	P253		
P061		403.3	P254		396.3
P062		403.3	P255		396.3

Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z	Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z
P063		381.3	P256		363.3
P064		405.3			
P065		385.2	P258		432.4
P066		385.3	P259		421.3
P067		385.2	P260		278.9
P068		407.0	P261		408.3

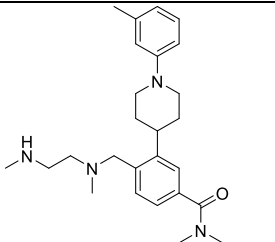
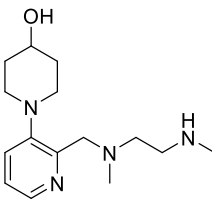
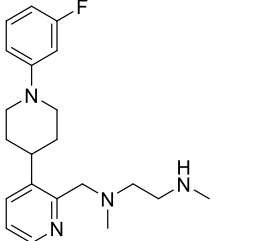
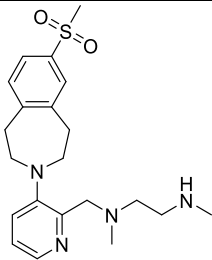
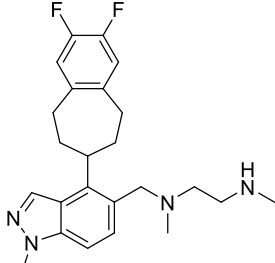
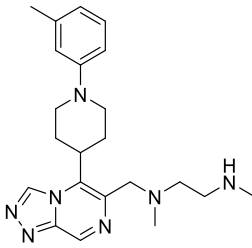
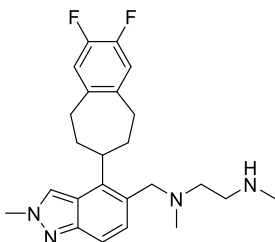
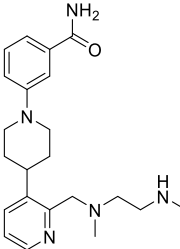
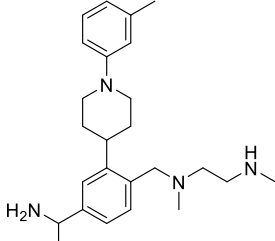
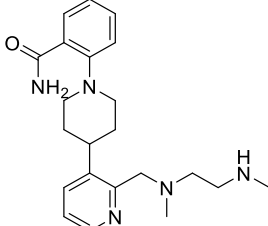
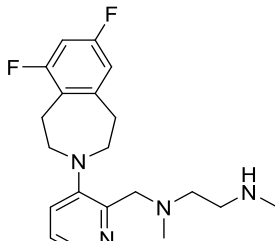
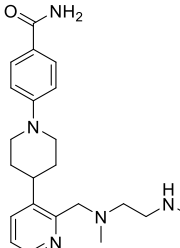
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P070		402.2	P263		362.2
P071		422.4	P264		
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P074		367.4	P267		356.3

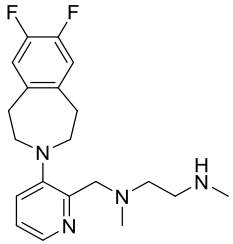
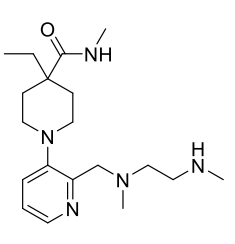
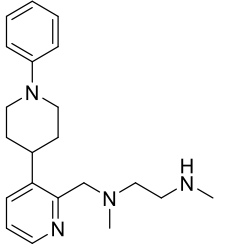
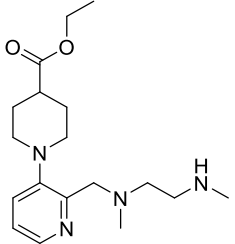
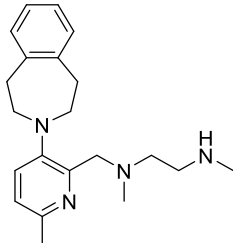
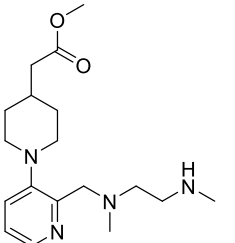
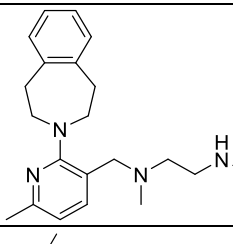
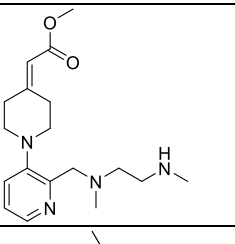
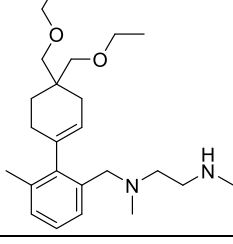
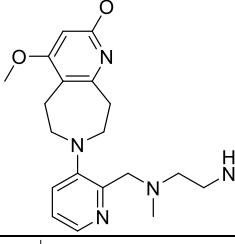
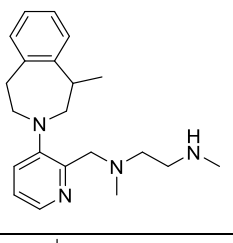
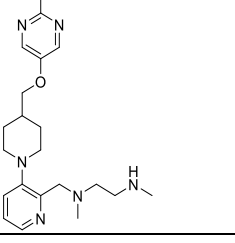
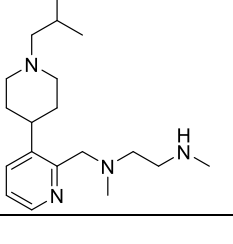
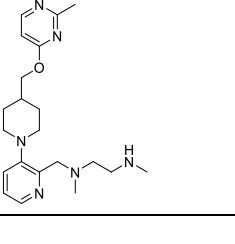
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P076		414.3	P269		356.3
P077		367.1	P270		382.3
P078		389.0	P271		327.9
P079		367.4	P272		384.3
P080		367.3	P273		363.0
P081		367.3	P274		337.1

Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z	Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z
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P083		396.3	P276		403.4
P084		437.3	P277		355.3
P085		371.2	P278		354.9
P086		371.3	P279		355.3
P087		398.3	P280		355.2

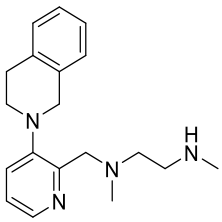
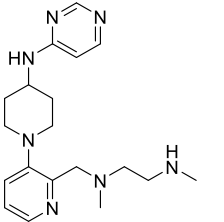
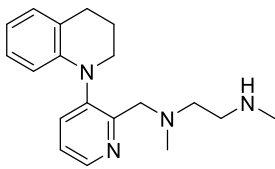
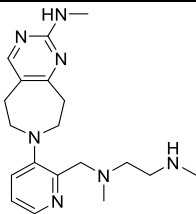
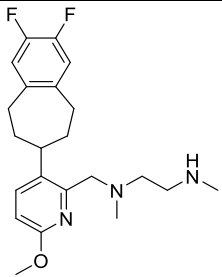
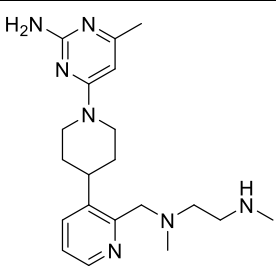
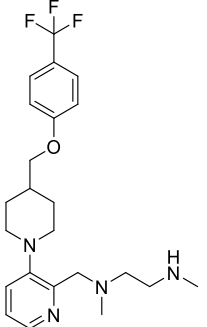
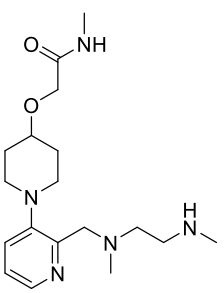
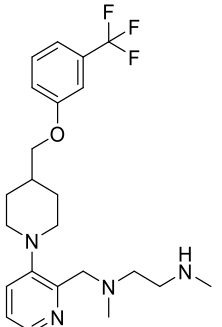
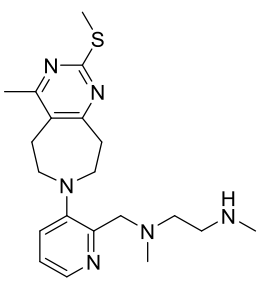
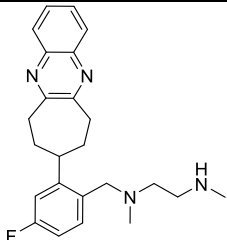
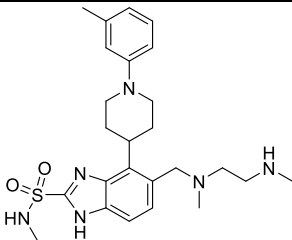
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P089		372.9	P282		
P090		353.3	P283		
P091		293.9	P284		417.0
P092		396.4	P285		383.3
P093		374.9	P286		370.3

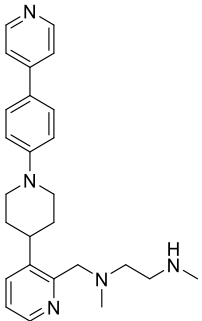
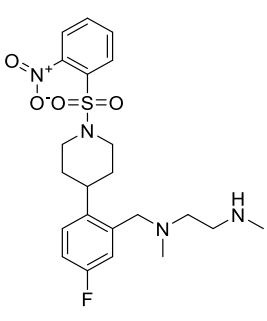
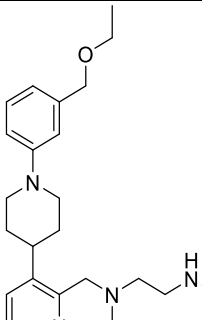
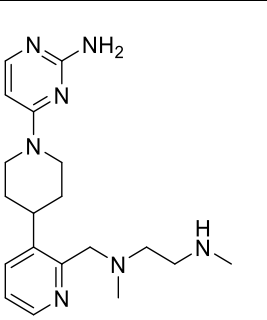
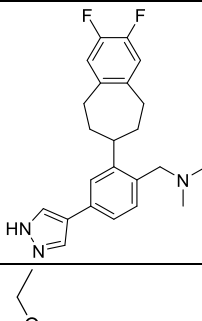
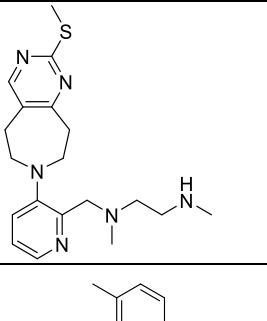
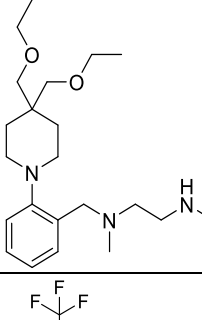
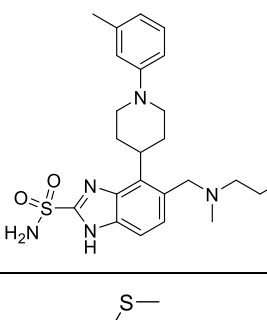
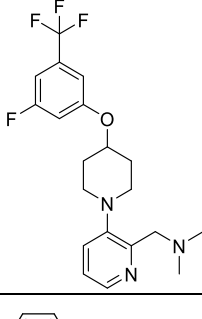
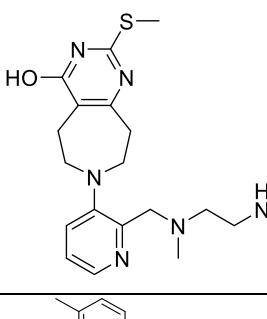
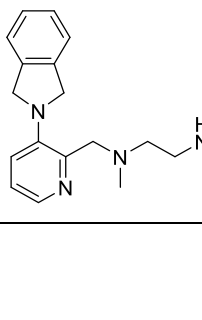
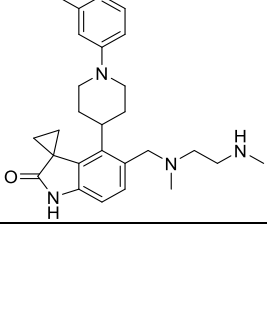
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P095		353.3	P288		341.3
P096		353.3	P289		341.3
P097		353.2	P290		340.9
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P100		423.2	P293		393.3

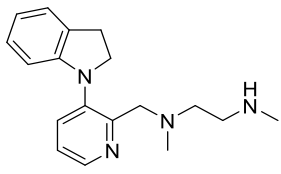
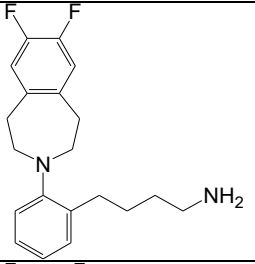
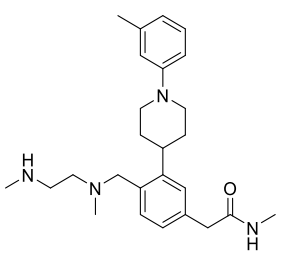
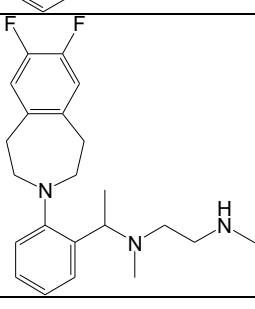
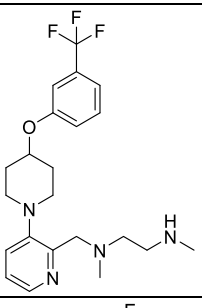
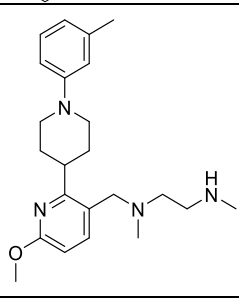
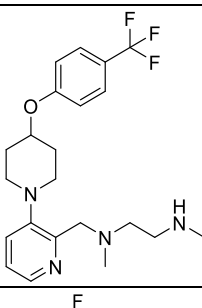
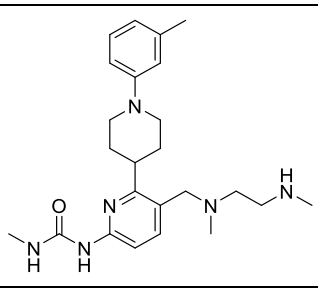
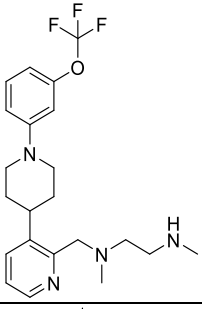
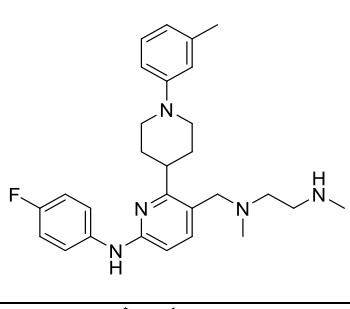
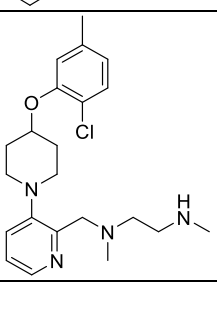
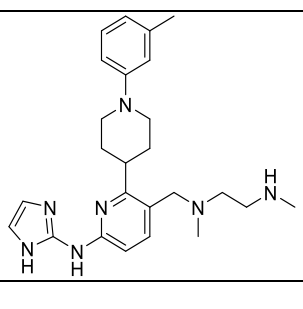
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P102		357.0	P295		403.2
P103		413.4	P296		
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P105		395.3	P298		382.0
P106		361.0	P299		382.0

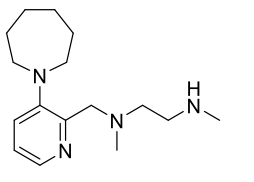
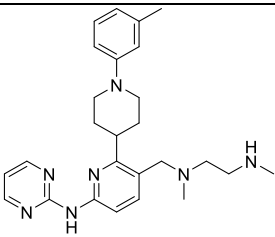
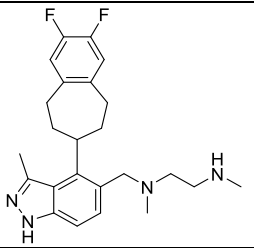
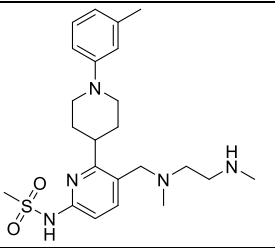
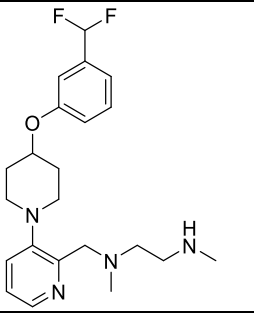
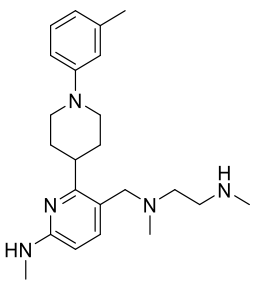
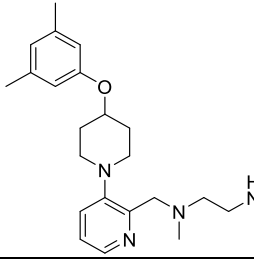
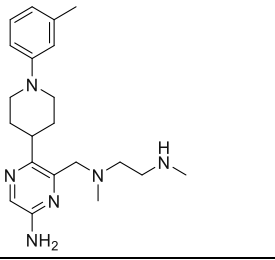
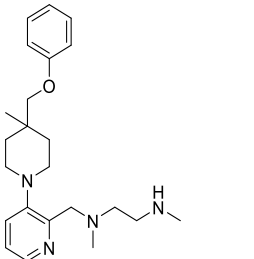
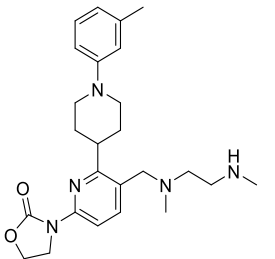
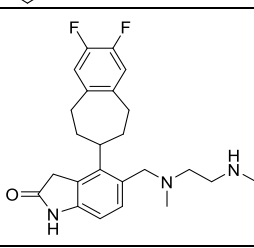
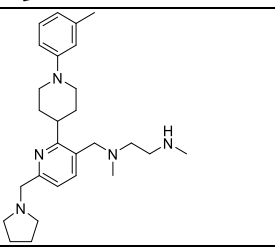
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P108		339.3	P301		335.0
P109		339.2	P302		335.0
P110		339.3	P303		333.2
P111		389.3	P304		386.0
P112		339.3	P305		385.0
P113		319.3	P306		385.3

Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z	Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z
P114		377.2	P307		368.3
P115		368.3	P308		
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P118		325.3	P311		
P119		337.0	P312		

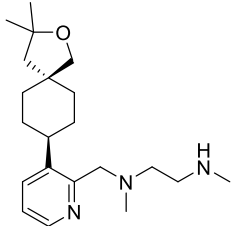
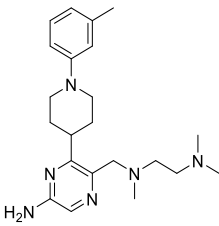
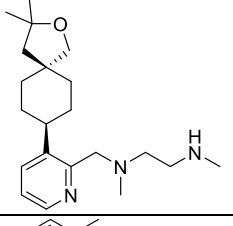
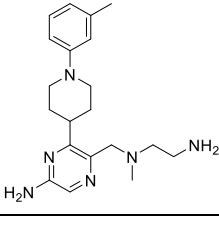
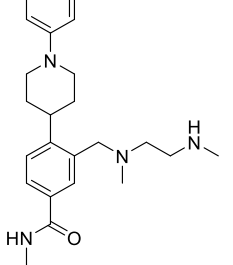
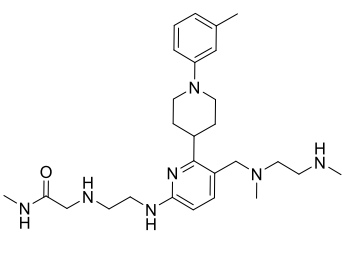
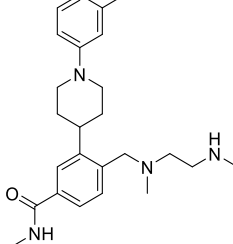
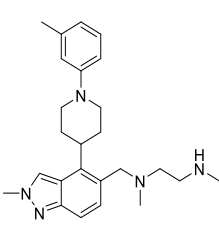
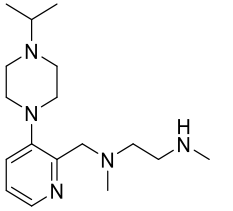
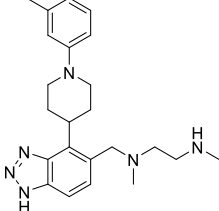
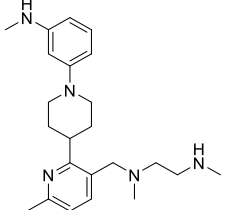
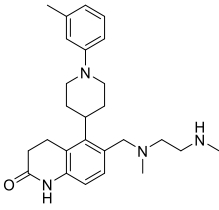
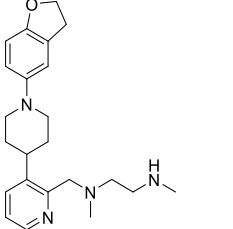
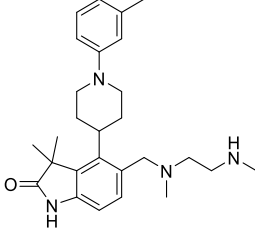
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P128		311.3	P320		356.2
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P132		393.1	P324		

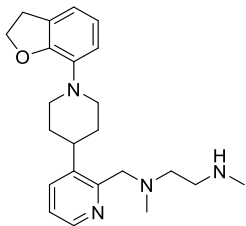
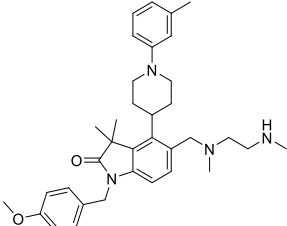
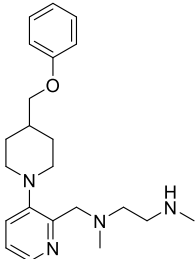
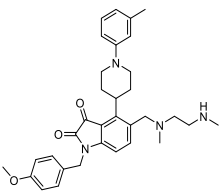
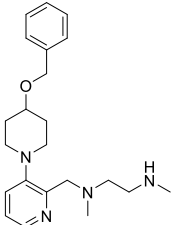
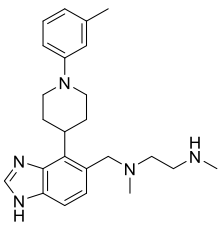
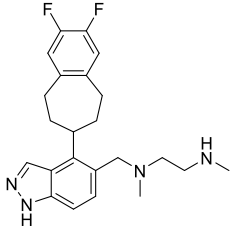
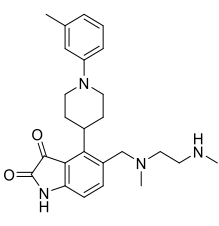
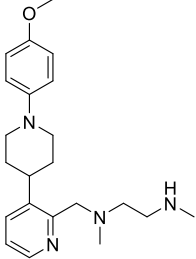
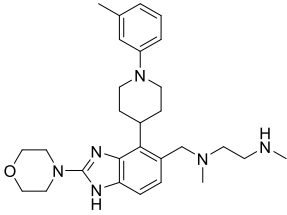
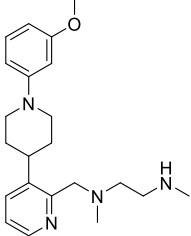
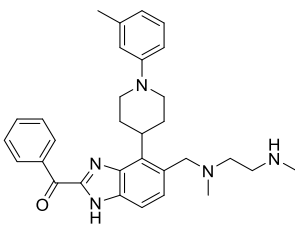
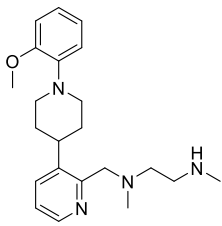
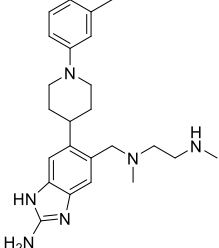
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P134		397.0	P326		356.2
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P138		297.2	P330		

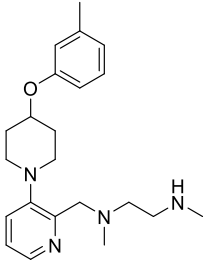
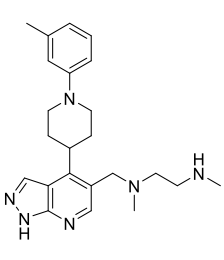
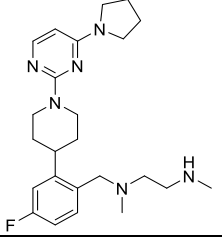
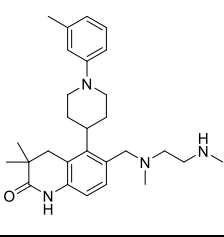
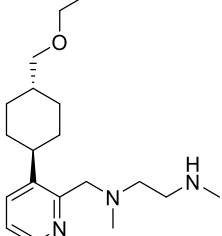
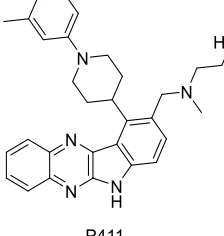
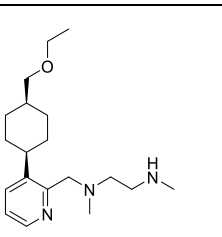
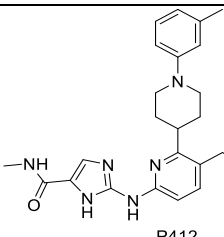
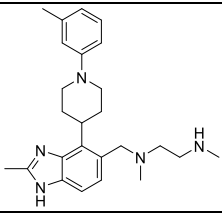
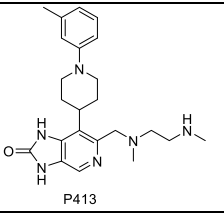
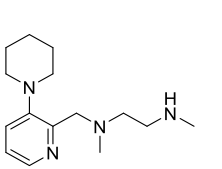
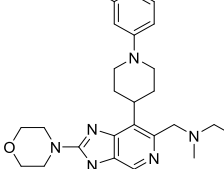
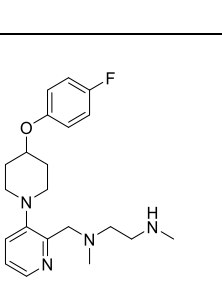
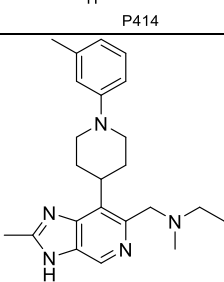
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P140		423.3	P351		374.2
P141		423.4	P352		383.4
P142		423.3	P353		425.3
P143		423.3	P354		462.3
P144		403.3	P355		434.3

Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z	Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z
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P146		413.4	P357		446.3
P147		405.4	P358		382.3
P148		383.0	P359		369.2
P149		383.0	P360		438.2
P150			P361		436.4

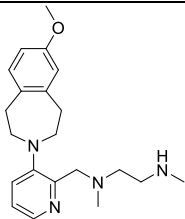
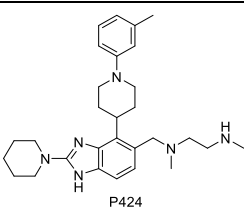
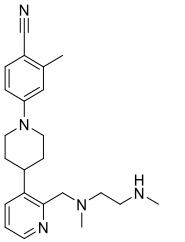
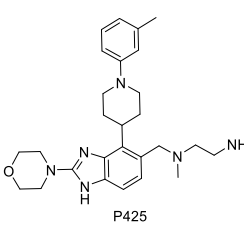
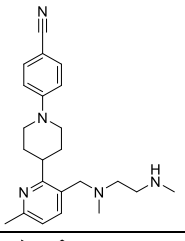
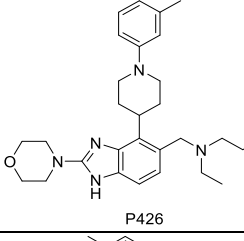
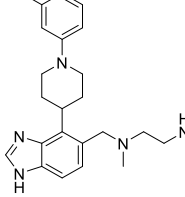
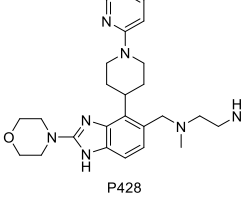
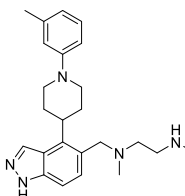
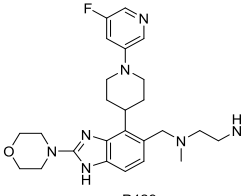
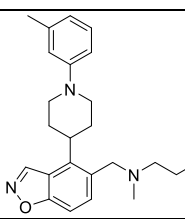
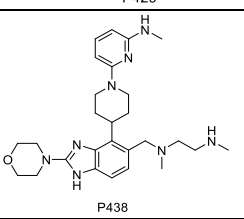
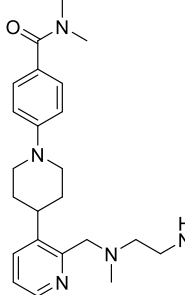
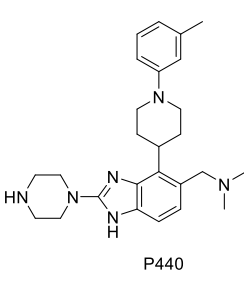
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P152		277.2	P363		439.4
P153		418.2	P364		412.3
P154		418.3	P365		475.4
P155		421.3	P366		484.3
P156			P367		506.5

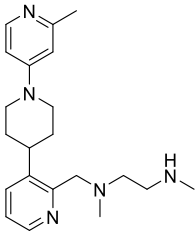
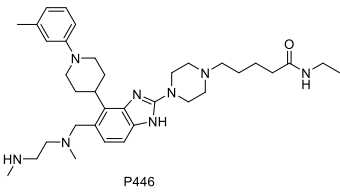
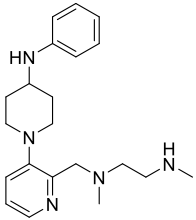
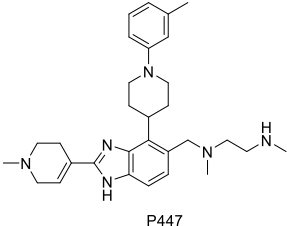
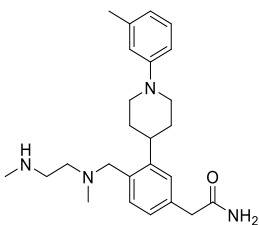
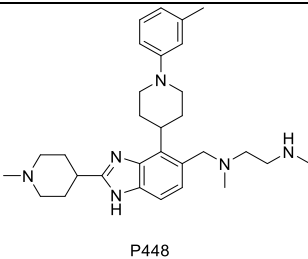
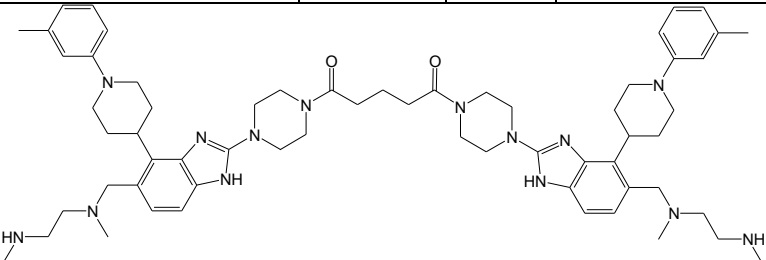
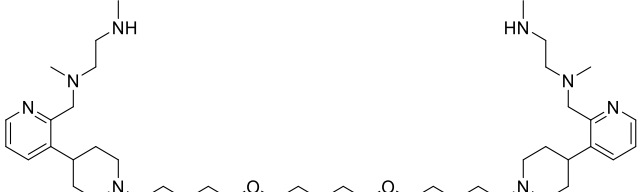
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P157		346.0	P368		383.3
P158		346.1	P369		355.2
P159		409.3	P400		482.4
P160		409.2	P401		406.3
P161		306.3	P265		393.2
P162		382.2	P155		421.4
P163		381.3	P402		435.3

Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z	Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z
P164		381.2	P403		555.4
P165		369.2	P404		541.3
P166		369.0	P189		392.4
P167		399.2	P405		421.3
P168		369.2	P406		477.3
P169		369.2	P407		496.4
P170		369.3	P408		407.2

Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z	Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z
P171		368.9	P409		393.2
P172		427.3	P410		449.3
P173		320.3	P411	 P411	494.3
P174		320.4	P412	 P412	491.3
P176		406.4	P413	 P413	409.3
P177		263.0	P414	 P414	478.3
P178		373.3	P415	 P415	407.3

Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z	Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z
P179		372.9	P416		460.3
P180		407.3	P418		484.4
P181		377.1	P419		502.4
P182		349.0	P420		484.4
P183		410.3	P421		476.4
P184		481.1	P422		474.4
P185		355.3	P423		490.4

Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z	Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z
P186		355.3	P424		475.4
P187		378.0	P425		463.3
P188		378.2	P426		491.4
P189		392.3	P428		478.4
P190		392.2	P429		482.3
P191			P438		493.4
P192		410.3	P440		476.4

Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z	Patent_ ID	Structure	[M+H] ⁺ (ESI) m/z
P193		354.3	P446		603.4
P194		354.4	P447		487.3
P195		409.3	P448		489.4
P442					1047.7
P257					771.8

Biological Test Example

Test Example 1: PRMT1 Enzyme Activity Test Methods

PRMT1 enzyme activity test were performed in a buffer prepared on the same day consisting of 10 mM Tris-HCl (pH = 8.0), 0.01% Tween-20 and 1 mM DTT. The compounds were prepared to the highest inhibitor concentration ultimately required in the 100X reaction with 100% DMSO and then transferred to one well of a 384-well Echo plate (Echo-eligible 384-well polypropylene microplates 2.0, transparent, flat-bottomed) and sequentially diluted in the next well with a 3-fold dilution of 100% DMSO, and so on, with a total of 10 concentrations based on Precision. 100% DMSO was added to two empty wells to serve as control well without compound and control well without enzyme in the same 384-well Echo plate. 250 nL of compound was transferred from each well of the 384-well Echo plate to a

384-well assay plate (384-well polypropylene storage microplate) via the Echo 550 liquid processor. For wells with compounds and control well without compound, a mixture (15 uL) containing PRMT1 enzyme was added to the 384-well assay plate. For control wells without enzyme, the mixture containing the assay buffer (15uL) was added instead. The compounds were allowed to incubate with PRMT1 for 15 minutes at room temperature, and then a mixture containing ³H-SAM and peptide (10uL) was added to start the reaction (final volume = 25uL). The final concentrations of the components were as follows: 0.5 nM for PRMT1, 0.25 uM for ³H-SAM, 0.1 uM for the peptide, and 1% DMSO. After 120 min of incubation, the assay was terminated by the addition of non-radiolabeled SAM (5 uL) to a final concentration of 125 uM, which diluted ³H-SAM to a level at which its incorporation into the peptide substrate was no longer detected. 25 µL of the reaction solution from the 384-well assay plate was then transferred to a 384-well detection plate (Streptavidin FlashPlate HTS PLUS, high volume, 384 wells). The biotinylated peptide was allowed to bind to the surface of the antibiotic protein streptavidin for at least 60 minutes at room temperature. The Flashplate was then washed three times with 0.1% Tween-20 in a BioTek plate washer. Plates were read on a microplate counter (MicroBeta2) to measure the amount of ³H-labeled peptide bound to the surface of the detection plate, measured in counts per minute (cpm).

Curve Fitting:

The raw data were copied from the Reader and the inhibition values were calculated in Excel by Equation (1), Equation (1): $\text{Inh \%} = (\text{CPMmax} - \text{CPMcmpd}) / (\text{CPMmax} - \text{CPMmin}) * 100$, wherein the Max signal was obtained from the enzyme-substrate interaction and the Min signal was obtained from the substrate. IC50 values were obtained by fitting the data through equation (2) using XLFit add-in for Excel version 45.4.0.8. Equation (2): $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + ((\text{IC50}/X)^{\text{HillSlope}}))$, wherein, Y represents inhibition percentage and X represents compound concentration.

Test Example 2:

Toledo Cell Proliferation Inhibition Assay Method

A. Purpose: to determine the effects of compounds on Toledo cells through a six-day cell proliferation assay.

B. Reagents and materials:

1. Cell culture medium: RPMI 1640 + 10% FBS
2. 384-well cell culture plate (Corning, item #3764)
3. 0.4% Taipan Blue Staining Solution (Thermo Fisher, item #T10282)
4. cell counting plate (Thermo Fisher, item #C10228)
5. 50ml reagent reservoir (Corning, item #4870)
6. 50 ml conical sterile polypropylene centrifuge tube (Thermo Fisher, item #339653)
7. Automatic cell counter (Thermo Fisher, item # AMQAX1000)
8. CellTiter-Glo Luminescent Cell Viability Detection Reagent (Promega, item #G7572)
9. SpectraMax i3x Multi-Mode Enzyme Labeling Instrument (MegaMan Molecular Instruments, item #5024062)

C. Experimental method

1. Resuspending the cells with a pipette.
2. 0.4% Taipan blue staining solution and Toledo cells were mixed in equal proportion, and the cells were counted using an automatic cell counter.
3. Toledo cells were diluted to a final concentration of 2000 cells per well and transferred to a 50 ml reagent reservoir.
4. Diluted Toledo cells were added to a 384-well cell culture plate, 40ul per well.
5. The cells were shortly centrifuged and settled.
6. The cells were incubated in a 37°C, 5% CO₂ cell culture incubator.
7. The substrate in the CellTiter-Glo Luminescent Cell Viability Detection Reagent was mixed with the solution.
8. After six days, the 384-well cell culture plate was taken from the incubator and 20 ul of configured CellTiter-Glo reagent was added to each well.
9. 384-well cell culture plate was mixed in an orbital shaker for 30 minutes.
10. Signal of luminescence was detected with a SpectraMax i3x multi-mode enzyme labeling instrument.

MV-4-11 cell proliferation inhibition assay method

Similar to the Toledo cell proliferation inhibition assay method, the difference was that MV-4-11 cells were used and the cell culture medium was IMDM + 10% FBS; in step 3 of the assay method 250 cells per well was used instead;

The results were shown in the following table.

Among them, the results of PRMT1 enzyme activity experiments were as follows:

A represents $IC_{50} < 50 \text{ nM}$;

B represents $50 \text{ nM} \leq IC_{50} < 500 \text{ nM}$; and

C represents $IC_{50} \geq 500 \text{ nM}$

Results of Toledo and MV-4-11 cell proliferation inhibition assay:

A represents $IC_{50} < 1 \text{ }\mu\text{M}$;

B represents $1 \text{ }\mu\text{M} \leq IC_{50} < 5 \text{ }\mu\text{M}$;

C represents $IC_{50} \geq 5 \text{ }\mu\text{M}$

The results of PRMT1 enzyme activity test, and Toledo and MV-4-11 cell proliferation inhibition assay were shown in the table below:

Patent_ID	PRMT1 IC ₅₀	Toledo cell proliferation inhibition IC ₅₀	MV-4-11 cell proliferation inhibition IC ₅₀	Patent_ID	PRMT1 IC ₅₀	Toledo cell proliferation inhibition IC ₅₀	MV-4-11 cell proliferation inhibition IC ₅₀
P001	A	A		P187	A	A	
P002	A			P188	A	B	
P003	A	A		P189	A	A	
P005	A	A		P190	A	A	
P006	A	B		P192	A	C	

Patent _ID	PRMT1 IC ₅₀	Toledo cell proliferation inhibition IC ₅₀	MV-4-11 cell proliferation inhibition IC ₅₀	Patent_ ID	PRMT1 IC ₅₀	Toledo cell proliferation inhibition IC ₅₀	MV-4-11 cell proliferation inhibition IC ₅₀
P007	A	A		P193	A	B	
P008	A	A		P194	A	B	
P009	A	A		P195	A	A	
P010	A	B		P196	A	A	
P011	A	A		P197	C	C	
P012	A	A		P198	A	A	
P013	A	B		P199	A	A	
P014	A	A		P200	A	B	
P015	A	A		P201	A	A	
P016	A	A		P202	A	A	
P017	A	B		P203	B	C	
P020	A	A		P204	A		
P021	A	A		P205	B	B	
P022	A	A		P206	B	B	
P023	A	A		P207	A	A	
P024	A	A		P208	A	A	
P025	A	A		P210	B		A
P026	C			P211	B		
P027	A	B		P212	B	C	
P028	A	C		P214	A	B	
P029	A			P215	A	B	
P030	A	C		P216	A	B	
P031	A	B		P217	B	B	
P032	C			P218	A	B	
P033	A	B		P219	A	B	
P034	A	A		P220	B		
P035	B	C		P221	A	A	
P036	A	A		P222	A	C	
P037	A	A		P224	A	B	
P038	A	A		P225	A	A	
P039	A	A		P226	A	A	
P040	A	A		P227	A	A	
P041	A			P228	A	A	
P042	A	A		P230	A	A	
P044	A	A		P232	B		
P046	A	B		P233	A	C	

Patent _ID	PRMT1 IC ₅₀	Toledo cell proliferation inhibition IC ₅₀	MV-4-11 cell proliferation inhibition IC ₅₀	Patent_ ID	PRMT1 IC ₅₀	Toledo cell proliferation inhibition IC ₅₀	MV-4-11 cell proliferation inhibition IC ₅₀
P047	A	B		P234	B	B	
P048	A	A		P235	A		
P049	A	A		P236	A	A	
P050	A	A		P238	A	A	
P051	A	A		P239	A	B	
P052	A	A		P240	A	A	
P053	A	A		P242	A	A	
P054	A	A		P243	A	A	
P055	A	B		P244	A		
P056	A	A		P245	A		
P057	A	A		P246	C		
P058	A	A		P247	B		
P059	A	B		P248	B	B	
P060	A	A		P250	A	A	
P061	A	A		P251	A	A	
P062	A			P252	A	A	
P063	A	A		P254	B	C	
P064	A	A		P255	A	B	
P065	A	A		P256	A		
P066	A	A		P257	A		
P067	A	A		P258	A	A	
P068	A	B		P259	A	B	
P069	A	A		P260	A	B	
P070	A	A		P261			A
P071	A	B		P262	A	B	
P072	A	A		P263	C	C	
P073	A	A		P265	A		
P074	A	A		P266	A	A	
P075	A	A		P267	A	B	
P076	A	B		P268	A	B	
P077	A	B		P269	A	B	
P078	A	A		P270	A	B	
P079	A	A		P271	A	B	
P080	B	A		P272	B	B	
P081	A	A		P273	A	B	
P082	A	B		P274	A		

Patent _ID	PRMT1 IC ₅₀	Toledo cell proliferation inhibition IC ₅₀	MV-4-11 cell proliferation inhibition IC ₅₀	Patent_ ID	PRMT1 IC ₅₀	Toledo cell proliferation inhibition IC ₅₀	MV-4-11 cell proliferation inhibition IC ₅₀
P083	A	A		P275	C	C	
P084	A	A		P276	C	C	
P085	A	A		P277	A	A	
P086	A	B		P278	A	B	
P087	A	B		P279	A	B	
P088	A	A		P280	A	C	
P089	A	A		P281	B	C	
P090	A	A		P282			
P091	C			P283			
P092	A	A		P284	A	B	
P093	A	A		P285	C	C	
P094	A	A		P286	A	B	
P095	A	A		P287	A	A	
P096	A	B		P288	A	B	
P097	A	B		P289	A		
P098	A	A		P290	A	B	
P099	A	B		P291	A	C	
P100	C	C		P292	A	A	
P101	B	B		P293	B	A	
P102	A	A		P294	A		
P103	A	A		P295	A		
P104	A	A		P297	A	C	
P105	A	A		P298	A	B	
P106	A	A		P299	A		
P107	A	A		P300	B	C	
P108	A	A		P301	A	B	
P109	A	A		P302	A	B	
P110	A	A		P303	A	B	
P111	A	A		P304	A	B	
P112	A	A		P305	A	A	
P113	A	A		P306	B	B	
P114	A	A		P307	A		
P115	A	B		P313	A	B	
P116	A	B		P314	A	C	
P117	A	A		P315	C	C	
P118	A	A		P318	A	C	

Patent _ID	PRMT1 IC ₅₀	Toledo cell proliferation inhibition IC ₅₀	MV-4-11 cell proliferation inhibition IC ₅₀	Patent_ ID	PRMT1 IC ₅₀	Toledo cell proliferation inhibition IC ₅₀	MV-4-11 cell proliferation inhibition IC ₅₀
P119	C	B		P319	A	C	
P120	A	B		P320	A	C	
P122	B	A		P321	A	B	
P123	A	B		P322	A		
P124	C	B		P323	A	A	
P125	A	A		P325	A	A	
P126	A	B		P326	A	B	
P127	A	B		P327	A	A	
P128	C	C		P329	B	C	
P129	A	B		P350	C		
P130	A	A		P351	B		
P131	A	A		P352	B		
P132	A	A		P353	A		
P133	A	A		P354	B		
P134	A	B		P355	A		
P135	A	A		P356	B		
P136	A	A		P357	B		
P137	A	A		P358	A		
P138	A			P359	B		
P139	B	C		P360	B		
P140	A	A		P361	A		
P141	A	A		P362	B		
P142	A	A		P363	B		
P143	A	A		P364	A		
P144	A	A		P365	B		
P145	A	B		P366	A		
P146	A	A		P367	A		
P147	A	A		P368	B		
P148	A	A		P369	A		
P149	A	A		P400			A
P151	A	B		P401	A		A
P152	A			P402	B		B
P153	A	A		P403	C		B
P154	A			P404	B		A
P155	A	A		P405	A		A
P157	A	A		P406	A		A

Patent _ID	PRMT1 IC ₅₀	Toledo cell proliferation inhibition IC ₅₀	MV-4-11 cell proliferation inhibition IC ₅₀	Patent_ ID	PRMT1 IC ₅₀	Toledo cell proliferation inhibition IC ₅₀	MV-4-11 cell proliferation inhibition IC ₅₀
P158	A	A		P407	B		A
P159	C	C		P408			C
P160	A	A		P409	B		A
P161	A	A		P410			A
P162	B	A		P411			
P163	A	A		P412			
P164	A	B		P413			A
P165	A	A		P414			A
P166	A	A		P415			A
P167	A	A		P416			A
P168	A	B		P418			A
P169	A	A		P419			A
P170	A	A		P420			A
P171	A	A		P421			A
P172	A	A		P422			A
P173	A	A		P423			A
P174	A	B		P424			A
P176	A	A		P425			A
P177	A	B		P426			A
P178	A	A		P428			A
P179	A	A		P429			A
P180	A	A		P438			
P181	A	B		P440			A
P182	A	A		P442			A
P183	A	A		P446			A
P184	B	A		P447			A
P185	A	A		P448			A
P186	A	A					

Test example 3 PRMT panel selectivity test

PRMT1 was tested as described in Test Example 1, and PRMT5 and PRMT7 tests and curve fitting were performed with optimized parameters with reference to PRMT1 test and data processing methods. PRMT3 was tested as follows:

PRMT3 test method:

This experiment was assayed in a buffer prepared on the same day consisting of 10 mM Tris-HCl (pH = 8.0), 0.01% Tween-20 and 1 mM DTT. The compounds were prepared to

the highest inhibitor concentration ultimately required in the 100X reaction with 100% DMSO and then transferred to one well of a 384-well Echo plate (Echo-eligible 384-well polypropylene microplates 2.0, transparent, flat-bottomed) and sequentially diluted in the next well with a 3-fold dilution of 100% DMSO, and so on, with a total of 10 concentrations based on Precision. 100% DMSO was added to two empty wells as control well without compound and control well without enzyme in the same 384-well Echo plate. 100 nL of compound was transferred from each well of the 384-well Echo plate to a 384-well assay plate (OptiPlate (384-well, white)) via the Echo 550 liquid processor. For wells with compounds and control well without compound, a mixture containing PRMT1 enzyme (5 uL) was added to the 384-well assay plate. For control well without enzyme, a mixture containing test buffer (5uL) was added instead. The compounds were allowed to incubate with PRMT3 for 15 minutes at room temperature, and then a mixture containing cold SAM and peptide (5uL) was added to start the reaction (final volume = 10uL). The final concentrations of the components were as follows: 0.1 nM for PRMT3, 15 uM for SAM, 0.05 uM for peptide, and 1% DMSO. After 60 min of incubation at room temperature, the reaction was terminated by the addition of donor and acceptor magnetic beads (15 uL) with a final concentration of 10ug/mL diluted with AlphaLISA Epigenetics Buffer. The 384-well assay plate was incubated at room temperature for 60 min and the relative fluorescence units (RFU) were nextly determined using a multi-mode plate reader in Alpha mode (Ex680/Em615).

Curve fitting: the raw data were copied from Reader and the inhibition values were calculated in Excel by equation (1). Equation (1): $\text{Inh \%} = (\text{RFU}_{\text{max}} - \text{RFU}_{\text{cmpd}}) / (\text{RFU}_{\text{max}} - \text{RFU}_{\text{min}}) * 100$, wherein, the Max signal was obtained from the enzyme-substrate interaction and the Min signal was obtained from the substrate. IC₅₀ values were obtained by fitting the data through equation (2) using XLFit add-in for Excel version 45.4.0.8. Equation (2): $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + ((\text{IC}_{50}/X)^{\text{HillSlope}}))$, wherein, Y represents inhibition percentage and X represents compound concentration.

PRMT4, PRMT6, and PRMT8 tests and curve fitting were performed with reference to PRMT3 tests and data processing methods using optimized parameters.

The following table showed the results of the PRMT panel selectivity tests, wherein, A represents IC₅₀ < 50 nM;

B represents 50 nM ≤ IC₅₀ < 500 nM; and

C represents IC₅₀ ≥ 10 μM

Compound	PRMT3	PRMT4	PRMT5	PRMT6	PRMT7	PRMT8
P207	B	A	C	A	C	A
P023	A	A	C	A	C	A
P118	B	B	C	A	C	A

Test Example 4 RKO in cell western assay method

RKO was seeded at a concentration of 20,000 cells/ml into a polylysine-coated 96-well plate (Corning#3599), with 2,000 cells per well and 100 μL of culture medium per well. 500 nL of compound was added to the 96-well plate. 3) The 96-well plate was incubated in a 37°C, 5% CO₂ incubator for 72 hours. After three days, the 96-well plate was taken from the

incubator, 100 µL of 8% paraformaldehyde solution was added to each well, and the plate was placed at room temperature for 15 min. After 15 min, the liquid in the plate was shaken out and the plate was washed three times with phosphate buffer(1*PBS). The liquid in the plate was shaken out and 200 µL of membrane-breaking buffer (0.1% (v/v) Tween-20 in PBS) was added and the plate was incubated on a shaker for 30 min. After half an hour, the liquid in the plate was shaken out, and blocking buffer was added and the plate was incubated for two hours at room temperature with shaking. After that, the liquid in the plate was shaken off, and the blocking solution containing primary antibody (MMA primary antibody, CST#8711S, 1:1000 v/v) was added to the 96-well plate and the plate was incubated at 4°C overnight with shaking. The next day, the plate was washed three times with washing solution (0.05% (v/v) Tween-20 in PBS), and a blocking solution containing secondary antibody (goat anti-rabbit IgG (H+L) Invitrogen#31460, 1:10,000 v/v) was added and the plate was incubated for two hours at room temperature. Afterwards, the 96-well plate was washed four times with washing solution. The TMB mixture was added to the 96-well plate and then the plate was incubated for 15 minutes at room temperature with shaking. After that, the reaction terminating solution was added, and the value was read at OD450 nm using a microplate reader. The plate was washed three times with washing solution, and 50 µL of janusgreen staining solution was added, and the plate was incubated for 15 minutes at room temperature with shaking. The reaction was washed ten times with water until no color residue was left. 200 µL of 0.5 M hydrochloric acid solution was added to each well and the plate was incubated for 10 min at room temperature. The value was read at OD595nm using Flexstation.

Calculations:

Firstly, the ratio OD450/OD595 was calculated for each well

Each plate had six DMSO negative control groups (ZPE) and six 10 µM positive control groups (HPE), and the average of the control group ratios was used to determine the percentage of activation for each test well. The compounds to be tested were triple diluted with DMSO for a total of 8 concentration points with a starting concentration of 5 µM. The equation for calculating the activation percentage of each test well was:

Activation percentage= 100 - [(HPE ratio - ratio of a certain well)/(HPE ratio - ZPE ratio)]*100

Table 4 Results of RKO ICW assays

A represents $EC_{30} < 250$ nM

B represents $250 \text{ nM} \leq EC_{30} < 2500$ nM

C represents $EC_{30} > 2500$ nM

Patent ID	RKO ICW EC_{30}	Patent ID	RKO ICW EC_{30}
P001	B	P118	A
P003	A	P122	C
P004	B	P130	B
P005	B	P131	B

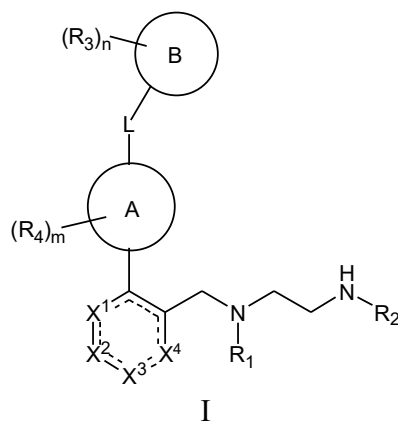
Patent ID	RKO ICW EC30	Patent ID	RKO ICW EC30
P007	A	P136	B
P008	B	P137	B
P009	B	P141	B
P014	B	P142	B
P015	B	P143	B
P021	A	P147	B
P022	A	P148	B
P023	A	P149	B
P025	A	P153	A
P039	B	P157	B
P044	B	P158	A
P049	A	P165	B
P050	B	P167	A
P051	B	P170	B
P052	B	P171	B
P053	B	P179	B
P054	A	P184	C
P056	B	P185	B
P057	B	P186	B
P069	B	P187	A
P074	B	P198	A
P075	B	P202	B
P078	A	P206	B
P079	A	P207	A
P080	B	P208	B
P081	A	P225	A
P083	A	P226	A
P085	A	P236	B
P088	B	P240	B
P089	A	P243	B
P094	A	P250	B
P095	A	P251	B
P106	B	P252	B
P107	B	P258	A
P112	B	P323	C
P114	A	P325	B

All documents referred to in the present invention are incorporated by reference herein as if each document is individually incorporated by reference. Further, it should be understood

that upon reading the above teaching of the present invention, various alterations or modifications may be made to the present invention by those skilled in the art, and those equivalents also fall within the scope defined by the appended claims of the present application.

Claims

1. A compound shown in formula (I), or a pharmaceutically acceptable salt thereof, or a deuterated compound thereof:



X^1 , X^2 , X^3 and X^4 are each independently selected from the group consisting of: CR, NR and N; the dash line is a chemical bond or absent;

ring A is selected from the group consisting of substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 4-8 membered carbocycle, and substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 4-8 membered heterocycle;

ring B is selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted C_6 - C_{10} aryl, substituted or unsubstituted 5-12 membered heteroaromatic ring, substituted or unsubstituted 3-12 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted C_1 - C_6 alkyl-6-10 membered aryl, substituted or unsubstituted C_3 - C_{12} carbocycle, substituted or unsubstituted C_2 - C_{10} acyl, substituted or unsubstituted C_2 - C_{10} ester group, substituted or unsubstituted C_6 - C_{10} aryloxy, substituted or unsubstituted C_1 - C_6 amide, substituted or unsubstituted C_1 - C_4 alkyl-S(O)₂, and substituted or unsubstituted C_1 - C_4 alkyl-SO-;

m and n are each independently selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6;

L is selected from the group consisting of chemical bonds, -O-, -(CHR⁶)_p-, -CHR⁶-O-, -CHR⁶-C(O)-, carbonyl, S, -NH-, -NHC(O)-, -NHS(O)₂-, -NHC(O)NH-, -NHC(S)NH-, -COO-, -O-S(O)₂-, -COO-CH₂-, -C(O)CH₂-, and -S(O)₂-, or L is absent;

p is selected from the group consisting of 1, 2 and 3;

R^1 and R^2 are each independently selected from the group consisting of H, substituted or unsubstituted C_1 - C_6 alkyl, and substituted or unsubstituted C_3 - C_6 cycloalkyl;

R^3 is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted C_1 - C_6 alkylamino, substituted or unsubstituted C_6 - C_{10} aryl, substituted or unsubstituted 5-12 membered heteroaryl, substituted or unsubstituted 5-7

membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₃-C₁₂carbocycle, substituted or unsubstituted C₂-C₁₀acyl, substituted or unsubstituted C₂-C₁₀ester group, substituted or unsubstituted C₆-C₁₀aryloxy, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-;

R is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-12 membered heteroaryl, substituted or unsubstituted 4-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₃-C₁₂carbocycle, substituted or unsubstituted C₂-C₁₀acyl, substituted or unsubstituted C₂-C₁₀ester group, substituted or unsubstituted C₆-C₁₀aryloxy, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-;

or two R located on adjacent ring atoms together with the ring atoms to which they are attached form a substituted or unsubstituted 5-11 membered carbocycle or heterocycle, and the ring is partially unsaturated or saturated; preferably, the carbocycle or heterocycle is a 5-9 membered carbocycle or heterocycle, more preferably a 5-7 membered carbocycle or heterocycle (the carbocycle or heterocycle is saturated, partially unsaturated or aromatic);

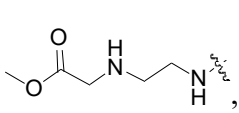
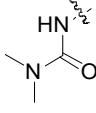
R⁴ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-12 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₃-C₁₂carbocycle, substituted or unsubstituted C₂-C₁₀acyl, substituted or unsubstituted C₂-C₁₀ester group, substituted or unsubstituted C₆-C₁₀aryloxy, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-;

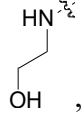
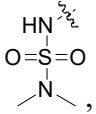
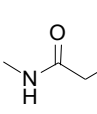
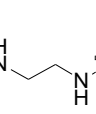
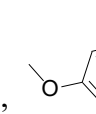
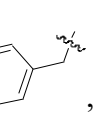
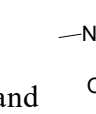
or two R⁴ on the same or adjacent ring atoms together with the ring atoms to which they attached form a substituted or unsubstituted 3-11 membered carbocycle or heterocycle, and the ring is a partially unsaturated ring, saturated ring or aromatic ring;

R⁶ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, acyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, and substituted or unsubstituted C₁-C₆alkylamino;

unless otherwise specified, in the above formulas, the “substituted” means that the hydrogen atom on the corresponding group is substituted by one or more substituents selected from the group consisting of: deuterium, tritium, halogen, hydroxyl, carboxyl, thiol, benzyl ,

oxo (=O), C₁-C₁₂alkoxycarbonyl, C₁-C₆aldehyde group, amino, C₁-C₆ amide, nitro, cyano, unsubstituted or halogenated C₁-C₆alkyl, C₂-C₁₀alkenyl, C₁-C₆alkoxy, C₁-C₆alkyl-amino, C₁-C₆alkyl-sulfonamide, C₁-C₆alkyl-ureido, C₁-C₆alkyl-S-, C₆-C₁₀aryl, five- or six-membered heteroaryl, five- or six-membered non-aromatic heterocyclyl, five- or six-membered non-aromatic heterocyclyl-(CH₂)-, -O-(C₆-C₁₀aryl), -O-(five or six membered heteroaryl), -NH-(C₆-C₁₀aryl), -NH-(five-membered or six-membered heteroaryl), C₁-C₁₂alkylaminocarbonyl, unsubstituted or halogenated C₂-C₁₀acyl, sulfonyl (-SO₂-OH), sulfonamide (-SO₂-NH₂), phosphoryl (-PO₃-OH), unsubstituted or halogenated

C₁-C₄alkyl-S(O)₂-, unsubstituted or halogenated C₁-C₄alkyl-SO-, , ,

10 , , , , , and , and ; in each formula, the heterocycle or heteroaromatic ring has 1-3 heteroatoms selected from the group consisting of N, S and O; each aryl, heteroaryl, and heterocyclyl can be independently substituted by 1-3 substituents selected from the group consisting of deuterium, tritium, halogen, hydroxyl, carboxyl, thiol, C₁-C₆alkyl, and C₁-C₆alkoxy.

15 2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a deuterated compound thereof, wherein R³ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted C₃-C₈carbocycle, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₆-C₁₀aryloxy, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-; and/or

R is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₃-C₈carbocycle, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₆-C₁₀aryloxy, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-; or two R located on adjacent ring atoms together with the carbon atoms to which they attached form a substituted or unsubstituted 5-9

membered carbocycle or heterocycle, and the ring is partially unsaturated, saturated or aromatic; and/or.

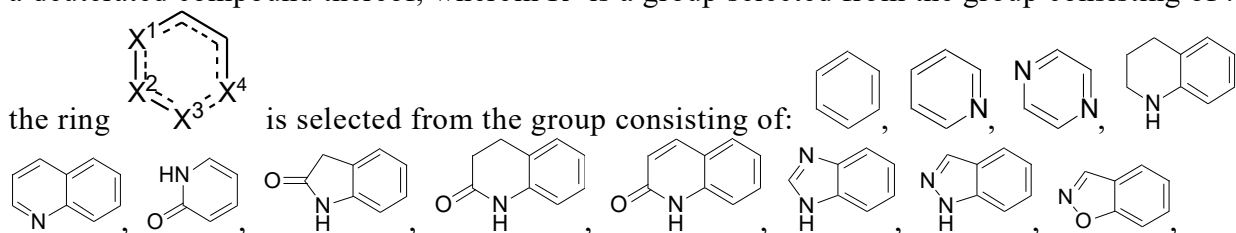
3. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a deuterated compound thereof, wherein, ring B is selected from the group consisting of: H, or substituted or unsubstituted phenyl, substituted or unsubstituted 5-10 membered heteroaromatic ring, substituted or unsubstituted 3-12 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, and substituted or unsubstituted C₃-C₁₂carbocycle.

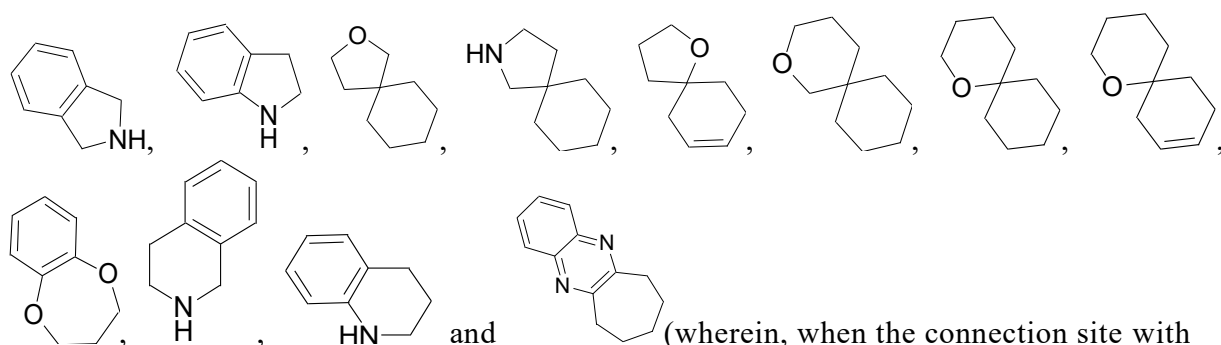
4. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a deuterated compound thereof, wherein R³ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-; and/or

R is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-; or two R located on adjacent ring atoms together with the ring atoms to which they are attached form a substituted or unsubstituted 5-7 membered carbocycle or heterocycle; and/or

R⁴ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₃-C₈carbocycle, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₁₀ester group, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-; or two R⁴ on adjacent ring atoms together with the carbon atoms to which they are attached form a substituted or unsubstituted 5-9 membered carbocycle or heterocycle, and the ring is partially unsaturated or saturated.

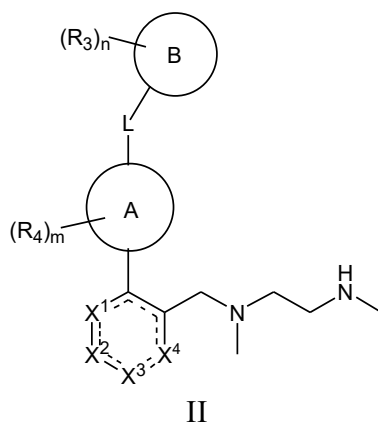
5. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a deuterated compound thereof, wherein R³ is a group selected from the group consisting of :





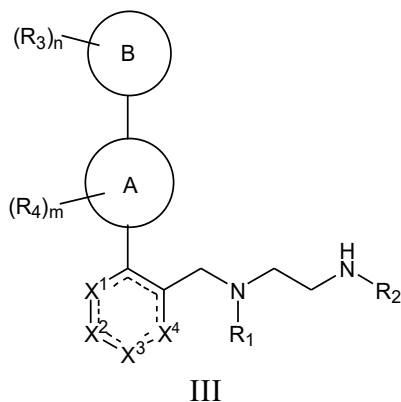
and (wherein, when the connection site with other structural fragments or substituents is NH, the hydrogen atom on NH is lost to form the connection site).

- 5 9. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a deuterated compound thereof, wherein the compound has a structure as shown in the following formula II:



10

10. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a deuterated compound thereof, wherein the compound has a structure as shown in the following formula III:



15

wherein,

ring A is selected from the group consisting of substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 4-8 membered carbocycle, and substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 4-8 membered heterocycle;

20

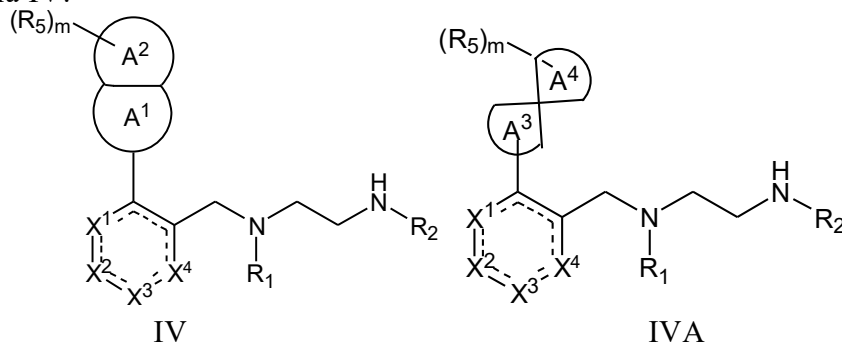
ring B is selected from the group consisting of substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-12 membered heteroaryl, substituted or unsubstituted 3-12 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen,

and substituted or unsubstituted C₃-C₁₂heterocycle;

preferably, R³ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-;

preferably, R⁴ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-7 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₃-C₈carbocycle, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-.

11. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a deuterated compound thereof, wherein the compound has a structure as shown in the following formula IV:



wherein,

ring A¹ is selected from the group consisting of substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 5-8 membered carbocycle, and substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 5-8 membered heterocycle;

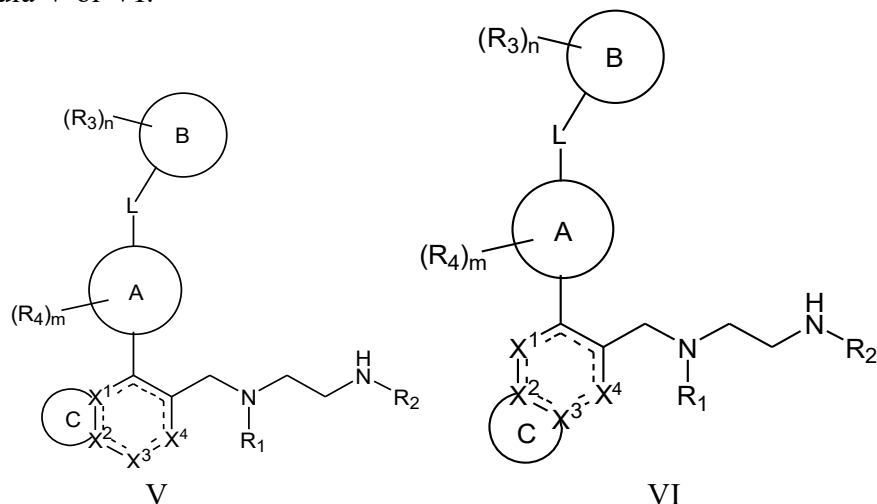
ring A² is selected from the group consisting of substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-12 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, and substituted or unsubstituted C₃-C₁₂carbocycle; and ring A² is fused with ring A¹;

ring A³ and ring A⁴ are each independently selected from the group consisting of substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 5-8 membered carbocycle, and substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 3-8 membered heterocycle;

m is 0, 1, 2, 3 or 4; R⁵ is selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted

C₁-C₆alkylamino, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₆-C₁₀aryloxy or heteroaryloxy, substituted or unsubstituted C₆-C₁₀arylamino or heteroarylamino, substituted or unsubstituted C₁-C₆ amide, substituted or unsubstituted -C₁-C₆alkyl-phenyl, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-; and R⁵ can be located on ring A¹, ring A², ring A³ or ring A⁴.

12. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a deuterated compound thereof, wherein the compound has a structure as shown in the following formula V or VI:



wherein, ring C is substituted or unsubstituted phenyl, substituted or unsubstituted 5-7 membered heterocyclyl, or substituted or unsubstituted 5-6 membered heteroaryl;

ring A is selected from the group consisting of substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 5-6 membered carbocycle, and substituted or unsubstituted saturated or partially unsaturated (non-aromatic) 4-8 membered heterocycle;

ring B is selected from the group consisting of substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-12 membered heteroaryl, substituted or unsubstituted 4-12 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, and substituted or unsubstituted C₃-C₁₂carbocycle;

preferably, R³ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-;

preferably, R⁴ is a group selected from the group consisting of H, halogen, cyano, amino, nitro, hydroxyl, thiol, aldehyde group, carboxyl, sulfonyl, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆alkylamino, substituted or unsubstituted C₆-C₁₀aryl, substituted or unsubstituted 5-7 membered heteroaryl, substituted or unsubstituted 5-7 membered heterocycle containing 1-3 heteroatoms selected from oxygen, sulfur and nitrogen, substituted or unsubstituted

-C₁-C₆alkyl-phenyl, substituted or unsubstituted C₃-C₈carbocycle, substituted or unsubstituted C₂-C₆acyl, substituted or unsubstituted C₂-C₆ester group, substituted or unsubstituted C₁-C₄alkyl-S(O)₂-, and substituted or unsubstituted C₁-C₄alkyl-SO-.

5 13. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a deuterated compound thereof, wherein the compound is any one of the compound of Example P1-P448.

10 14. A pharmaceutical composition, comprising a therapeutically effective amount of the compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients, adjuvants, accessories and/or diluents.

15 15. A use of a compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof, in the preparation of a pharmaceutical composition for the treatment or prevention of diseases associated with PRMT; preferably the PRMT is type I PRMT.